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ABSTRACT BOOK

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**CAPE TOWN • SOUTH AFRICA
2–6 DECEMBER 2015**

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The International Journal of Tuberculosis and Lung Disease

The Official Journal of the International Union Against Tuberculosis and Lung Disease

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EDITORIAL OFFICE	The International Union Against Tuberculosis and Lung Disease (The Union) 68 boulevard Saint Michel, 75006 Paris, France Tel: (+33 1) 44 32 03 60 Fax: (+33 1) 43 29 90 83 e-mail: journal@theunion.org website: www.theunion.org		

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46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) Cape Town, South Africa, 2–6 December 2015

SYMPOSIA: FRIDAY 4 DECEMBER 2015

02. Best practice in management of side effects among DR-TB patients to improve quality of care

Addressing side effects of MDR-TB treatment during ambulatory phase in the community

S Islam,¹ M Siddiqui,¹ S Reza,¹ M Basher,¹ M Akramul Islam,¹ S Sultana,² F Khanam³ ¹Health, BRAC, Dhaka, ²World Health Organization, Dhaka, ³NTP, Dhaka, Bangladesh.

Background and Challenges: Drug-resistant TB has become a significant public health problem that threatens progress made in TB care and control worldwide. In Bangladesh, the rate of MDR-TB among new cases is relatively low, based upon the last drug resistant survey (2010–2011). The NTP began introducing a strategy of programmatic management of drug-resistant TB (PMDT) at community level in 2012. As DR-TB patients are shifting to the community earlier (between 6 to 8 weeks) with the prescribed injectable agent, local management of side effects is essential.

Intervention: All MDR-TB patients were hospitalized at the start of treatment in facilities designed for management of DR-TB (central/regional). Sputum microscopy is done weekly for admitted patients. If two consecutive sputum samples become negative, condition is clinically improved and drug is well tolerated, the MDR-TB patients are shifted to the community for ambulatory care. At sub-district level, there is an 'Outpatient DR-TB Team' formed by Upazilla Health and Family Planning Officer and other health staff. This team selects a DOTS provider for the patient. If a patient develops any adverse effects, the assigned DOT provider contacts immediately with the team for assistance. All health care providers related to MDR-TB management receive basic orientation before starting of MDR-TB management at community level.

Results and lessons learnt: Due to the scale up of community based management of MDR-TB in the

country in 2012, the gap between diagnosed and enrolled MDR-TB patients under treatment reduced and there was an improvement of treatment success rate. In 2010, among the diagnosed cases, 70% of MDR-TB patients were enrolled in treatment which became 95% in 2014. The lost-to-follow-up rate is also less (around 1%) in the ambulatory phase than during the hospital stay (14%). A total of 140 patient records were reviewed from January 2011 to April 2015 for their side effects status during treatment and 28 (20%) patients were reported with joint pain, 23 (16%) with vomiting, 16 (11%) with hearing disturbance, who were treated accordingly in the community settings.

Conclusion: During the ambulatory phase, MDR-TB patients could stay with their family and get adequate psychosocial support. Side effects during this period could be managed by a local DR-TB team immediately. This approach may contribute to minimizing the challenges related to treatment adherence and ensure a high treatment success rate for Bangladesh.

03. Pre-approval of access to new TB drugs: what, where and how

Pre-approval access from the industry perspective: Janssen

C Kambili ¹Janssen Pharmaceutical Companies of J&J, Raritan, NJ, USA.

Pre-approval/expanded access, also called 'compassionate use' (CU), is the use of an investigational medicinal product outside of a clinical trial. The willingness by patients with life-threatening conditions to assume greater risks (than is ordinarily the case in clinical practice) in exchange for potential benefits, is the driving force for CU. Several forms of CU exist, some of which can provide data for analysis. The following elements are crucial to implementing pre-approval access for TB drugs: (1) protect patients from unnecessary harm; (2) minimize the risk of treatment failure and emergence of resistance; (3) exercise fairness; and (4) comply with prevailing laws and regulations. Although fulfilling these tenets should be everyone's responsibility, complying with laws and regulations requires special attention for drug developers. In the USA, the Food,

Drug, and Cosmetic Act sets out the legal framework that establishes regulations for access to investigational treatment for serious diseases, if and when certain conditions are met. Not every country has such a legal and regulatory framework. The lack of a harmonized approach creates challenges for a sponsor wishing to implement a global CU program. Resources must be mobilized to ensure that due diligence is done and that local laws and regulations are adhered to. Clear and simple guidelines and minimally burdensome requirements coupled with the availability of expert consultation to treating physicians appear to streamline the review process thus reducing delays in the delivery of the investigational product to eligible patients. High-level political commitment and support are critical. Dialogue with stakeholders helps clear misunderstandings that can erode trust between the sponsor and the broader community. Janssen's bedaquiline CU program, which started in late 2011 and ended in September 2015, provided access to over 700 patients from over 40 countries. Treatment outcome data were not collected on all patients, but physicians did report serious adverse events, including deaths, to the company. Pre-approval access should not and cannot be a substitute for product registration. For diseases of public health importance such as TB, there must exist push-and-pull mechanisms that ensure speedy but safe and sustained access to novel products. Supportive policies must be in place so that those in need are not denied innovative health solutions.

04. Outstanding issues in HIV/AIDS treatment

Pros and cons: empiric TB treatment is critical to reducing TB mortality among PLHIV but would adversely affect national TB programmes

F Mavhunga ¹National Tuberculosis and Leprosy Programme, Ministry of Health and Social Services, Windhoek, Namibia.

Background: Diagnosis and confirmation of tuberculosis (TB) remains a challenge in many settings, particularly in settings with high TB-HIV coinfection rates. Consequently a number of patients are commenced on TB treatment late or not at all, resulting in high mortality and morbidity. A 2015 meta-analysis (Gupta et al., 2015) based on post-mortem findings among people with HIV suggests that TB remained undiagnosed at death in 45.8% (95%CI 32.6–59.1%) of TB cases. A 2011 systematic review found that 17% (median) of people starting antiretroviral therapy (ART) developed TB within one year. Among the suggested interventions for the management of TB-HIV in high TB burden settings is empiric TB treatment for all people living with HIV in high TB-HIV settings.

Potential implications for TB programmes: While the rationale for empiric TB treatment in PLHIV sounds plausible, there are a number of potential negative

implications for TB programmes. TB programmes in most high burden settings are already overburdened and have limited capacity to provide and support treatment of diagnosed TB patients. Adding empiric treatment to this burden is likely to stretch the programmes further with consequent reduction in overall treatment adherence and increased risk of development and spread of drug resistance. Lessons from the implementation of IPT also highlight the challenges with implementation of such a blanket approach when it comes to ensuring treatment completion under programmatic conditions. The other risk associated with empiric treatment is the consequent under-investment in efforts to diagnose TB in PLHIV, resulting in patients with conditions mimicking TB being diagnosed late as a result of the 'TB' label, thus further adversely affecting treatment outcomes. While the Reducing Early Mortality and Early Morbidity by Empiric Tuberculosis Treatment Regimens (REMEMBER) trial (Hosseinipour et al., 2015) has shown no excess toxicity compared to IPT, it also showed no mortality benefits with empiric treatment. Thus adding these patients to the TB treatment cohort might overestimate 'TB deaths'.

Conclusion: While empiric TB treatment for PLHIV may theoretically improve outcomes in these patients, recent evidence appears to suggest otherwise. Additionally the long term system-wide risk on TB control requires attention in the context of existing treatment support systems. Investments should rather focus on improving screening systems and diagnostics for TB in people with HIV.

Pros and cons: empiric TB treatment is critical to reducing TB mortality among PLHIV but would adversely affect national TB

M Hosseinipour ¹UNC Project, Lilongwe, Malawi;
²University of North Carolina, Chapel Hill, NC, USA.

Strategies for reducing tuberculosis (TB) mortality among TB-HIV co-infected patients in sub-saharan Africa are needed. Autopsy studies in both the pre and post antiretroviral therapy era demonstrate TB to be either a primary or contributing cause of death in the majority of cases, and often undiagnosed pre-mortem highlighting missed opportunities for TB treatment intervention. Prompt, near co-administration of antiretroviral therapy and TB treatment can reduce mortality, particularly in those with the lowest CD4 counts (<50 cells) in whom microbiologic confirmation of tuberculosis disease may be difficult. While strategies for improving diagnosis, including systematic screening and implementation of GeneXpert, have the potential to identify tuberculosis earlier, the impact on mortality has been less than expected. Gaps exist in the continuum of care for suspected TB patients as they fail to navigate multiple steps within health systems. One such gap, between presumed TB and confirmed TB diagnoses and initiation, can be addressed by the use of Empiric TB treatment. TB treatment initiation based on clinical acuity and associated signs and symptoms suggestive of

TB before or without microbiologic evidence can result in same day initiation. The substantial time savings in initiating life-saving therapy is particularly relevant when screening and diagnostic services are limited. Empiric therapy does not add additional value when TB screening is well performed and ART and isoniazid preventive therapy are initiated in a timely fashion (A5274 REMEMBER trial). However, in many settings TB screening and routine availability of GeneXpert, standardized symptom evaluation, culture and time to spend with each participant are not readily available and therefore empiric therapy likely still has advantages when new rapid diagnostics are not readily available. Arguments for empiric strategies will be highlighted.

05. Zoonotic TB session I - Trends, diagnostics and infections models

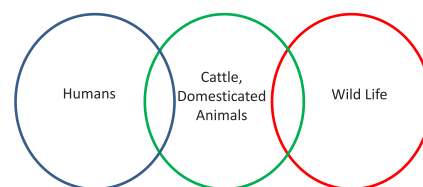
Zoonotic tuberculosis in India: challenges and opportunities

C P Churamani,¹ A K Rastogi,¹ A K Tyagi,² K P Hanumanthappa,³ A Kumar,³ P S Narwal,⁴ D S Chauhan,⁵ V M Katoch⁶ ¹Central Military Veterinary Laboratory, Meerut Cantt, ²Department of Biochemistry, University of Delhi South Campus, New Delhi, ³Department of Biotechnology, All India Institute of Medical Sciences, New Delhi, ⁴RVC Centre and College, Meerut, ⁵National JALMA Institute for Leprosy and other Mycobacterial Diseases, (ICMR), Dr. M. Miyazaki Marg, Taj Ganj, Agara, ⁶Department of Health Research, Director General, Indian Council Medical Research, Ansari Nagar, New Delhi, India.

A quarter of the global burden of human tuberculosis occurs in India (Global TB Report 2014, WHO). Implementation of the 'Stop TB program' has reduced the rates of incidence, prevalence and mortality, (TB INDIA 2014). However the occurrence of mycobacterial pathogens in species other than humans has been ignored. The capability of pathogenic mycobacteria to cross the species barrier and sustain transmission among diverse hosts; the proximity of cattle to humans and human dependence on animal derived meat and dairy products thwarts the current preventive strategies. The estimated livestock population of India is 512 million (19th Livestock Census-2012), while the estimated human population is 1.2 billion. The precise burden of tuberculosis among non-human hosts is unknown. Limited studies have demonstrated the presence of *Mycobacterium bovis* and *M. tuberculosis* in human and bovine samples, denoting that these mycobacterial pathogens could potentially infect humans as well as cattle. Besides the need to recognize the enormity of the problem, it provides a challenging opportunity to confront tuberculosis wherever it occurs. Vaccination of cattle is the practical option that would be acceptable in the Indian context as opposed to the test and slaughter policy practiced in several countries. Tuberculosis research in cattle has been beneficial to humans. Hence utilizing bovines to test and screen vaccine candidates for protection against tuberculosis would be apt. The

currently used BCG vaccine has not been successful in imparting protective immunity to humans and cattle. Five vaccine candidates heat killed *M. indicus pranii*, and recombinant BCG (rBCG) over expressing α -crystallin (Rv2031c), Ag85C (Rv3803) and DNA vaccines (α -crystallin; super oxide dismutase, Rv3846), shown to be efficient in protection against a challenge of virulent *M. tuberculosis* in small experimental animals were assessed (Khera et al., Vaccine 2005; 23: 5655–5665; Jain et al., PLOS ONE 2008. 3: e3869). The induction of central memory T cells (TCM), has been considered crucial for protective immunity (Hope et al., Clin Exp Immunol 2005; 139: 48–56). PBMC isolated from the immunized and control cattle, stained with a panel of monoclonal antibodies specific for TCM cells (CD4/8/ $\gamma\delta$, CD45RO, CCR7, CD62L, IL-2, IFN- γ) were flow cytometrically analyzed. The results showed that TCM cells were sustained up to a period of 30 months in rBCG 85C immunized cattle compared to BCG immunization.

Figure The nexus-plexus of mycobacterial pathogens: the challenge



Rapid bTB: a novel lateral flow test able to differentiate *Mycobacterium bovis* and *Mycobacterium tuberculosis* in sputum

L Stewart,¹ I Grant,¹ M Sander,² F Egbe² ¹Institute for Global Food Security, Queen's University Belfast, Belfast, UK, ²Tuberculosis Reference Laboratory - Bamenda, Bamenda, Cameroon.

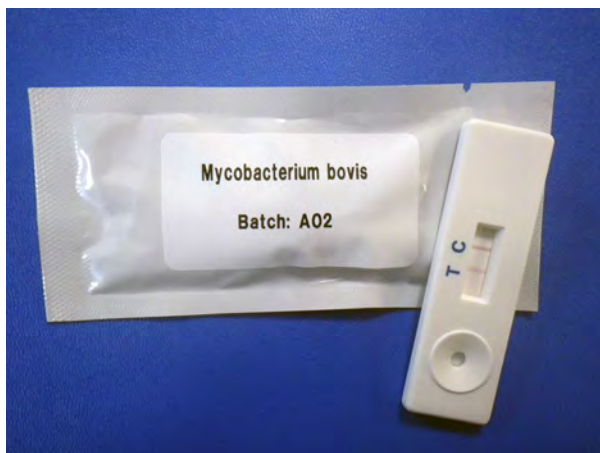
Background: A novel lateral flow, immunochromatographic assay (LFD) specific for *Mycobacterium bovis*, the cause of bovine tuberculosis and zoonotic TB, was recently developed at Queen's University Belfast. The LFD detects whole *M. bovis* cells, in contrast to other commercially available LFD tests (BD MGIT™ TBc ID, SD Bioline TB Ag MPT 64, Capilia TB-Neo kit) which detect MPT64 antigen secreted during growth. The new LFD test has been evaluated in the veterinary context, and its specificity for *M. bovis* in the broadest sense (i.e. subsp. *bovis*, subsp. *caprae* and BCG) and sensitivity to detect *M. bovis* in positive MGIT™ liquid cultures was demonstrated comprehensively.

Methods: Preliminary work was carried out by researchers at Queen's University Belfast to optimise sputum sample preparation, estimate the limit of detection (LOD) of the LFD with *M. bovis*-spiked sputum samples, and check LFD specificity by testing a broad range of non-tuberculous mycobacteria spp. (NTM) and other bacterial genera commonly encountered in sputum samples (*Haemophilus*, *Klebsiella*, *Pseudomonas*, *Staph-*

yllococcus). In the Cameroon laboratory direct detection of *M. bovis* in human sputum was attempted, and 50 positive sputum MGIT™ cultures and 33 cultures of various *Mycobacterium* spp. originally isolated from human sputum were tested.

Results: Sputum sample preparation consisted of digestion with 1% NALC for 30 min, centrifugation at 3000 xg for 20 min, PBS wash, centrifugation again, and pellet resuspended in KPL blocking buffer before 100 µl was applied to the LFD. The LOD of the LFD applied to *M. bovis*-spiked sputum was estimated to be 10⁴ CFU/ml. A small number of confirmed Ziehl-Neelsen '3+' *M. bovis* positive sputum samples were tested directly but no positive LFD results were obtained. All of the sputum MGIT™ cultures and mycobacterial cultures (including *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. intracellulare*, *M. scrofulaceum*, *M. fortuitum*, *M. peregrinum*, *M. interjectum*) tested LFD negative when read after 15 min except for the *M. bovis* cultures, thereby confirming specificity of LFD for *M. bovis* in the clinical microbiology context.

Conclusions: Results indicate that the 'Rapid-bTB' LFD is a very specific test, able to differentiate *M. bovis* from *M. tuberculosis*, *M. africanum*, and a range of NTM isolated from human sputum in MGIT™ liquid cultures. However, the LFD lacks sufficient sensitivity to be applied earlier in the diagnostic process to directly test human sputum.



Ferrets: a small animal model for zoonotic tuberculosis transmission

F Quinn,¹ B He,¹ T Ross,¹ C C Whalen^{1,2} ¹Infectious Diseases, University of Georgia, Athens, GA, ²Epidemiology and Biostatistics, University of Georgia, Athens, GA, USA.

Tuberculosis epidemics develop when one case is replaced by one or more cases among contacts. Case studies, molecular epidemiology and clinical trials all agree that transmission in the community is the driving force behind TB epidemics, and blocking transmission is the most effective way to intervene in an epidemic and reduce its impact. Current tuberculosis control strategies are not designed to interrupt transmission, but instead

focus on detecting active disease and then culling infected animals or treating infected humans. Yet, unfortunately, diagnosis is often delayed or methodologies are not sufficiently sensitive, and infected individuals continue to transmit *Mycobacterium bovis* or *M. tuberculosis* bacilli to contacts. The overall goal of our program is to define transmission dynamics of *M. tuberculosis* and *M. bovis* in animal and human populations and implement novel control strategies that interrupt the processes. The practical and logistical challenges and overall high costs associated with appropriate transmission studies in relevant hosts; the calf or cow for bovine TB and the macaque for human TB, have limited our understanding of the process. Numerous investigators over the years have shown the ferret to be an appropriate model for the study of influenza virus transmission, and now, preliminary studies show that the ferret can develop acute disease with pathology similar to humans and cattle and transmit *M. tuberculosis* and *M. bovis* bacilli animal-to-animal. It is widely recognized that improved understanding of the mechanisms of pathogenesis and host response to natural infection by *M. bovis* or *M. tuberculosis* are needed in order to develop the most efficacious vaccines, diagnostics and therapeutics. Ongoing studies may show the ferret to be an acceptable small animal TB model of natural transmission.

How zoonotic tuberculosis is laying new ground for approaches in mycobacterial research in Tanzania

S G Mfinanga,¹ E Ngadaya,¹ R Kazwala² ¹National Institute for Medical Research, Muhimbili Centre, Dar es Salaam, ²Sokoine University of Agriculture, Dar es Salaam, Tanzania.

Background: During the early 1990s, there were limited studies on bovine tuberculosis (TB) in the country. The aim of this article is to highlight various research approaches used in the country for the epidemiology of *M. bovis*, and advise on the way forward.

Intervention: The information reported in this article was obtained by searching eligible articles published in scientific journals from 1990 to 2015. The search engines from PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Google Scholar (<http://scholar.google.com>) and Hinari (<http://www.who.int/hinari/en/>) were used and key words included bovine TB and Tanzania.

Results: International consultation lead by World health Organization in 1993 addressed the potential threat in view of limited data for *M. bovis* in Tanzania and Zambia. During the 1990s, the approaches for investigations of *M. bovis* were mainly unilateral, whereby the veterinary institutions were engaged. Since then various approaches have been used including south-north bovine networks, which basically involved veterinary discipline and thus perceived as a unilateral approach. In early 2000s, the medical institutions joined the networks and hence advanced the networks into one health approach. As a result of these approaches, research capacity was built across east and western African Institutions and

scientific contributions have been published. Studies on the magnitude of *M. bovis* in cattle and wildlife carried out across the country from 1996 to 2015 have reported varying prevalences of 0.2% to 13.3%. In humans, a few small-scale studies, which mostly involved extra pulmonary samples, reported varying prevalence of 10% to 16%. Diverse RFLP and spoligotype patterns including the predominance of SB1467, SB2190 and SB0133 have been observed. Studies have identified risk factors and demonstrated inadequate public knowledge and perception on bovine TB control. The initial impact of these studies was a policy change by the National TB Control Program, where in its earlier manuals, *M. bovis* was considered rare but in its new manual the statement has changed and now *M. bovis* is considered one of pathogens in human TB in Tanzania.

Conclusions: One health approach achieved more capacity development and more quality studies in the investigation of *M. bovis*. Prevalence of *M. bovis* in humans and animals seems to be low and endemic. Nevertheless, its potential risk remains a public health concern; underscoring the need for further research.

Prevalence, molecular epidemiology and risk factors of tuberculosis infection among cattle and livestock workers in Nigeria

S Cadmus,¹ V Akinseye,¹ O Adedipe,¹ AKwaghe,² F Ejeh,³ E Cadmus⁴ ¹Veterinary Public Health & Preventive Medicine, University of Ibadan, Ibadan, ²Veterinary Medicine, University of Maiduguri, Maiduguri, ³Veterinary Microbiology and Parasitology, University of Maiduguri, Maiduguri, ⁴Preventive Medicine and Primary Care, University of Ibadan, Ibadan, Nigeria.

Background: Tuberculosis (TB) and bovine TB (bTB) continue to decimate human and cattle populations in Africa. Recently, TB infrastructure was scaled up to control human TB in Nigeria (ranked 13th among TB burdened nations globally); however, nothing was done to assuage the zoonotic bTB threat. Bovine TB, a neglected zoonosis, remains a major public health challenge because those primarily afflicted [livestock workers (LW)] are neglected. Hence, need to gather valuable data on prevalence, molecular epidemiology and risk factors of TB infection among cattle and LW in Nigeria with a view to influencing Public Health policy. **Methods:** We conducted a cross-sectional study among cattle and LW (butchers and marketers) between 2013 and 2015 in Nigeria. Animal screening involved post mortem identification of cattle with suspected tuberculous lesions (TLs) at abattoirs and tuberculin testing of cattle herds. Sputum samples from humans and TLs were cultured and subjected to a two-step multiplex PCR technique based on genus typing and genomic regions of difference, respectively. Interviewer-administered questionnaire was used to assess LW TB related knowledge, attitude and practices.

Results: Overall, 3595 cattle (abattoirs=3133; herds=462) and 266 LW were screened. More than three quarters (76.3%) of cattle screened were from northern Nigeria; and 5.0% (156/3133) of those from the

abattoirs had positive culture. Furthermore, 10.4% (48/462) and 42.9% (18/42) individual and herd prevalences were obtained, respectively. Among LW, 69.2% (184/266) were from southern Nigeria. Overall, 4.6% (7/152) of butchers and 6.1% (7/114) of marketers, respectively, had positive cultures. Additionally, molecular characterization identified 86 strains of *Mycobacterium bovis* (all from cattle), seven *M. tuberculosis* (all from humans) and 21 non-tuberculous mycobacteria (from cattle and humans). Again, age ($P = 0.001$), educational status ($P = 0.02$) and duration in livestock business ($P = 0.002$) were identified as important risk factors associated with TB infection among respondents.

Conclusion: Our findings reveal high burden of bTB among cattle herds (individual prevalence=10.4%; herd prevalence=42.9%). Additionally, isolation of 86 strains of *M. bovis* from slaughtered cattle in a setting with poor knowledge/practices towards bTB, portend major health risks. Consequently, there is an urgent need for implementation of Public Health policies towards addressing bovine tuberculosis threat in Nigeria.

06. One pilot after another: how can we move toward a sustainable scale-up of child lung health interventions?

Viet Nam: TB CARE I project leading to the country-wide scale-up of symptom-based contact screening

T H Nguyen ¹KNCV Tuberculosis Foundation, Hanoi, Viet Nam.

Background: Viet Nam is a high TB burden country but accurate data on the burden of TB in children are not available. The annual risk of TB infection (NTP prevalence survey in 2006–2007) was 1.7%. Approximately 351 000 children are estimated to be infected with TB annually and around 13 000 children are estimated to develop TB annually. However, the NTP reports only 1200–1300 child TB cases each year. Further, contact screening and preventive therapy were introduced as recommendation only in 2011 and are not widely implemented.

Objectives: To describe and evaluate the establishment and development of the child contact screening and management in Viet Nam.

Methods: Community-based contact screening was introduced in 4 provinces following training of health workers and establishment of a recording-reporting system, in collaboration with the NTP. The WHO recommended symptom-based screening approach was implemented focusing on: i) Screen and manage children that are household contacts of a sputum smear positive TB case in the community; ii) Provide IPT for eligible child contacts (aged <5 years and HIV-infected once TB excluded) at commune (primary care) level; iii) Introduce a diagnostic algorithm for diagnosis of TB in children at the district (second care) level; iv) Develop IEC material; v) ensuring availability of isoniazid 50 mg; and vi) engage

the wider health care sector by the NTP strengthening links and collaborating with the child health sector.

Results: The WHO screening strategy has been implemented in 4 provinces covering a total of 38 districts and 704 communes since quarter 4, 2012. 1578 health care staff (in NTP, general hospitals and paediatricians and commune health workers) in the health system have been trained on the new strategy. In the period quarter 4 2012 to quarter 1 2015, 9741 children that were household contacts of sputum smear-positive TB patients were screened and registered. 715 (7.3%) were diagnosed with TB (all forms). Among 3858 eligible children for IPT, 2514 (65%) children accepted IPT. The IPT completion rate was 84% among 1,154 children. With success of this new strategy in 4 pilot provinces, NTP has utilised funds from the Global Fund to scale up this strategy to 6 provinces for the period 2013–2014 and to all communes across the country in 2015. Major challenges have been clinical diagnosis and decentralisation of diagnosis and management of TB in children, a lack of diagnostic tools, the establishment of collaboration between paediatricians and NTP, and awareness of the rationale for preventive therapy among families and health workers.

Conclusion: Viet Nam is among the first countries globally to implement and scale up the WHO symptom-based strategy in management of child TB contacts. Lessons learned will inform improving effective implementation as contact screening and managing is rolled out in Viet Nam.

07. Role of surgery in management of TB: a promise or redundancy?

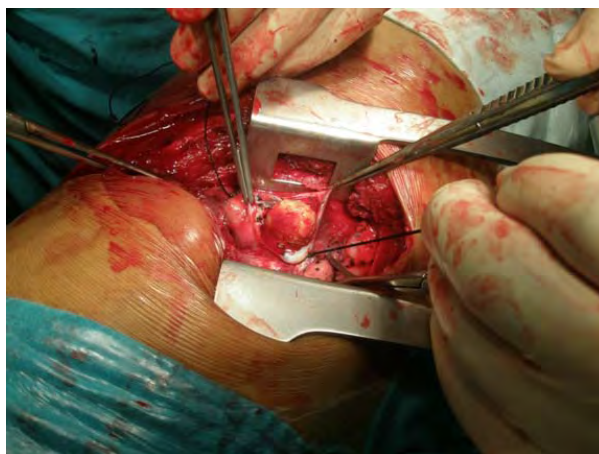
Experience from India: main indications and realities of thoracic surgery in TB patients

R K Dewan¹ Thoracic Surgery, National Institute of TB and Respiratory Diseases, New Delhi, India.

Surgery in TB patients: TB Surgery is a high-cost intervention with moderate to high risks of complications. The main indications for surgery are a persistent sputum positive state, recurrent hemoptysis or chest symptoms, empyema and diagnostic.

Experience of TB Surgery at the NITRD, New Delhi: India is being presented which includes all the cases operated upon for Pulmonary Tuberculosis at NITRD from 1995 to 2014. A total of 107 patients were operated upon as they were persistently sputum positive. MDR status was demonstrated in 15 and XDR status in 4. There were 80 male patients and 27 female patients with an age range of 21 to 52 years. Pneumonectomy was carried out in 67 cases, lobectomy in 20, bilobectomy in 5, thoracoplasty in 12 and other lung resections in 3. There were three early deaths; 98 patients became sputum negative after surgery. 22 patients became sputum positive again in follow up. Eight of these died of progressive disease. 76(71%) remained sputum negative. 18 were lost to follow up later on. BPF developed in 8 cases. In the group taken up for surgery

for complications and sequel, 1316 patients were operated upon for hemoptysis; 32 had undergone bronchial artery embolization before surgery. 15 cases were taken up as an emergency and 95 cases were taken up for chest symptoms other than hemoptysis. Pneumonectomy was done in 524 patients, lobectomy in 710, bilobectomy in 85, segmental resection in 18 and non-anatomical resections were done in 18 patients. There were 27 early and 52 late deaths. Most patients became symptom free. Many different procedures were done for empyema cases with complete closure of space and healing of chest wall sinus being achieved in almost all the cases. Overall, the results of surgery in carefully selected patients for TB surgery are highly gratifying.



Experience from the Russian Federation: main risks and benefits of surgical interventions in TB

D Krasnov,¹ I Felker² ¹Surgical, Novosibirsk TB Research Institute, Novosibirsk, ²International, Novosibirsk TB Research Institute, Novosibirsk, Russian Federation.

The Novosibirsk TB Research Institute has more than 60 years of experience in the surgical treatment of people with pulmonary TB. Over 400 surgical interventions for pulmonary TB are carried out every year. Basically, the following surgical procedures are performed: lung resections, pneumonectomies, thoracoplasty, operations on the bronchi, endobronchial valve (EbV) implantation etc. When identifying indications and contraindications for surgical treatment, we largely rely on the consensus paper titled 'The role of surgery in the treatment of pulmonary TB and multidrug- and extensively drug-resistant TB' and released by the WHO Regional Office for Europe. All patients undergoing surgery keep receiving drug therapy according to the susceptibility of MTB. Most patients who have undergone surgery are still smear positive for M/XDR, even though they had had proper chemotherapy for 6 months or longer. We consider that the first priority for surgery in TB, especially in the regions with high prevalence of M/XDR, is to deal with smear positiveness. In Russia 5–6% of people with cavernous (CV) TB undergo surgery,

while, in our opinion, this figure should be increased to 20%. In our opinion, an extensive use of surgery in patients who have long been smear-positive and on whom drug therapy fails is what both the affected people and the society as a whole will benefit from at large. However, patients with M/XDR-TB are the most difficult for surgery, for the course of TB process in them is often accompanied by progression, distributed CV with an ongoing infiltration and the occurrence of pathology as foci in the bulk of lung tissue, the presence of CV in both lungs, and specific bronchi lesions. This fact reveals the main risks of the surgical treatment of TB. The other major risks of the surgical treatment are high levels of comorbidity, low functional levels, and unsuccessful operations on the lungs for TB in the past. Resection interventions are contraindicated in most of these cases. A novel technique for performing mini-access extrapleural thoracoplasty with an excellent cosmetic result has been developed in our clinic for patients with cavernous TB with a high risk of complications following lung resections. This procedure has been applied to 414 patients. The clinical effect in the form of bacteriological conversion and the absence of CV at discharge was attained in 87% of cases. In most of these patients, thoracoplasty had been carried out in combination with EbV.

08. Maternal and infant TB: advancing our understanding of pathogenesis, treatment and prevention

Challenges in the management of maternal and perinatal TB: cases from the field

S Naik ¹Obstetrics & Gynecology, B J Government Medical College, Pune, India.

India accounts for 26% of the world's burden of tuberculosis (TB). The clinical and laboratory similarities between TB and pregnancy pose a diagnostic dilemma. The data on burden of TB among pregnant women in India are limited but increased obstetric morbidity and mortality has been reported. Late diagnosis and delayed treatment are associated with a nine- fold increase in preterm labour, poor nutritional status, hyperproteinemia and anemia. Intensified search for TB in pregnancy is the need of the hour. The BJ Government Medical College (BJGMC) is affiliated with Sassoon General Hospitals (SGH) in Pune, India, a tertiary care public teaching hospital that primarily cares for an urban and semi-urban underserved population. BJGMC-SGH evaluates approximately 4000 suspected TB cases annually including varied presentations of TB in pregnancy, ranging from normal to very atypical presentations. This presentation will:

- Review typical and atypical TB cases in the peripartum period.
- Highlight the challenges of managing TB in peripartum women.

- Review adverse outcomes of maternal TB in mothers and infants.
- Discuss critical gaps in maternal-infant TB research.

Current research on the pathophysiology, immunology, prevention and treatment of TB in pregnant women

J Mathad,¹ A Gupta² ¹Weill Cornell Medical College, New York, NY, ²Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Tuberculosis (TB) incidence in women peaks during reproductive age with more than 200 000 pregnant women diagnosed with active TB disease annually. The period of elevated risk appears to be highest in the early postpartum period—with a twofold increased risk observed in epidemiologic studies. When TB occurs during pregnancy and postpartum, it is a major cause of both maternal and infant morbidity and mortality. However significant scientific gaps in pathogenesis, treatment and prevention remain. As a result, national guidelines for screening and management vary widely, with a lack of data preventing a global consensus. Available TB diagnostics do not account for the immune changes that occur during pregnancy and the postpartum period. Safety data for TB drugs during pregnancy is minimal, especially for drug-resistant infections. Case reports are common but offer little useful guidance. Practitioners in TB-endemic countries have little evidence by which to guide their management of TB infection and disease in pregnancy. This presentation will review: 1) The pathophysiology of tuberculosis in pregnant and postpartum women; 2) What is known about the interaction between immune changes of pregnancy and the host immune response to *Mycobacterium tuberculosis*; 3) Current recommendations and ongoing research on the prevention of TB in pregnant and postpartum women; and 4) Current recommendations and ongoing research on the treatment of active TB in pregnant and postpartum women, including HIV-TB co-infection and drug-resistant TB.

The pharmacokinetics and treatment of first line TB drugs for infants

A Bekker,¹ H S Schaaf,¹ H R Draper,¹ L Van Der Laan,¹ A Hesselink,¹ L Wiesner,² H McIlleron,² S Murray³

¹Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, ²Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa; ³Department of Clinical Research, Global Alliance for TB Drug Development, New York, NY, USA.

Background: There are limited pharmacokinetic data available for first-line anti-tuberculosis drugs in infancy (<12 months of age), a period of rapid growth and maturation, which potentially influences drug disposition.

Methods: Intensive pharmacokinetic sampling was performed in infants on tuberculosis treatment including rifampicin, isoniazid, pyrazinamide and ethambutol

using 2010 World Health Organization recommended doses. Regulatory approved single-drug formulations were used on the day of pharmacokinetic sampling, including two rifampicin suspensions. Assays were conducted using liquid chromatography mass spectrometry; pharmacokinetic parameters were generated using non-compartmental analysis.

Results: Thirty-nine infants (26 male) were included; 14 (36%) with culture-confirmed tuberculosis. Fifteen (38%) infants were premature (<37 weeks); 5 (13%) were HIV-infected. The mean corrected age and weight was 6.6 months and 6.45 kilograms, respectively. The mean maximum plasma concentration (C_{max}) for rifampicin, isoniazid, pyrazinamide and ethambutol were 2.9, 7.92, 41.9 and 1.26 µg/ml, and mean area under the concentration curve (AUC₀₋₈) 12.12, 24.68, 239.4 and 5.09 µg.h/ml, respectively. Adjusting for age and weight, rifampicin formulation differed for the two formulations used, C_{max} and AUC₀₋₈ (GM/Ratio=2.55, 95%CI (1.47-4.41), *P* = 0.001; GM/Ratio=2.52, 95%CI (1.34-4.73), *P* = 0.005, respectively). HIV status was associated with a lower pyrazinamide C_{max} and AUC₀₋₈ (GM/Ratio=0.85, 95%CI (0.75-0.96), *P* = 0.013; GM/Ratio=0.79, 95%CI (0.69-0.90), *P* < 0.001). No other important differences were observed due to age, weight, prematurity, ethnicity or gender; 33 (85%) infants had favorable tuberculosis treatment outcome.

Conclusions: Isoniazid and pyrazinamide concentrations compared well to proposed adult target concentrations; ethambutol concentrations were lower, but equivalent to other paediatric studies. The low rifampicin concentrations observed in infants require further investigation, especially with consideration of future treatment shortening trials in children.

09. The cost of TB and lung health interventions: methodologies and implications for health systems and patients

Modelling the cost-effectiveness for health systems of the Xpert MTB/RIF scale-up by district profile in Tanzania

I Langley,¹ B Doulla² ¹Liverpool School of Tropical Medicine, Liverpool, UK; ²National TB and Leprosy Programme, Dar Es Salaam, Tanzania.

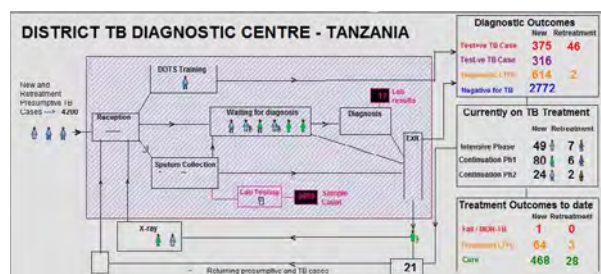
Background: The computer modelling of patient pathways (known as Virtual Implementation) has been used to assist national policy makers to assess options for the scale-up of new diagnostics (including Xpert MTB/RIF) for pulmonary tuberculosis in Tanzania. This presentation will demonstrate how a new version of the model designed for local staff from the National Tuberculosis Programme to use themselves has been employed to model diagnostic algorithms at district level.

Design/Methods: A model using the Virtual Implementation approach has been developed which is easy to use and contains an Excel user interface for data input and

reviewing outputs in a 'TB diagnostics dashboard'. Individuals in Tanzania have been trained and software installed to enable staff to model for themselves the impact of alternative diagnostic algorithms. The model has been used to assess eight different diagnostic algorithms including those using Xpert MTB/RIF in 10 different diagnostic districts and 5 diagnostic district types. Incremental cost effectiveness ratios have been calculated.

Results: Implementation of Xpert MTB/RIF in all diagnostic districts modelled would be cost effective and have the greatest benefit, measured in DALYs averted and cures, but with highest additional health system costs. Depending on the objective of implementation the priority sequence for implementation of new diagnostic algorithms across the country varies. The projections show that same day LED is particularly effective when funds are tight and reduction in DALYs and increasing cures is top priority. If more funds are available full roll-out of Xpert is the preferred strategy starting with the largest centres and those with high HIV. If MDR-TB detection is the top priority then LED same day will not assist greatly and early roll-out of Xpert is preferred. Similarly if time to start treatment is top priority then reducing high levels of empirically diagnosis becomes the priority so implementing Xpert in districts with a high proportion of smear negative TB should be considered first.

Conclusion: The analysis suggests that an effective policy for pulmonary TB diagnostics in Tanzania would be full roll-out of Xpert MTB/RIF in larger districts with high HIV first and same day LED microscopy elsewhere. The Virtual Implementation approach is a useful tool that should be retained in Tanzania to model new implementations of Xpert at district level and other new tools as they become available.



Costing the practical approach to lung health strategy in Malawi

M McHenga,¹ E Gama² ¹Reach Trust, Lilongwe, Malawi; ²Liverpool School of Tropical Medicine, Liverpool, UK.

Background and challenges to implementation: Chronic airway diseases (CADs) pose a serious financial challenge to both health systems and patients in most developing countries, particularly in sub-Saharan Africa. A diagnosis for people with chronic or persistent cough is usually delayed because of individual and health system barriers. However, delayed diagnosis and treatment facilitates

further transmission, severity of disease with complications and mortality and also increases the costs incurred by patients and the health system. To reduce the financial burden of chronic airway diseases, some countries have successfully used the practical approach to lung health, a patient-centred approach for diagnosis and treatment of common respiratory illnesses in primary healthcare settings.

Aim: The aim of this study is to assess the cost of implementing the practical approach (PAL) to lung health strategy in primary healthcare settings in Malawi. **Intervention or response:** A retrospective analysis of health systems and patient costs. Information on patients' socio-economic status, household assets and chronic airway diseases related costs will be collected by administering an adaptation of a questionnaire recommended by the Stop TB partnership. The ingredients approach will be used to estimate information on health systems cost and the data will be entered directly into a standard excel program developed for the costing study. For analysis, descriptive as well as regression techniques will be used.

Conclusions and key recommendations: We hope to demonstrate the cost of implementing the practical approach to lung health from both health systems and patient perspective. If the cost of the practical approach to lung health interventions is deemed reasonable, the approach could be scaled up to all primary healthcare centres.

The cost of serious adverse events in MDR-TB: experience from Ethiopia

M Girma,¹ E Gama,² J Madan,³ I Langley,² S B Squire²

¹Addis Ababa Science and Technology University, Addis Ababa, Ethiopia; ²Centre for Applied Health Research and Delivery (CAHRD), Liverpool School of Tropical Medicine, Liverpool, ³Warwick Medical School, University of Warwick, Coventry, UK.

Background: Multi-drug-resistant tuberculosis poses a big economic burden to both the health system and patients globally. This burden is exacerbated by serious adverse events which increase the costs incurred by both the health system and patients, through prolonged hospitalisation, additional diagnostic tests, auxiliary drugs and rehabilitation activities. The aim of this study was to estimate the costs associated with serious adverse events during multi-drug-resistant tuberculosis treatment from both health systems and patient perspectives in Addis Ababa, Ethiopia.

Methods: A retrospective analysis of health systems and patient costs related to treatment and management of serious adverse event. To estimate the costs, the ingredient approach was used alongside case reference forms, case notes and receipts from diagnostic suppliers and hospital records. A total of 44 cases were included in the study.

Results: Preliminary results show that, over 60% of the cases involved hospitalisation lasting up to 15 days; 80% required diagnostic tests, auxiliary drugs were adminis-

tered to 75% and 35% underwent rehabilitative activities.

Conclusion: While multi-drug resistant tuberculosis treatment is providing a better solution to a majority of patients, serious adverse events are increasing the costs for other groups of patient and pushing them into poverty. Similarly, hospitalisation, auxiliary drugs, diagnostic test and rehabilitation activities entails that health system costs are also increasing.

Modelling health system costs to support decision making for MDR-TB diagnostics in Cape Town

R Dunbar,¹ P Naidoo,¹ N Beyers,¹ I Langley² ¹Desmond Tutu TB Centre, Cape Town, South Africa; ²Liverpool School of Tropical Medicine, Liverpool, UK.

Background: Improving multidrug-resistant tuberculosis (MDR-TB) control requires access to accurate and rapid diagnostics for drug susceptibility testing. New molecular diagnostic tests for tuberculosis (TB) such as Xpert MTB/RIF (Xpert) hold the promise of improving TB and multidrug-resistant (MDR) TB diagnosis. Whilst accurate data are readily available from laboratory and demonstration studies, many operational questions remain and are most readily answered through modelling.

Methods: South Africa moved from a smear and culture based algorithm for diagnosis of TB to an Xpert-based algorithm. The Witness package was used to model all aspects of both algorithms to reflect the diagnostic pathways, including the laboratory procedures, as close to reality as possible, based on information and data collected during the PROVE IT (Policy Relevant Outcomes from Validating Evidence on Impact) study. Routine operational data was used to validate the model. The model was used to assess the effect of operational changes on yield and laboratory costs.

Results: Routine data showed a declining trend in the yield of TB cases identified over time in both algorithms. A binomial regression analysis showed no significant difference in yield between the algorithms when the time effect was taken into consideration, with a risk difference of 0.2% (95% CI -1.8% to 2.3%) ($P = 0.818$) in the Xpert-based algorithm. Total TB diagnostic costs were increased by 43% from \$440 967 in the smear-culture-based algorithm to \$632 262 in the Xpert-based algorithm. The cost per patient diagnosed with TB increased by 158% from \$49 in the smear/culture-based algorithm to \$125 in the Xpert-based algorithm. The total cost per MDR-TB case diagnosed was decreased by 3%, from \$205 in the smear-culture-based algorithm to \$199 in the Xpert-based algorithm. The model was used to demonstrate the effect of an optimised algorithm, increased case-finding and other operational changes on TB yield and laboratory costs.

Conclusion: This study used a combination of operational data and discrete event simulation to answer important operational questions that could not be readily addressed through other methods. Modelling is an attractive and viable option to guide policy makers in

making decisions about the implementation of new diagnostic tools and algorithms.

10. Research is needed to increase children's access to drug-resistant TB care

Consensus research priorities on children with drug-resistant TB

B Velayutham,¹ D Nair,¹ S Ramalingam,¹ S Swaminathan,¹ C Perez-Velez,² M Becerra³ ¹National Institute for Research in TB, Chennai, India; ²Banner Good Samaritan Medical Center, University of Arizona College of Medicine, Phoenix, AZ, ³Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.

Background: Numerous knowledge gaps hamper prevention and treatment of childhood drug-resistant tuberculosis. Identification of research priorities is vital to fill these gaps and develop strategies to address this neglected but important problem.

Methods: To identify and rank research priorities in childhood drug-resistant TB, the Child Health and Nutrition Research Initiative methodology was adapted. Research questions related to Epidemiology, Diagnosis, Treatment and Prevention were framed and the questions were classified according to research type: Descriptive, Development and Discovery. Respondents with expertise in childhood drug-resistant TB were invited to score these questions using an online survey.

Findings: The top-ranked research question was to identify the best combination of existing diagnostic tools for early diagnosis of drug-resistant TB in children. Highly ranked treatment-related questions centered on reasons for poor treatment outcomes, adverse effects of anti-TB drugs, optimal treatment duration and interventions for improving treatment outcomes. The prevalence of drug-resistant TB was the highest-ranked question in the epidemiology area. The development type questions ranked highest focused on interventions for optimal diagnosis, treatment and modalities for treatment delivery. The predominant discovery type questions focused on new drug evaluation and models for preventive therapy and for preventing new infections.

Interpretation: This was an effort to establish research priorities for this neglected childhood infectious disease through a systematic global survey of stakeholders. The consensus research priority questions identified in this exercise can serve as a framework that can be updated periodically and as a shared resource to guide new research to improve the prevention and treatment of drug-resistant TB in children.

From estimates to action: setting screening and treatment targets for children with TB

C Yuen ¹Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA.

Around 1 million children fall sick with tuberculosis each year, but only 300 000 pediatric cases were notified in

2013. Household contact investigations provide one method for programs to find children with tuberculosis. Children living in the households of adult tuberculosis patients are at high risk for tuberculosis disease and infection, and they are readily accessible since the adult patients are already known to the health system. To facilitate planning and resource allocation, tuberculosis programs would benefit from estimates of the numbers of children they should expect to evaluate and treat for disease or infection if they were to perform household contact investigations around all newly diagnosed adult tuberculosis patients. Using an example from Malawi, we present a method that can be used to generate national and regional household evaluation and treatment targets based on locally available adult pulmonary case notifications, census data, and HIV prevalence estimates, as well as disease and infection risk estimates from the literature. Nationwide, during a 1-year period, we predict that around 21 000 child household contacts will require evaluation, of whom almost 2000 will require treatment for tuberculosis disease and 7800 will require isoniazid preventive therapy. We use a generalized version of this method to generate evaluation and treatment targets for all countries based on case notifications, World Bank indicators, and Demographic Health Survey data. We estimate that globally, 7 million children living in households with known adult pulmonary tuberculosis patients require evaluation each year, and that over 623 000 cases should be detected among these children. In 24% of countries in 2013, the number of notified pediatric tuberculosis cases was less than 20% of the number predicted. Methods for generating evaluation and treatment targets for children exposed at home to tuberculosis can help programs plan and monitor activities designed to find and treat these children.

A bitter pill to swallow: developing paediatric formulations of second-line drugs

J Furin ¹Harvard Medical School, Boston, MA, USA.

The large and growing access gap between the number of children who become sick with drug-resistant tuberculosis (DR-TB) and those who are treated for the disease each year represents a significant health systems failure. While there are multiple reasons why children with DR-TB are not diagnosed and treated for their disease, one serious challenge is the medications used to treat the disease. This presentation will discuss some of the problems with the existing second-line medications. Challenges, including perceptions that the drugs are more dangerous than the disease, lack of proper dosing recommendations and formulations, and the high costs of current therapy, all contribute to a perverse situation in which the most vulnerable pediatric patients are provided a lower standard of care. This situation can be reversed with novel partnerships and training models, pharmacokinetic studies of the relevant drugs, increased collaboration, and dedicated funding all grounded in a rights-based approach to DR-TB in children.

11. TB surveillance in health care workers: challenges and approaches in high-burden, low-resource settings

Challenges in implementing TB screening for health care workers in Zimbabwe

A Maruta,¹ V Robertson,¹ S Balachandra² ¹Zimbabwe Infection Prevention and Control Project, Harare, ²US Centers for Disease Control and Prevention, Harare, Zimbabwe.

Background and challenges to implementation: Zimbabwe continues to be severely burdened by both TB and HIV with a prevalence of 0.43% and 14.7%, respectively. The pressure of disease burden on an inadequately staffed and underfunded health service has resulted in overcrowded facilities and serious training gaps for healthcare workers (HCWs). A 2010 health facilities survey showed that only 21% had an infection prevention and control (IPC) training program and 12% had infection control plans. Though 96% had an IPC focal person, only one had formal training in IPC, and two of 27 facilities had an annual TB screening program for HCWs.

Intervention: ZIPCOP, an IPC project established in 2011, has included TB infection control in its IPC program. The intervention includes training in TBIC (including HCW screening) and mentorship. A standardized checklist is used at each visit to gather information about each facility's TBIC activities. In the first three years, the program prioritized 60 sites across Zimbabwe.

Results and lessons learnt: Among the 60 priority sites, 13 implemented HCW TB screening; 10 used a screening tool and 3 used radiography. Barriers to TB screening included HCW reluctance based on fear, stigmatization, and lack of confidentiality. There is no systematic data collection of TB incidence among HCWs.

Conclusions: Given the higher risk of acquiring TB, regular HCW screening should be a key component of facility-based TB IPC programs and could serve as a proxy measure of effectiveness in reducing nosocomial transmission. With ZIPCOP's support, HCW screening has been incorporated in the new National IPC Policy and Strategic Plan and the National TB Program is introducing a quarterly TB surveillance tool for HCWs. However, the introduction of a policy and data collection tool may not be sufficient without a more comprehensive approach. Based on a literature review and the above results, we propose: an accountability framework with measures improving confidentiality, increased sensitization, strengthening occupational health systems and use of improved diagnostic tools.

Current state of TB surveillance among health care workers in China

C Xu ¹National Center for Tuberculosis, China CDC, Beijing, China.

In China, tuberculosis (TB) ranks as the leading cause of death from infectious disease, with over 1.3 million people developing active TB each year. TB infection

control, however, is still at an early stage in China. Several studies have found that healthcare workers (HCW) in China have higher rates of latent TB infection than the general population. Even though HCWs are considered as a high risk group for contracting TB, many Chinese healthcare facilities lack the policies and resources for implementing effective TB control programs, such as medical surveillance. There is currently no national policy for screening or surveillance for TB among HCWs. Latent TB infection is not treated and, often, TB is not recognized as an occupationally-acquired disease. Operational research is necessary to evaluate the costs and benefits of promoting medical surveillance for TB among Chinese healthcare workers.

Screening and treatment for latent tuberculosis infection in health workers at Maputo Central Hospital in Mozambique

E Nunes,¹ A Hassane,¹ S Amade,¹ S Peleve,¹ O Augusto,² S Viegas,² F Torriani,³ S Graves³ ¹Maputo Central Hospital, Maputo, ²National Institute of Health, Maputo, Mozambique; ³University of California, San Diego, CA, USA.

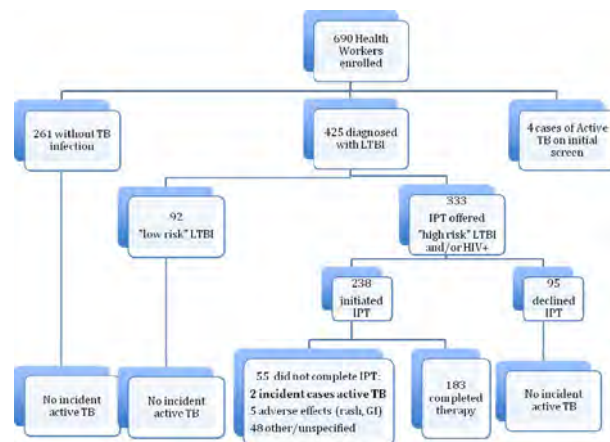
Background: In Mozambican hospitals, the high burden of tuberculosis (TB), and limited infection control put health workers (HW) at risk for TB. We aimed to evaluate operating characteristics of tuberculin skin testing (TST) and Quantiferon (QFT), establish the prevalence latent TB (LTBI) and incidence of active TB among HW, and assess feasibility and tolerability of isoniazid preventive therapy (IPT).

Design/Methods: 690 enrolled HW completed symptom screening, chest X-rays, HIV and tuberculin skin testing (TST). Those without active TB and TST > 10 mm (>5mm if HIV+) underwent QFT testing. Logistic multivariate analysis was used and adjusted odds ratios of LTBI reported. HW with LTBI were risk-stratified by HIV status and quantitative TST and QFT. Those with HIV or TST > 15mm and QFT > 1.0 were classified as 'high risk' and offered IPT. Adherence and adverse reactions are reported. The symptom screen was repeated at one year.

Results: Among 690 HW, 4 active TB cases were diagnosed and 12% were HIV+. The positive predictive value of TST for QFT positivity is 82% in HIV+ individuals (95%CI 63-94), not significantly different from HIV- (79%, 95%CI 74-84). We observed highest concordance in TST/QFT when TST was > 10 mm. In the multivariate analysis, duration of service >10 years was significantly positively associated with LTBI (OR 1.67, 95%CI 1.21-2.30), as was service in the departments of Surgery, Emergency and Critical Care, Pathology, and Obstetrics ($P < 0.05$ for all) when compared with the Internal Medicine department. 425 (62%) workers were diagnosed with LTBI of whom 284 (67%) were classified as high-risk LTBI. Of 333 workers with HIV or high-risk LTBI counseled to take IPT, 183 completed 6 months, 48 abandoned treatment and five discontinued therapy due to side effects (rash, gastrointestinal symptoms); no cases of hepatitis occurred. At one year follow-up, two HW

had developed active TB. Both of these were on IPT at the time of diagnosis. Due to loss-to-follow-up, only 502.1 person-years were observed. Overall active TB incidence was 398/100 000 person-years (95%CI 48.2-1438).

Conclusion: Active TB incidence among HCWs at MCH is similar to background incidence in Mozambique: 552/100 000 (WHO 2014). Several departments have higher LTBI prevalence, suggesting occupational risk and targets for intervention. QTF and TST results were moderately concordant. IPT was well-tolerated, however attrition was high.



The provision of isoniazid prophylaxis therapy (IPT) to health care workers: a Swaziland experience

P Mamba ¹Swaziland Wellness Centre, Manzini, Swaziland.

Background: Swaziland has the highest per capita HIV prevalence in the world as well as a high burden of TB. The Swaziland Nurses Association established a nurse-managed wellness centre in the country in collaboration with the International Council of Nurses in 2006 to provide confidential and comprehensive health service delivery to health care workers (HCWs) and their families. From October 2012 to September 2013, the Swaziland Wellness Centre screened HCWs for TB using nurse coordinated wellness corners that were established in 14 sites. A total of 3107 HCWs were targeted to be screened; 2391 (77%) were screened, 746 (31%) were presumptive cases and 31 (1%) were confirmed to have active TB and enrolled on treatment. It was then that a need to strengthen the 3 I's was noted; this included strengthening the isoniazid preventive therapy (IPT) uptake among all HCWs with emphasis to HIV-positive HCWs.

Intervention: In the 14 sites where TB screening was conducted, all HCWs were sensitized and trained on IPT to increase awareness and uptake from January 2014 to March 2015. Existing structures were used for sensitization; departmental meeting, in-service trainings and workshops. The wellness Corner nurses were trained on provision and management of IPT, follow up and documentation. The Swaziland Wellness Center and

URC teams visited these facilities providing information and education on benefits of taking IPT. The team held discussions where HCWs voiced their perceptions and concerns about IPT. Data collection tools were distributed to all the project sites.

Results: Out of the 3107 targeted health care workers 188 (6%) were enrolled on IPT, of the 188, 52 (28%) of them are HIV-positive, 154 (82%) completed IPT, 3 (2%) transferred out, 9 (5%) defaulted and chose not to continue due to minor side effects. Three (2%) were discontinued due to minor persistent side effects and 19 (10%) are still on treatment. HCWs had several concerns about taking IPT such as side effects caused by INH and INH stock outs nationally.

Conclusion: TB is an important public health issue, especially in Swaziland where HCWs are exposed to a high burden of TB and infection prevention and control measures are inadequate. The increased uptake of IPT, intensified case finding through TB screening and strengthening of infection control measures can reduce infection among HCWs.

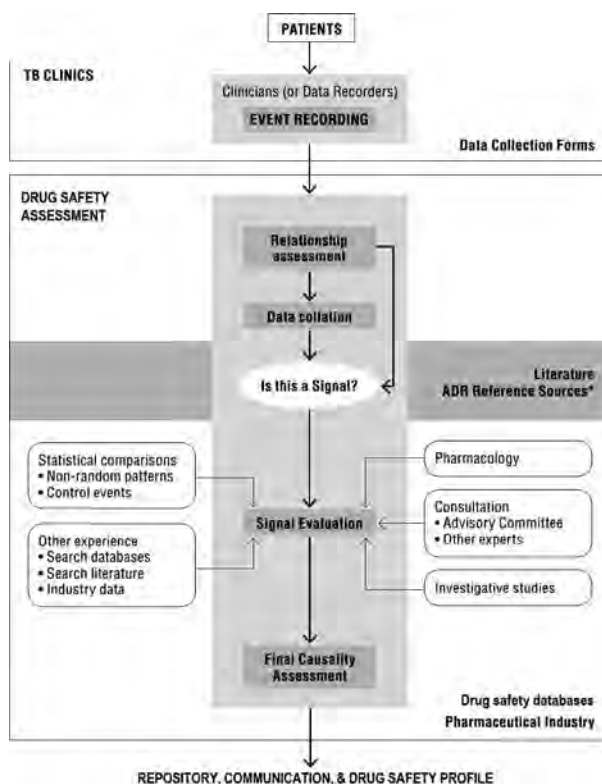
12. Managing pharmacovigilance systems: optimising the rational use of new TB medicines and novel regimens

Cohort event monitoring methodology: data collection, indicators and drug safety profiles

D Falzon ¹Global TB Programme, World Health Organization, Geneva, Switzerland.

Drug-related harms can lead to a tuberculosis (TB) patient interrupting treatment before completion and can thus contribute to chronicity, death, reduced quality of life, treatment failure, transmission of infection, or emergence of drug-resistance. It is thus important that adverse events (AEs) — especially serious events (SAEs) — be monitored and addressed in TB patients on treatment. National TB programmes which systematically monitor harms associated with anti-TB medication are better placed to achieve good outcomes when introducing more complicated regimens, such as those for multidrug-resistant TB (MDR-TB) and TB-HIV. The progressive global scale-up of treatment for MDR-TB will see more populations with a diverse mix of age, ethnic profile and comorbidity patterns receiving combinations of second-line TB drugs, some of which are new or repurposed. This is a welcome development and brings with it an increased likelihood of cure for many of these patients. However, vigilance for adverse drug reactions (ADRs) and drug-drug interactions—some of which as yet unrecognized—will be an important complement. Active pharmacovigilance is currently recommended by WHO when new drugs such as bedaquiline and delamanid are used as part of the treatment of patients with MDR-TB. Cohort-based approaches to monitor actively for AEs can provide data for the dual purposes of protecting the individual patient and informing local and global policy. Dialogue with

different stakeholders, including drug developers, regulators and national drug-safety authorities, will be needed to ensure appropriate mechanisms are in place to report safety concerns alongside the monitoring of response to treatment. This presentation will outline the approach of the WHO Global TB Programme to active TB patient drug-safety management and monitoring based on standard methods for the surveillance of drug-safety concerns (Figure). These methods and their adaptations for the context of national TB programmes reflect discussions held with technical and funding partners as well as national authorities in recent years on the practicalities of implementing functional monitoring systems under programmatic conditions. The presentation will use lessons learnt and best practices from countries to illustrate how common challenges in data collection and organisation, generation of indicators and the analysis for causality and signal detection were addressed.



Strengthening pharmacovigilance systems: improving TB patient safety and reducing the adverse drug reaction burden

A Kwiecien,¹ K Kakanda¹ ¹USAID's Systems for Improved Access to Pharmaceuticals and Services Program, Arlington, VA, USA.

Active pharmacovigilance (drug safety) is one of the five conditions set out in the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis for introducing new medicines (e.g., bedaquiline and delamanid) and novel

regimens (e.g., short regimens) for the treatment of drug-resistant tuberculosis. The purpose of the active drug safety component is to:

- Ensure TB patient safety through the adequate monitoring and management of adverse events
- Identify inappropriate medicine use
- Report adverse events for new drugs and novel regimens from broader clinical practice for more populations (e.g., with diverse age, sex, and ethnic profiles)
- Provide drug safety data for analysis to guide National TB Programs' decisions for improving patient safety
- Report adverse events, drug-drug, and drug-disease interactions for all TB regimens to inform global policies on their use

Inadequate active safety monitoring and management could cause unnecessary harm to patients, lead to poor adherence, and amplify drug resistance. However, few resource-limited countries have all the structures, systems, or resources necessary to support active drug safety activities. This talk will focus on approaches for developing or strengthening systems for active MDR-TB drug safety monitoring. It will also provide an overview on the importance of NTPs coordinating with National Pharmacovigilance Programs to foster a culture of adverse events reporting and knowledge sharing at all levels to ensure the best possible clinical outcomes for all patients. An update on the bedaquiline donation program and technical assistance available through USAID and partners for developing or strengthening systems for active MDR-TB drug safety monitoring will also be discussed.

13. Can mobile technology improve lung health in poorer countries and communities? Benefits and opportunities

Russia's experience in using mobile technology to educate, monitor and enforce compliance with tobacco control legislation

I Berezhnova,¹ E Zeynalova² ¹International Union Against Tuberculosis and Lung Disease, Moscow, ²Centre for Public Health Cooperation, Krasnoyarsk, Russian Federation.

Background: In 2013, Russia adopted one of the world best Tobacco Control legislations, which fully bans smoking in all public places. The legislation came into force in June 2013, but the government and civil society have continued developing various mechanisms to improve the enforcement of the law and to involve the population in compliance monitoring. Mobile applications are one of the innovation technologies used by the Ministry of Health and its Tobacco Control allies in putting the law implementation forward.

Intervention: In October 2014, the Ministry of Health launched a mobile app 'Здесь не курят' (No smoking here). Several other agencies developed similar applications, including Tatarstan, which launched its regional

mobile application incorporating tobacco control among information on other public health policies. One of The Union grantees developed the 'Smoke-free Russia' mobile application, which in addition to compliance monitoring, provided information on the law, penalties, etc. The Ministry of Health's mobile app is currently available for the general public, and could be downloaded from the website and by searching in the apps store. It is an interactive program that accepts comments and suggestions for the application's further improvement. It has also been developed on the basis of other existing applications to create a more efficient for the compliance monitoring tool.

Results: The app was developed for Android and iOS and meets the following objectives: to provide an efficient mechanism to register the law violations, to report to the enforcement agencies, to cumulate data about number, locations of the violations. It includes a brief description of the law provisions, proposes a complaint form, and its tracking system. The mobile apps allows to quickly and effectively prepare the complaint, attach a photo of a case, automatically determine the enforcement agency which deals with each particular case, call the police if necessary, call a quit hotline if required, and repeat the text if needed.

Conclusions: The mobile app 'No smoking here' is provided to be a useful tool to report about non-compliant cases, help citizens to familiarize themselves with the law. The 'Smoke Free Russia' application was used in a few regions to conduct compliance monitoring. In Orenburg, it allowed volunteers to report and highlight violations on a digital map in 100 public places. Overall, the applications do not duplicate each other, but cover specific areas, which make the applications user friendly and efficient.

Using mobile technology successfully for early diagnosis of TB in a rural setting

P Banuru Muralidhara,¹ S Chadha,¹ A Trivedi,¹ V Rajput,¹ D Tamang,¹ R J Singh,¹ R Shekhar,² L Olson² ¹International Union Against Tuberculosis and Lung Diseases, South-East Asia Office, New Delhi, ²Dimagi Inc., New Delhi, India.

Background: Reaching the Unreached is the principle of global TB control strategies. Rural areas of India, like any developing country, have difficulty in accessing the services for early diagnosis. In these areas, healthcare is provided by rural health-care providers (RHCPs). RHCPs, are first point of contact for many illness and refer TB symptomatics. The outcome of referrals made by RHCPs to nearest sputum testing center is not known. We therefore developed a mobile based application with an aim to track referrals from RHCPs for early diagnosis of TB.

Intervention: With support from Dimagi, two 'ComCare' mobile platform applications were developed: one application exclusively for RHCPs, and the other for laboratory technicians (LT) at respective sputum testing centers in the intervention district of Hazaribagh, Jharkhand, India. Hands-on training was provided to RHCPs/

LTs about the use of the application for referrals. In addition, the RHCPs were oriented on the DOTS module. Following referral of identified symptomatics by RHCP to the nearest sputum examination center, basic information is entered into the CommCare RHCP application. This information is received on the LT mobile application through a central server. When the symptomatic reaches the DMC, the LT conducts a sputum examination (2 samples) and the results are entered into the application. The results then show-up on the RHCP application against the name of the referral. In case the sputum result is positive, the patient is initiated on DOTS and the RHCP referred would have the highest probability of being a DOTS provider. Information at regular intervals about DOTS is entered until the completion of treatment. The process is monitored on a real-time basis.

Results: Out of 50 trained RHCPs (phased manner), 29 RHCPs are regularly using the application for referrals. Nearly 66 referrals are made by RHCPs over a period of 9 months and 45% were found to be sputum smear-positive. Among the RHCPs, 12 are currently providing DOTS for 22 TB patients and monitored regularly by programme and project.

Conclusion: Use of a mobile based application among RHCPs in rural and remote areas for early referrals and follow-up highlight positive results. Continued monitoring with RHCPs and LTs is needed to ensure data entry is regularly made. An incentive based approach for referrals as per programme guidelines is being reviewed for increasing referrals and ensuring early diagnosis.

14. Spelunking for treasure: searching for candidate biomarkers as prognostic indicators for treatment outcome

Potential and limitations of current candidate host biomarkers for treatment response

G Walzl,¹ K Ronacher,¹ S Malherbe,¹ D Alland,² D Zak,³ G Schoolnik,⁴ G Dolganov,⁴ J Winter⁵ ¹Stellenbosch University Immunology Research Group, DST/NRF Centre of Excellence in TB Biomedical Research, MRC Centre for TB Research, Cape Town, South Africa; ²Rutgers Biomedical and Health Sciences, Newark, NJ, ³Center for Infectious Disease Research, Seattle, WA, ⁴Stanford University, Stanford, CA, ⁵Catalysis Foundation for Health, Emeryville, CA, USA.

Biomarkers for TB treatment response and outcome would facilitate shortening of clinical trials of new anti-TB drugs. We have investigated clinical, microbiological, imaging and immunological parameters and their changes during treatment of pulmonary TB patients to define biosignatures that are associated with different treatment phases and outcomes and to explore the feasibility of predictive models for poor treatment outcomes. Although clinical and microbiological markers represent important predictors for poor outcomes, they are not sufficient on their own. Whole blood transcriptomic and immunological markers in the serum of TB patients

change with distinct kinetics during treatment and cured, failed and relapse outcomes exhibit different response patterns. Promising predictive abilities of multi-marker models for failed treatment and relapse are found in small cohorts but require prospective testing. [18F]-Fluoro-2-deoxy-D-glucose positron emission tomography/computer tomography (FDG-PET/CT) imaging was evaluated for predictive ability in 100 TB patients from pre-treatment until one year after completion of therapy. End of treatment imaging parameters suggest that there is significant ongoing inflammation even in the absence of detectable *Mycobacterium tuberculosis* in sputum and such ongoing inflammation may indicate subclinical TB infection and non-sterilizing cure with a high risk for relapse. The correlation between needs to be investigated in future studies. Together these studies point towards the importance of combined bacterial and host-based biomarker research to predict the outcomes of anti-TB chemotherapeutic therapy.

Prospective T-cell activation markers for monitoring treatment and predicting cure

C Geldmacher,^{1,2} N Heinrich,^{1,2} A Rachow,^{1,2} M Hoelscher,^{1,2} E Ntinginya,³ M J Boeree,^{3,4} G Kibiki,⁴ H Semvua⁴ ¹Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich, Munich, ²German Centre for Infection Research (DZIF), Partner Site Munich, Munich, Germany; ³NIMR-Mbeya Medical Research Center, Mbeya, ⁴Kilimanjaro Clinical Research Institute, Moshi, Tanzania.

On behalf of the PanACEA consortium; other institutions involved: Radboud University Medical Center, Nijmegen, University Centre for Chronic Diseases, Dekkerswald, Groesbeek, Netherlands. Identification of predictive diagnostic markers of tuberculosis (TB) treatment outcome would in theory allow to tailor treatment duration to individual needs and to identify patients in need of a longer or different course of treatment. Recent advances in the field of blood-based biomarkers demonstrate that novel immunodiagnostic approaches can improve the diagnosis of active TB in adults and children. These flow cytometry based approaches detect and characterize *Mycobacterium tuberculosis*-specific Interferon gamma positive T cells after short term in vitro restimulation of whole blood or Peripheral Blood Mononuclear Cells with *M. tuberculosis*-specific antigens. The phenotypic characteristics of *M. tuberculosis*-specific T cells can differentiate with high accuracy between latent and active tuberculosis and hence mirror at least partially Mycobacterial activity in vivo. Furthermore, recent research shows that expression of these T cell activation and differentiation markers on *M. tuberculosis*-specific T cells changes after TB treatment initiation and hence this novel immunodiagnostic approach could potentially help to monitor TB treatment, to predict TB treatment outcome and – as a consequence – to individualize TB therapy. This presentation will provide an overview on the current state of research in this field and the most recent results from our own studies.

Use of the simple biomarker suPAR to assess severity of TB disease and to monitor treatment

C Wejse^{1,2} ¹Department of Public Health, Aarhus University, Aarhus, ²Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark.

White blood cells, as well as endothelial cells, express the urokinase plasminogen activator receptor (uPAR). The soluble form of the receptor, suPAR, is cleaved from the cell surface during periods of inflammation and increased inflammation secondary to activation of the immune system thereby produces increased concentrations of suPAR in body fluids. Elevated suPAR levels are prognostic of a poor outcome in several infectious diseases including tuberculosis and HIV. It is not specific for a particular disease, and therefore not a useful diagnostic marker, but has shown a good prognostic utility. However, in combination with a clinical score, the Bandim TB score, high suPAR levels have been associated with a high probability of a diagnosis of active TB among presumptive TB patients. The suPAR levels have been shown to be elevated in patients with active TB compared with TB-negative individuals and were highest in smear positive (3.17 ng/ml), followed by smear negative but culture positive (2.41 ng/ml) and by patients diagnosed on clinical grounds (2.13) compared with TB-negative individuals (1.73 ng/ml). After treatment, suPAR levels had decreased to the levels of TB-negative individuals. Mortality during treatment has been shown to be higher in TB patients with high suPAR, as well as among presumptive TB patients not diagnosed with TB. Increase in suPAR at 1 and 2 months of treatment has been associated with a Mortality Rate Ratios (MRR) of 4.5 and 2.1, respectively, for the remaining treatment period. Plasma suPAR levels have also shown to be higher in MDR-TB patients with relapse and predicted therapy failure in this group better than ESR. The data on the use of suPAR to assess severity of disease and monitor treatment are limited and not an established part of clinical management, but hold some promise of becoming a candidate marker for treatment outcome.

15. TB-HIV epidemiology within the context of national TB prevalence surveys in Africa

Progress of national TB prevalence surveys in Africa, and the burden of TB-HIV co-infection among prevalent TB cases from these surveys

I Onozaki ¹World Health Organization, Geneva, Switzerland.

Background: Quite a few Asian countries carried out a series of nationwide tuberculosis (TB) prevalence surveys with chest X-ray screening and bacteriological confirmation with culture along the WHO guidelines published in 1958. However, such a survey had never been carried out on the African continent for five decades until

Ethiopia completed the first national survey in 2011. Since then, 11 African countries completed a national survey. In many countries, national TB prevalence surveys are the only way to reliably measure the burden of TB disease. These surveys could also provide evidence about the current performance of TB care and control and how this could be improved. However, carrying out HIV testing in the TB prevalence survey to learn about the TB-HIV situation in the community is still a challenge in most countries. Out of 11 countries, only Zambia offered HIV testing to all survey participants, and three surveys, namely Rwanda, Tanzania and Uganda, covered TB screening positive, while other countries tried to determine HIV status of the survey participants and TB patients through routine HIV and TB services.

Major findings: Observed prevalence of bacteriologically positive TB is often higher than previous estimates. The TB prevalence survey always detects bacteriologically positive TB patients more than annually notified. Smear-positive TB accounts for only 30-40% of bacteriologically positive TB cases when culture is done properly. Males show significantly higher prevalence than females. The older the age group, the higher the prevalence is in most countries. However, the majority of TB patients are still in the reproductive age group in most countries. Many countries show higher prevalence in urban clusters despite their better access to medical services including hospitals. Although available data are limited, the prevalence of HIV-positive bacteriologically positive TB seems to be declining. Most people in community know their HIV status in sub-saharan African countries. In these countries, HIV-negative TB is under-estimated. AFB smear-positive does not mean TB. Introduction of quality culture, Xpert and chest X-ray have proven that half or more participants with a smear-positive condition may not have TB disease in some countries of the TB prevalence survey. In this symposium, we will learn from the experiences of three most recent national surveys in high TB-HIV burden countries in Africa.

16. Scaling up MDR-TB services in resource-limited settings: progress and challenges from the field

Rapid scale-up of MDR-TB services through a decentralised patient management system in Ethiopia

M Aseresa Melese,¹ D Habte,¹ Y Molla,¹ P G Suarez,² I Jemal Abdulahi³ ¹HEAL TB, Management Sciences for Health, Addis Ababa, Ethiopia; ²Center for Health Services, Management Sciences for Health, Arlington, VA, USA; ³Communicable Diseases, Oromia Regional Health Bureau, Addis Ababa, Ethiopia.

Background: Ethiopia, one of the high MDR-TB countries, started its MDR-TB program in 2009 in one tertiary care center in Addis Ababa. However, the service was inaccessible to the majority of Ethiopia's population. As part of the effort to address this challenge, a

decentralized MDR-TB service using ambulatory care model was designed.

Intervention: Together with the Ministry of Health, the USAID-funded Help Ethiopia Address the TB Performance (HEAL TB) project started expansion of MDR-TB services in 2012. The project support included renovation of MDR-TB treatment centers training and orientation of health workers, case finding, and building the regional capacity for sputum sample culture and drug sensitivity testing. Also, the regional sample transport system was strengthened and GeneXpert sites expanded from none to 51. To ensure the quality of services clinical mentoring for treatment centers established, organized MDR-TB clinic days whereby patients come only on a scheduled day for follow-up, provided continuing medical education, and instituted a mortality audit. Besides the expansion of treatment initiating centers, patients after two months of admission discharged to health centers to continue the DOT.

Results and lessons learnt: These interventions helped expand treatment initiating centers (TIC) from 2 to 23 (Figure); testing for presumptive MDR-TB from 662 to 20 200; and patients ever enrolled from 56 to 700. More than 300 health facilities are providing monthly DOT for patients discharged from TICs. Six-month culture negativity rate improved from 41% to 76.4%. The cure and treatment success rate for the first cohort of 36 patients were 65% and 74.9%, respectively. The proportion of death, failure of treatment and lost to follow up for the first cohort were 11.1%, 2.8% and 11.1%, respectively. The main challenges were sample transport for presumptive cases, as most of the health centers are far from the Xpert or culture diagnostics health facilities, frequent failure of the Xpert machines, expensive to maintain, and lack of ancillary investigations. From the patient side, the daily visit to health centers for medication for two years is challenging coupled with poor family income.

Conclusion: The decentralized MDR-TB service model implemented in the two regions in Ethiopia contributed to improved case finding and access to quality treatment. The feasibility of further decentralization of DOT follow up to community level should be evaluated.



Expanding MDR-TB diagnosis and community-based MDR-TB management by community health workers in Bangladesh

M Akramul Islam,¹ M Siddiqui,¹ M Rana,¹ S Islam¹

¹Tuberculosis Control Programme, BRAC, Dhaka, Bangladesh.

Background and challenges to implementation: Anti-tuberculosis drug resistance is a major public health problem worldwide. According to the last drug resistance survey of Bangladesh, the MDR-TB burden is 1.4% among new cases and 28.5% among retreatment cases. NTP has been introducing Community based Programmatic Management of DR-TB known as cPMDT since 2012.

Interventions: Initially the community based approach to MDR-TB services only covered a small percentage of the country compared to that of the drug-susceptible TB programme, which has nationwide community based coverage. That is why to ensure all high risk MDR-TB symptomatics have access to DR-TB testing and services, the MDR-TB services have been scaled up throughout the country by the NTP. Currently there are 39 Xpert MTB/RIF sites through the country, vs. 28 in 2012. Diagnosed MDR-TB patients admitted in hospital for a minimum one month of intensive phase of treatment initially and ambulatory phase at community level. Currently sputum microscopy is done weekly for admitted patients. If two consecutive sputum samples become negative, then the MDR-TB patients are shifted to the community for ambulatory care. Monthly sputum follow up tests at the field level and quarterly culture at the National TB Reference Laboratory (NTRL) is done throughout the treatment course. All the health care providers related to MDR-TB management receive a basic one day orientation before starting of MDR-TB management at community level.

Results and lessons learnt: In 2008, a total of 103 confirmed patients were enrolled and received standardized MDR-TB treatment. Out of 103 MDR-TB patients, the treatment success rate was 66 (64%). Death and default rate was 8 (8%) and 28 (27%), respectively. In 2012, a total of 286 confirmed patients were enrolled and the treatment success rate was 204 (72%). Death and default rate was 34 (12%) and 43 (15%), respectively. In 2008, 22% patients absconded from hospital and 5% from community during treatment, which decreased 14% and 1%, respectively, in 2012.

Conclusion: Patients' adherence during hospital stay seems to be a difficulty of the hospitalization treatment system as they had to stay for a long time during intensive phase. The currently implemented Community based MDR-TB treatment modality may contribute to minimize this challenge and ensure high treatment success rate for the National Tuberculosis Control Programme in Bangladesh.

Achieving rapid scale-up of MDR-TB patient treatment in Uganda using the mixed model (hospitalised and ambulatory) MDR-TB treatment

M Kenneth,¹ H Luwaga,¹ M Ruhweza,¹ D Sama,¹ S Stavia,² F Mugabe,² S Balcha,³ P G Suarez⁴

¹Management Sciences for Health (MSH)/Track Tuberculosis Activity (TRACK TB) Project, Kampala, ²Ministry of Health, National TB and Leprosy Program, Kampala, ³United States Agency for International Development, Kampala, Uganda; ⁴MSH, Arlington, VA, USA.

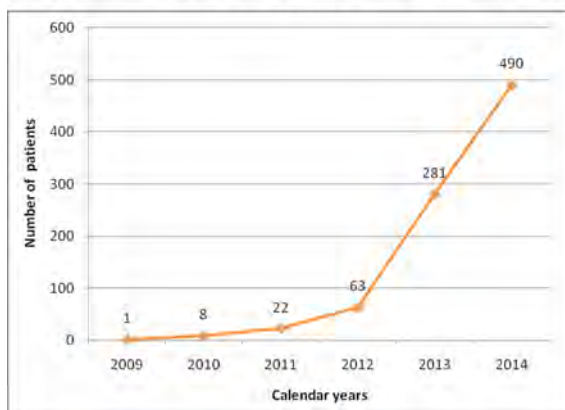
Background and challenges to implementation: Uganda is one of the 22 high burden TB countries in the world with an annual notification of 47 000 TB cases. A 2010 drug resistance survey for Uganda estimated MDR-TB prevalence at 1.4% among new bacteriologically confirmed TB cases and 12/1% of previously treated TB patients. By 2012 an estimated 300 MDR-TB cases had been notified but not enrolled on treatment due to health system constraints. Prior to July 2012, MDR-TB treatment could only be accessed at 2 treatment facilities and under research or project settings.

Intervention: With support from the USAID funded TRACK TB project, GFTAMTB and other partners, the National TB and Leprosy Programme mobilised efforts to decentralise treatment of drug resistant TB to more hospitals using the mixed model of care (combination of ambulation with hospitalisation as required). Multi-disciplinary MDR-TB care teams were established at each hospital through training and mentorship, provision of logistical and operational support for capacity building at peripheral DOT facilities, contact screening and investigation and patient support with transport. MDR-TB cohort review activities were conducted on a quarterly basis and the MTB/RIF technology was rolled out to enhance early detection of rifampicin resistance.

Results: MDR-TB treatment was decentralised to 15 hospitals by the end of 2014. The implementation of the mixed model improved enrollment from 63 to 490 patients by the end of 2014; 90% MDR-TB patients were enrolled on the mixed model of MDR-TB management. There were significant improvements in sputum culture conversion rates at 12 months of treatment from 23% to 74% ($P = 0.002$) and the proportion of patients with unknown culture results reduced from 72% to 7% ($P = 0.021$) for patients enrolled before and after introduction of the mixed model of care. Similarly, sputum culture conversion improved from 54% to 75% at 6 months and the proportion of patients with unknown culture results reduced from 16% to 2% ($P = 0.706$) for patients enrolled before and during implementation of the mixed model. However, the improvements in interim outcomes at 6 months were not statistically significant possibly due to small patient numbers in the cohorts that were compared.

Conclusion: The implementation of the mixed model of MDR-TB care improved access to treatment for MDR-TB as well as the interim results at 12 months for patients in Uganda. More work remains to improve the interim results at 6 months of treatment.

Figure 1: Cumulative number of MDR-TB Patients enrolled on treatment, 2009–2014



17. Maximising opportunities for integrating TB services into maternal and child health programmes

Global burden of TB in pregnancy: from epidemiology to programme implications

C Colvin¹ United States Agency for International Development/Global Health Fellows Program, Washington, DC, USA.

TB is not a condition for which pregnant women presenting at antenatal care are routinely screened. There is a need to prioritize settings and potential interventions such as symptom screening and diagnostic tests to ensure that those at highest risk have access to the full range of TB care services. This presentation will include an overview of recent literature on efforts aimed at improving TB screening in antenatal care and the current estimates of TB burden among pregnant women. Future direction for research and programmatic action based on these findings will be suggested, along with recommendations for leveraging platforms such as PMTCT programs and rapidly expanding community based DOTS efforts.

WHO guidance on integrating TB and TB-HIV services into maternal, neonatal and child health programmes

A Kanchar,¹ A Baddeley,¹ H Getahun¹ ¹World Health Organization, Geneva, Switzerland.

Background and challenges to implementation: Tuberculosis caused more deaths among women than all causes of maternal mortality taken together (510 000 vs. 289 000 in 2013). It is among the five leading causes of death among adult women (20–59 years) in low-income countries. The TB epidemic is intertwined with the HIV epidemic and it affects women disproportionately particularly in the African region where about 60% of all PLHIV are women. Very few national TB or maternal and child health programmes collect or report pregnancy

specific TB data, however research indicates high rates of TB particularly in HIV-positive pregnant and postpartum women ranging between 0.7% to 7.9% and as high as 11% in tuberculin skin test positive women. TB increases the risk of pregnancy related complications such as pre-eclampsia and eclampsia, vaginal bleeding, miscarriage and prematurity, low birth weight, etc. and post-partum is associated with 2 to 3 fold increase in maternal and infant mortality.

Results: WHO recommends the integration of tuberculosis services into reproductive, maternal, neonatal and child health (RMNCH) service delivery platforms, particularly PMTCT programmes to ensure its early detection and prompt treatment. National TB and RMNCH programmes should systematically collaborate and ensure utilization of all existing service delivery options to provide integrated TB, RMNCH/PMTCT services. The WHO Global TB Programme is developing a toolkit to assist policy makers, national programme managers and staff in establishing such integrated services along with its implementation and monitoring. This toolkit consolidates existing WHO recommendations for the management of TB in women and children, TB screening and diagnostic algorithms, country best practices and operational experience and job aids to facilitate implementation.

Conclusions and key recommendations: National TB and RMNCH/PMTCT programmes should consider the integration of tuberculosis services for HIV-positive and negative, pregnant and post-partum women, new-born, children under five years and older children along with integration into the family planning, STI and infertility services.

18. Five years of Xpert® MTB/RIF implementation: lessons learnt for increasing the impact of future new diagnostics

Impact of Xpert MTB/RIF on TB case detection and treatment: experience of the Brazil NTP

R Ruy De Souza,¹ A De Paula Lobo,¹ D Pelissari,¹ P B Oliveira,¹ F Reis,¹ M B Ferreira De Freitas Hamerle,¹ F. Dockhorn,¹ D Barreira¹ ¹National Tuberculosis Program, Ministry of Health, Brasilia, DF, Brazil.

Brazil began to deploy its network of Xpert MTB/RIF in May 2014. Until June 2015, 168 535 tests were carried out, as reported by the laboratories. This monitoring network is done using Excel spreadsheets, in which are reported the production of each laboratory, the results in terms of positivity, resistance, errors and problems of devices. Initially, is important to inform that data from May to December 2014 are much variable because of the growing and scaled installation of the net and data from January 2015 are still being analyzed to produce an annual report on the Xpert test network and still cannot be calculated correctly. Analyzing the data available, mainly data from 2014, it seems that: i) there was no

increase in the detection of cases, but of laboratory confirmed cases, as it happened in other countries; ii) there was also a decrease in the time to onset of treatment, but because of the faster response of the test and not because a desirable reorganization of the health system; iii) the time to start patients treatment with rifampicin resistance also seems to have diminished in many states, as the algorithm designed by NTP gives priority to those patients in referral hospitals. Analyzing data from July to December 2014, the average positivity of the tests ranged from 8.6% to 12.3%. The detection of resistance ranged from 1.4% to 6.3%. These initial findings seem to support the study of deployment of the technology that was conducted in 2012 in two municipalities, Rio de Janeiro and Manaus. In this study it was possible to measure the decrease in time for the notification of the case, which fell from 19.4 to 11.4 days, and the time to onset of treatment, which fell from 11 to 8 days. The authors also observed a 35% reduction in TB-related mortality, which may be explained by less advanced disease among the smear-negative patients diagnosed by Xpert.

Impact of Xpert MTB/RIF on MDR-TB case detection and treatment: experience of the Belarus NTP

A Skrahina,¹ A Zalutskaya,¹ A Astrauko,¹ D Klimuk,¹ H Hurevich,¹ W Van Gemert,² M Dara,³ V Rusovich⁴

¹Ministry of Health, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; ²Global TB Programme, World Health Organization (WHO), Geneva, Switzerland; ³Regional Office for Europe, WHO, Copenhagen, Denmark; ⁴WHO Country Office, Minsk, Belarus.

Introduction: Accurate and rapid detection of TB, including smear-negative TB and drug resistant-TB, is critical for improving patient outcomes and decreasing TB transmission. In early 2011, WHO endorsed a novel, rapid, automated, cartridge-based nucleic acid amplification test, the Xpert® MTB/RIF assay, which can simultaneously detect TB and rifampicin resistance.

Methods: We describe experience from the rollout of Xpert in Belarus, a country with a high burden of MDR-TB.

Results: Whilst Xpert represents a major advance over smear microscopy, cost was a major obstacle to widespread rollout. There has, however, been a rapid decline in cartridge costs for high burden countries. However, at present time in Belarus, Xpert is used as primary test for all TB suspects. With Xpert other tests, at least microscopy and liquid culture, are always performed at the same time with the same sample. One of the most challenging aspects of the implementation was the implementation of a revised national TB diagnostics and treatment algorithm. There is a need for clear, simple, unambiguous and feasible algorithms to be developed and piloted well in advance of Xpert implementation so that adequate training of laboratory and clinical staff can be ensured. Although a number of issues related to the use of Xpert for EPTB still need to be

addressed, in Belarus Xpert is used for testing EPTB samples (pleura, CSF, lymph nodes). The test is also used for children presumed to have TB and as screening tests for PLHIV.

Conclusion: Xpert is an important new tool for the diagnosis of TB, which has the potential to impact not only individual patient outcomes, but also the course of the TB epidemic in high burden countries. Perhaps most importantly, Xpert has established the principle that nucleic acid amplification tests for TB can be sensitive, specific and feasible for implementation in poorly resourced settings. However, there is much work to be done to better understand how Xpert can be utilized in a programmatic setting to maximize its potential impact and cost-effectiveness. Finally, the diagnosis of TB is one component of the overall control strategy; without effective linkage into care and strong systems for delivery of treatment and patient retention, there will be little impact on the TB epidemic.

Maximising the potential for rapid use of test results: e/m-tools

J Takle ¹Global Connectivity, Boston, MA, USA.

Background and challenges to intervention: The recent proliferation of connectivity for the Cepheid GeneXpert (e.g. GxAlert, RemoteXpert, CDX and others) evidences the tremendous potential for the rapid use of test results. However, like most technology-enabled initiatives in the developing world, getting the most out of these systems is not easy. Mobile networks are fragile. Power is intermittent. And lab staff unfamiliar with these systems can forget to plug in the modems, use them for personal use, or change the configuration settings after initial setup. Today, more than 800 labs connect their GeneXperts to a digital reporting system in order to enhance patient care, enable EQA programs, and improve laboratory supply chain. Most programs start out successfully with labs reporting nearly every day; but over time some of the programs saw a reduction in use primarily due to the following: 1. Insufficient network coverage or network too intermittent; 2. Complicated installation process; 3. Lack of centralized, MOH support, e.g., being project-led causes issues when the project ends; 4. Lack of a designated individual responsible for maintaining the network, IT security, and uptime

Intervention: Introduction of multi-SIM modems that search for 'best available network' across several networks; Development of streamlined installation software; Procurement of 1-2 enterprise-class agreements with in-country mobile network operators (MNO); MOH-led national-level rollouts, versus project led.

Results and lessons learnt: Programs that utilize one or more interventions above see more consistent and sustainable solutions. National planning and stewardship is critical to long-term success. Connectivity experiences 'network effects' where the more GeneXperts in a country that are connected, the greater the overall value of the network.

Conclusions: Connectivity for the GeneXpert used to be initiated by small projects that wanted an easier way to collect programmatic indicators. Increasingly, connectivity is used as a major tool for MOHs to improve linkage to care, optimize supply chain, and institute remote QA on lab diagnostic performance. National-level budgets and the MOH leadership required for long term success are becoming the norm. When executed well, the rapid use of GeneXpert test results will continue to lead towards better healthcare.

19. Quality laboratory services and impact on patient care

Rapid turnaround equals better care: designing county solutions for effective data exchange

J Takle ¹Global Connectivity, Boston, MA, USA.

Background and challenges to intervention: The growing coverage of mobile networks is changing how labs can support clinical care in the field. Rather than relying solely on paper ledgers and motorcycle couriers to communicate test results, diagnostic devices like the Cepheid GeneXpert, Alere PIMA / Q, and others can be configured to send an electronic copy of their test results over a mobile network as soon as the test is finished. The potential benefits span from immediate patient follow up, to a digitized view of the lab supply chain, to remote EQA improvements, and more. However, most health information systems (HIS) are not equipped to receive this rapid communication. Electronic Medical Records (EMR), case management tools, and Laboratory Information Systems (LIS) are logical recipients of digital lab results, but were never designed to exchange data amongst themselves. As a result, there is no simple way to match a digital diagnostic result to an existing patient record automatically, with the necessary degree of confidence.

Intervention: Perfection—in the form of a truly unique national ID for each country—is not on the horizon, so programs must currently administer the same diligence with digital records that they do with paper records: results should be matched manually in other HIS and quality controls put in place. But, new digital systems must be equipped with the patient demographics necessary for accurate matching into the other records systems, e.g. age, sex, HIV status, name, phone number, etc. And, systems can be designed with integration in mind—built with the mechanisms to accept digital lab results for effective linkage to care.

Results and lessons learnt: MOHs and their programs can make tremendous strides by applying the same criteria they use on paper records as they develop the matching algorithms and technology bridges necessary to enable automatic matching.

Conclusions: The rapid turnaround of test results, and the ability to digitally send them anywhere in the health system in near-real-time via SMS text, email, or database connection, holds amazing potential to improve health

care. Better quality data delivered faster logically leads to better healthcare. New algorithms and technologies are being built to help automate this direct Linkage to Care. Thoughtful design on effective data exchange will lead to rapid turnaround of patient results to where they are needed most.

20. The unaddressed health challenge of TB in prisons: applying End TB Strategy concepts of patient-centred care

20 years of TB control in penitentiary systems in Azerbaijan: achievements and challenges

R Mekhdiyev,¹ E Gurbanova,¹ F Huseynov,¹ O Baghirov,² R Tahirli² ¹Main Medical Department of the Ministry of Justice, Baku, ²Specialized Treatment Institution for Detainees with TB, Baku, Azerbaijan.

Background: The Main Medical Department (MMD) of Azerbaijan Ministry of Justice provides healthcare including TB services to 24 penitentiary institutions with 16 000 population.

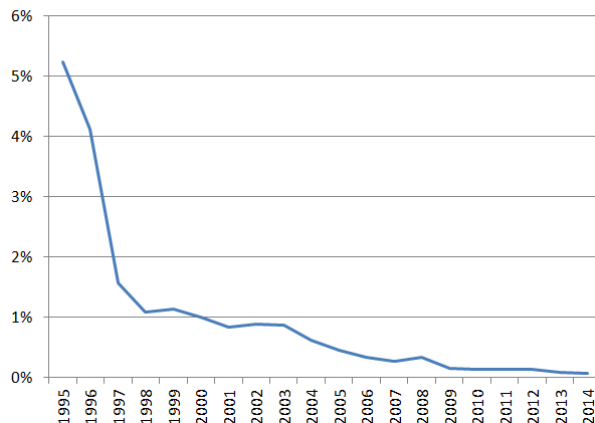
Design and methods: Following political commitment, a TB Control Program has been successfully developing in accordance with WHO recommendations over 20 years. It includes early TB case finding, qualitative and rapid diagnostics, standardized TB treatment, strict compliance to DOT and infection control (IC) protocols as well as uninterrupted supply with certified drugs. Quality assured TB laboratory is equipped with phenotypic and genotypic diagnostic tools for precise TB diagnostics. Both drug-susceptible (DS) and drug-resistant (DR) TB treatment is centralized at the Specialized Treatment Institution (STI) with appr. 900 bed-places. IC include administrative (patient segregation in accordance with infectiousness, drug sensitivity profile, treatment phase and detention regimen) environmental (input and extract ventilation, UV lamps) and individual measures. Patients are offered permanent support of adherence via additional food and hygienic packages as well as psychological support to overcome stress related to disease and imprisonment. Uncompleted TB treatment, initiated within the PS, proceeds after release. Having ensured appropriate juridical basis MMD has been collaborating with MoH and NGO to provide support and follow-up of TB patients after release.

Results: Comparing with 1995 in 2014 mortality from TB among Azerbaijan prison population decreased by >65 times (Figure). The Programme achieved significant treatment success rate both for new smear positive DS-TB and MDR-TB cases equal 91% and 80% respectively. 100% of inmates pass through TB screening in pre-trial isolators and 95% of the prisoners pass through annual mass screening for TB including questionnaire, X-ray, and sputum investigation. Special attention is paid to identification and prevention of TB among HIV-infected. Training Center functioning since 2012 at the STI was declared WHO CC on TB prevention and control in prisons and trained >700 medical and non-medical staff

of PS. Moreover, delegations from more than 15 countries visited the Program to get acquainted with the practice. Operational researches are performed on the Programme's theoretical and practical basis.

Conclusions: Today Azerbaijan TB Control in Prison Programme is an internationally recognized model for penitentiaries in and beyond the European Region.

Diagram. TB mortality among Azerbaijan prison population



21. TB contact management in children: closing policy-implementation gaps

Cross-border approaches to IPT: treating immigrant children from high-prevalence settings in the USA

A Cruz ¹Pediatrics, Baylor College of Medicine, Houston, TX, USA.

Background: The most effective strategy for preventing cases of TB disease in low incidence nations is by identifying and treating patients with TB infection. However, screening for risk factors and testing for infection assume access to medical care, which may not be readily accessible for high-risk patients.

Objectives: In this symposium, we will discuss the barriers to current prevention strategies and methods to provide preventive therapy to high-risk individuals, such as unaccompanied children crossing the Mexico-United States border into Texas. These approaches include screening and testing in nontraditional venues (e.g., schools), use of interferon gamma release assays to decrease false-positive results in a BCG-immunized population, use of shorter-course regimens, and administration of medication(s) under directly-observed preventive therapy.

Is mHealth an effective strategy to improve IPT adherence in child contacts?

K Du Preez,¹ L Du Plessis,¹ A Hesselings¹ ¹Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Desmond Tutu TB Centre, Cape Town, South Africa.

Background: Current international and national South African guidelines recommend 6 months of daily Isoniazid preventive therapy (IPT) for young and HIV infected children following documented household TB exposure. Reported adherence in high-burden TB settings is poor, with the minority of children completing 6 months' IPT. Innovative supporting tools are needed to improve adherence.

Methods: Against the background of a multi-level intervention to improve IPT delivery in the Khayelitsha sub-district, Cape Town, we investigated the impact of monthly text message (sms) reminders for 6 months to caregivers of children initiated on IPT. As children were recorded to have started IPT in paper-based registers at two health clinics during 2014/5, their parents were included in the reminder sms campaign if their cellular telephone number had been recorded by routine staff. Block randomisation was performed for a 14 month period, to allocate 50% of the months to the sms intervention (sms-months), and 50% to the control arm (no sms-months). Children initiated on IPT during sms-months were included in the campaign, and children initiated during no sms-months received standard-of care. Routine health care providers at the clinics were blinded to the sms status of each month. Outcomes (IPT completion, and number of months completed) were compared between the intervention and control arms, adjusting for household clustering.

Results: 235 children were entered into the registers from Jan-December 2014; 187 (80%) with recorded cellular telephone numbers. Of the total 235, 185 (79%) were from clinic 1 and 50 (21%) from clinic 2. Cellular telephone numbers were recorded for 142 (77%) and 45 (90%) of children from clinic 1 and 2 respectively. Analysis is ongoing.

Increasing children's access to IPT in Western Kenya

D Szkwarko,¹ E J Carter,^{2,3} L Kamule,³ N Buziba,^{3,4} P Owiti³ ¹University of Massachusetts, Worcester, MA, ²Warren Alpert Medical School of Brown University, Providence, RI, USA; ³Academic Model Providing Access to Healthcare (AMPATH), Eldoret, ⁴Hematology, Moi University, College of Health Sciences, Eldoret, Kenya.

Background: Isoniazid preventive therapy (IPT) delivery to child contacts exposed to tuberculosis remains a major problem in low-resource settings. This is closely intertwined with the operational challenges that tuberculosis (TB) programs globally continue to face in fulfilling World Health Organization recommendations for child contact management and screening. Despite new National Program recommendations in Kenya to initiate IPT in children under 5 years, major screening barriers

including cost of screening and transportation prevent child contacts from being brought into care for screening and IPT initiation. Intervention Funded by TB Reach, child contacts under five years exposed to smear positive index cases in 18 clinics throughout western Kenya became eligible for a 'child contact screening package' during a 17-month period. The package included screening chest X-ray, transport fees for index case and child, and registration fee. Outcomes included the number of child contacts who were screened and their diagnoses (active TB or IPT initiation) after program completion.

Results and lessons learned: 18 sites underwent implementation; 4 failed to complete any tracking, screening, or treatment initiation. Five sites initiated screening during quarter 1; the remaining 9 sites were functional by month 11. 631 child contacts under five years completed screening. 522 (83%) children initiated IPT; 99 initiated active disease treatment. Although 1137 smear positive index cases were identified, only 540 of these were queried regarding child contacts. Challenges included limited healthcare staff to conduct interviews, data collection difficulty, and child contacts transferring treatment monitoring to other facilities.

Conclusions: IPT delivery to child contacts exposed to tuberculosis can be improved by eliminating cost to screening and transportation. However, challenges in implementation of child contact screening and treatment initiation and monitoring still exist.

22. A community-based approach to reaching the missing 'three million'

Nigeria: walking the walk with nomadic populations: strategies that work

A Habib,¹ M Hamza,¹ K Karaye,¹ M Bello,¹ B Usman,² I A Abdulkadir² ¹College of Health Sciences, Bayero University, Kano, ²Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria.

Background: Nomadic societies are marginalized and vulnerable to infections. Their relative illiteracy, culture, pastoral lifestyle and living conditions with livestock predisposes to Tuberculosis (TB), including bovine TB especially among cattle herders. Community mobility limits opportunities for detection and access to care.

Methods and Discussions: Lessons from cases and case studies on TB among the nomadic Fulani in Nigeria and the Manyatta TB project in Kenya will be discussed. Clinical and socio-cultural factors among Fulani patients attending our TB Directly Observed Therapy Short Course clinic will be presented. Comparison will be made to native populations in other parts of the world. Results of a recent large integrated survey of TB prevalence among 229 nomadic Fulani adult population and 204 of their cattle herds in Rano, Kano, Nigeria will be presented (2014). Use of SD Bioline TB Ag MPT64 in speciation cattle and human mycobacterial isolates to aid TB detection (9.6%) will be described. Practical inter-

ventions that increased smear microscopy, smear-positive notifications, treatment outcomes and explored use of Xpert[®] MTB/RIF among nomads in Nigeria will be discussed.

Recommendations: Existing programmes for nomads afford opportunities for absorption and integration of TB services using the 'One-World One-Health' approach. In Nigeria, the National Commission for Nomadic Education has established an HIV/AIDS desk that focuses on mobilisation and awareness campaigns, and TB services could be provided along their migration routes. Nomadic communities should be provided with basic TB services, including education, counselling, screening, detection and treatment. These services should be taken to nomadic communities using novel outreach approaches such as mobile units, extension services, case management, directly observed care, and treatment supporters linked to neighbouring facilities in a hub-and-spoke model. Stronger collaborations are recommended between veterinary programmes for nomads' livestock and TB/public health services. Community participation should be encouraged to ensure the sustainability of TB care delivery.

Conclusions: There is inequality, inadequacy and inaccessibility of TB services among nomadic populations and concerted efforts should be made to improve care.

Nepal: community outreach challenges and successes in a post-earthquake setting

R S Gopali,¹ G Shrestha,¹ N Ishikawa,² K Okada²

¹Department of Public Health, Japan-Nepal Health and Tuberculosis Research Association, Kathmandu, Nepal; ²Department of International Cooperation, Research Institute of Tuberculosis/JATA, Tokyo, Japan.

Aim: To improve the health status of internally displaced people by screening tuberculosis symptomatics for early case finding.

Method: The earthquakes that struck Nepal in April and May 2015 caused destruction of houses and massive displacement of the population. Some of the internally displaced persons live in overcrowded makeshift settlements or share houses with their relatives, damage of health care infrastructure and displacement of health care workers lead to disruption of health care services, including TB diagnostic and treatment services. The National Tuberculosis Programme raised concern about interruption of TB treatment and increased TB transmission due to overcrowding and appealed to partners for support with early detection of TB among displaced persons and host communities. JANTRA carried out active screening of these populations through symptom screening, mobile microscopy camps at highly affected districts in Kathmandu valley. The bacteriologically confirmed TB cases are referred for TB treatment in nearby DOTS centres or volunteers.

Results: A total of 2783 people (1232 males and 1551 females) residing in the 10 IDP sites in Kathmandu valley were screened for tuberculosis using a structural questionnaire. Among total screened 42% (1182) were found with TB signs and symptoms. Among the total presumed

cases, 85% participated in the microscopic camp providing two sputum samples (morning and spot). Seven (0.7%) new smear-positive TB patients were diagnosed from this initiation and all the diagnosed cases are referred to nearby DOTS centres for treatment. Total 150 Female Community Health Volunteers and 10 Health Care Providers including laboratory staffs actively participated to implement this approach closely with health care providers working in local level.

Conclusion: The prevalence of tuberculosis in intervening IDP sites is relatively high (700/100 000 population), which is roughly four times higher compared than the national prevalence estimated by the WHO (241/100 000). 56% of participants were female and 44% male, which is unusual in NTP's laboratory activity, where the participation of males is always higher than females. On the other hand, the segregate male and female prevalence among total suspects examined, it is higher in males 0.78% (3/383) than females 0.64% (4/617). Similar types of activities must be expanded to other IDPs to determine the real prevalence of TB.

Greater Mekong sub-region: accessing hard-to-reach populations in politically sensitive settings

D Punpiputt,^{1,4} A Innes,^{1,4} K Z Aye,^{2,4} I Ling^{3,4} ¹Asia Pacific Regional Office, Family Health International, Bangkok, Thailand; ²Myanmar Country Office, Family Health International, Yangon, Myanmar; ³China Country Office, Family Health International, Kunming, China; ⁴USAID Control and Prevention Tuberculosis Project, Bangkok, Thailand.

Background: Effective multidrug-resistant tuberculosis (MDR-TB) control is a challenge for TB platforms and health systems, as evidenced by the large diagnosis and treatment gaps reported from global data. Despite progress since 2009, fewer than 50% of estimated MDR-TB cases worldwide were diagnosed in 2013, and the global success rate remains <50%. The USAID Control and Prevention Tuberculosis (CAP-TB) Project has focused on strengthening MDR-TB control in the Greater Mekong Sub-region of Yunnan Province, China; Myanmar; and Thailand.

Response: Starting in 2012, the CAP-TB project developed a model for MDR-TB control using a 'patient-centered' perspective to identify gaps in the health system. The CAP-TB model starts with finding presumptive TB and MDR-TB patients in the community; linking presumptive patients with the TB system for early diagnosis and initiation of treatment; and supporting those diagnosed throughout their 20-24 month regimen. Community mobilization to support patients used both standard and innovative methods: by engaging volunteers and outreach workers to provide support and accountability through a bundle of patient-support interventions; as well as through social media, creating virtual communities comprising patients, peers with TB or MDR-TB, and health care providers. This patient-centered, community-mobilized model was developed first in urban and centralized levels of the health system,

with the idea to adapt the model to more rural and inaccessible areas in each country.

Results: In China, the project mobilized community support for 79 MDR-TB patients diagnosed since May 2012 in Kunming, Yunnan Province, and improved coordination between the hospital and public health sectors to maximize continuity of care between inpatient and community settings. These patients are currently completing their treatment, with approximately 74% treatment success rate, 17% loss to follow-up, and 1% mortality. In 2014, the urban Kunming model was adapted to the rural setting in Yunnan's Zhenxiang County, which has the highest number of TB patients and second highest TB prevalence in the province. Scaling up further, Xinjiang Province, which reports the second highest TB prevalence in China, requested technical assistance from CAP-TB to improve treatment success rates. Political turmoil in Xinjiang likely contributes to challenges for TB control; the Chest Hospital in Xinjiang has now adapted CAP-TB's social media strategy to improve patient-provider communication with the overall goal to improve treatment adherence. In Myanmar, the CAP-TB project has supported 1101 MDR-TB patients since January 2013 in Yangon and Mandalay, which are the centers for MDR-TB control in Lower and Upper Myanmar. Developing a model based in these regional centers has laid the foundation for expansion to more rural and hard-to-reach areas of the country. These MDR-TB patients in Yangon and Mandalay are completing their treatment with a success rate of approximately 75%. In Thailand, CAP-TB focused on Rayong Province, which has the third highest MDR-TB case notification rates among all provinces in Thailand. This industrial, coastal province attracts internal migrants from throughout the country as well as cross-border migrants from Cambodia and Myanmar. Since 2012, the CAP-TB project has supported 79 MDR-TB patients currently on treatment in Rayong, focusing on building multi-disciplinary teams at the provincial level that coordinate among different levels of the TB system to improve patient support. Treatment success rates for the CAP-TB supported Rayong patients are currently 65%, higher than the national average of 49%.

Conclusions: Developing a patient-centered model that mobilizes the community, leverages technology and social media, and strengthens TB platforms can impact MDR-TB control. Strategic focus on urban, more central levels of the TB system facilitates development of the model, which can then be adapted to access marginalized, hard-to-reach populations.

23. Moving towards universal access to drug susceptibility testing: progress and challenges

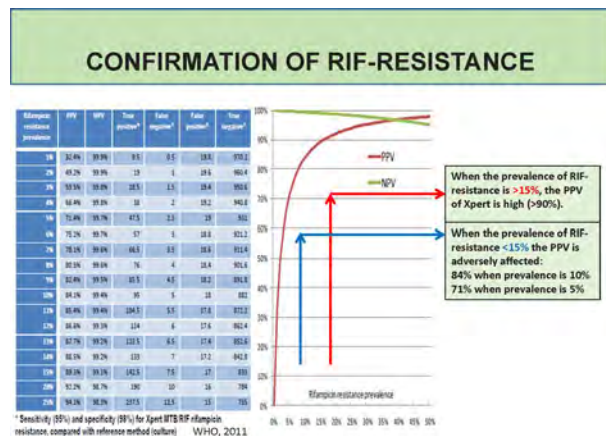
Poor access to follow-on DST for rifampicin-resistant (RR) TB cases: root-cause analysis done in MSF projects in African & Asian settings

M Rumaney,¹ E Fajardo,¹ C Metcalf,¹ M Casenghi,² M De Melo Frietas,³ E Mbofana,⁴ P Isaakidis,⁵ E Mohr⁶

¹Southern African Medical Unit, Médecins Sans Frontières (MSF), Operational Centre Brussels, Cape Town, South Africa; ²Access Campaign, MSF, Geneva, Switzerland; ³Mozambique Project, MSF, Operational Centre Brussels, Maputo, Mozambique; ⁴Zimbabwe Project, MSF, Operational Centre Brussels, Harare, Zimbabwe; ⁵India Project, MSF, Operational Centre Brussels, Mumbai, India; ⁶South African Project, MSF, Operational Centre Brussels, Cape Town, South Africa.

In multidrug-resistant tuberculosis (MDR-TB) prevalent settings, the World Health Organization (WHO) recommends that Xpert RIF-resistant results be confirmed with the Line Probe Assay (LPA) or phenotypic drug susceptibility testing (DST) before initiating patients on treatment. For low prevalence settings a second Xpert test should be performed and if RIF-positive, treatment should be initiated while awaiting confirmation. LPA is not routinely available in remote settings and is validated for smear-positive samples only. DST is available as centralised testing with long turnaround times (TAT) to results, leading to lengthy transportation, cold-chain requirements and poor sample quality. This study aims to describe the challenges associated with confirmatory TB testing, and the differences in high vs. low prevalent settings, taking discordant results and its effect into consideration. Qualitative and quantitative data was collected from six sites – two high prevalent settings, South Africa (Cape Town); India (Mumbai), and four low prevalent settings Mozambique (Maputo; Tete); Zimbabwe (Buhera); Kenya (Kibera). Qualitative data was collected via a survey. Quantitative data was compiled by retrospective patient folder review from 2012-2014. Statistical analysis was performed using Stata version 12 (StataCorp. Texas, USA). Qualitative data analysis revealed: 1) a second Xpert test was performed routinely in 1/6 sites, 2) the distance from the health facility to the laboratory is between 10-2000km, depending on the site, 3) 5/6 sites use road as the medium of transport, 4) first line DST is performed in all sites, 5) treatment is initiated without a DST result in 2/6, and while awaiting a DST result in 3/6, sites. Challenges include sub-par transportation, sample contamination, insufficient specimen volume, poor sample quality, inadequate DST follow-up, delayed entry of results, and missing data. Quantitative data analysis presented using statistical analysis. There is an urgency to strengthen diagnostic capacity to confirm DR-TB, referral networks for sample transport and rapid result-delivery. Although repeat testing increases cost, it offers a

practical alternative for resource limited settings to decide on initiating treatment earlier while awaiting DST confirmation.



Improving access to DST and adherence to diagnostic algorithms: lessons learnt in Nigeria through the Xpert MTB/RIF scale-up

P Nwadike,¹ M Gidado,¹ S Useni,¹ J Onazi,¹ P Ajiboye,¹ C Ehimanre,¹ R Eneogu,¹ E Elom² ¹KNCV/TB CARE 1 Project, Abuja, ²National Tuberculosis & Leprosy Control Program, Federal Ministry of Health, Abuja, Nigeria.

Introduction/Background: Prior to Xpert MTB/RIF implementation, Nigeria had only 2 functional culture/DST laboratories. Conventional DST has a limitation for access in a huge country like Nigeria with weak referral mechanism and sample movement limiting the diagnosis of DR-TB patients. Xpert MTB/RIF was adopted in 2010 with the aim of improving access to DST among the increasing DR-TB patients. Currently the country has 144 Gene Xpert sites and 5 functional culture/DST laboratories. The process of scaling up DST was associated with updating of the diagnostic algorithm from one priority group (Cat 2 failure) to eight priority groups (PLHIV, Contact of DR-TB patients; children with TB symptoms, EPT) among others. However, because Xpert provided only RIF resistance, more culture/DST were also scaled up for diagnostic confirmation of PMDT patients.

Objective: This paper describes the additional role of GeneXpert MTB/RIF machine in providing access to DST and early enrollment of patients for MDR-TB management using multistage algorithm development process

Methodology: This is a retrospective review of routine quarterly report of both programmatic and supervision reports to DST and Gene Xpert sites between 2011-2014. Additionally, desks review of all the existing guidelines were carried out.

Results: Prior to the adoption of the GeneXpert in 2011, about 126 cases of DR-TB were diagnosed across the country between 2007 and 2010 through culture/DST and LPA in the five functional laboratories across the country. In 2013, 10 652 presumptive DR-TB cases were

screened using Xpert MTB/RIF; out of which 764 were MTB detected/RIF resistant. Review and expansion of the NTBLCP algorithm to include other priority groups led to the screening of 24 313 using the Xpert machine in 2014, out of which 798 isolates were resistant to Rifampicin.

Lessons learnt: Rapid expansion of either culture culture/DST or Xpert MTB/RIF to increase DST access will be difficult to achieve without proper logistics for referral and sputum transportation

Conclusion: Access to DST and adherence to algorithms has improved via Xpert scale up and appropriate coordination by the NTBLCP with increased and targeted supportive supervision funded by partners.

24. Why and how to use tobacco taxes as funding mechanisms for financing health in low- and middle-income countries

How tobacco taxes can be used to create funding mechanisms for health financing

J Tesche Tobacco Control, International Union Against Tuberculosis and Lung Disease, Edinburgh, UK.

The lack of sufficient funding for health is a serious issue in many countries. Increasing tobacco taxes is one way of increasing government revenues, including funding for health. There is ample scope to increase tax rates and cigarette prices in order to increase revenues and funding for health since tax rates in most countries remain below rates recommended by the WHO (total taxes of at least 75% of the retail sales price (2015 Report on the Global Tobacco Epidemic). Comparable retail prices of cigarettes are also significantly lower in middle and lower income countries than in richer countries. There are theoretical and practical arguments both for and against earmarking. Economic theory can support earmarks, but only in the case of a benefit or user fee. Since smokers use more health resources than others this is an appropriate use of dedicated funds. Politically, voters are more likely to support an increase in taxes if they know that the money is going toward health. One argument against earmarks is that they are irrelevant in that funds are not secure, they can be used for other purposes. Earmarked funds decrease the flexibility of elected governments. If the funds go to an off-budget fund, there can be a decrease in transparency as well. Governments may also decrease budget allocations for health if a dedicated tax source goes directly to the health sector or such dedicated revenues may be insufficient to cover expenditures over time. If tobacco taxes are to be earmarked for health, there are a number of decisions that follow: How much of which taxes will be used and will they be used for health in general or more specific areas like cancer research? Will the earmark be 'hard', passed in legislation or 'soft', with only a stated intention of where funds should be used? Are the funds allocated through a direct line in the budget, and if so, along with other funds or used only for health? If funds are off budget, is it through

a government fund or a separate foundation? In practice, a wide variety of earmarks and uses are in use, including health, research, cancer treatment and health promotion. Fewer countries fund tobacco control directly. The central issue is the need for governments to commit sufficient resources for health. Increasing revenues from tobacco taxes makes it easier for governments to make that commitment and there is ample space to increase tobacco taxes in most countries.

25. Can tuberculosis immunisation prevent initial infection (not just disease complications)?

What is the evidence that BCG prevents infection?

T Hawn School of Medicine, University of Washington, Seattle, WA, USA.

The development of effective immunoprophylaxis against tuberculosis (TB) remains a global priority, but is hampered by a partially protective *Bacillus Calmette-Guérin* (BCG) vaccine and an incomplete understanding of the mechanisms of immunity to *Mycobacterium tuberculosis*. Thus far, preventing TB disease, rather than infection, has been the primary target for vaccine development. Several areas of research highlight the importance of including pre-infection vaccines in the development pipeline. First, modeling data indicate that a pre-infection vaccine would have high population-level impact for control of TB disease. Second, targeting host responses that prevent infection may be more effective during acute as compared to chronic infection. Third, epidemiologic data from natural history studies indicate that resistance to *M. tuberculosis* infection occurs in a small percentage of the population. Fourth, retrospective case-control studies suggest that BCG is associated with protection from infection. Together, these areas suggest biologic plausibility and epidemiologic support for expanding the focus of TB vaccine development efforts to include prevention of infection as a primary goal along with interventions that reduce transmission and reactivation.

Defining TB infection

E Nardell Global Health Equity, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA.

The question of whether TB immunization can prevent infection is heavily dependent on the definition of infection in the absence of microbiologically proven disease. Until recently, vaccines like BCG that can convert the tuberculin skin test (TST) could not be studied for their ability to prevent infection as defined by the TST. The advent of interferon gamma release assays (IGRAs) have already provided observational evidence that BCG appears to reduce IGRA positivity among contacts of active disease – another common definition of

infection. But both TST and IGRAs are indirect immunological markers of response to infection, not infection itself, and recent studies suggest the potential for transient TST and IGRA positivity, presumably correlating with transient infection – a foreign concept in traditional TB pathogenesis. Failure to reactivate TB under the pressure of immunosuppression has been used in the laboratory to further define the presence or absence of infection. Less invasively, long-term follow up of presumed human infection in normal and immunocompromised hosts who decline chemoprophylaxis provides another window to true infection vs. a harmless residual immunological footprint of infection. Potential for disease as a marker of infection, however, is complicated by differences in strain virulence, host resistance, and perhaps dose. The definition of infection in humans is clearly harder to assess than in experimental animals where organs can be cultured. Moreover, the question has been raised on whether infections prevented by immunization are primarily those that might naturally clear infection anyway, with little or no impact on those who become infected and progress to disease. Clearly the question is complex and perhaps not answerable with today's tools. For now, vaccine impact on infection might best be studied in animal models where true infection can be investigated thoroughly. In humans, outcomes should include both immunological markers of infection and progression to disease.

Immunisation to prevent TB infection of medical travelers: the TIPI trial

N Aronson,¹ E Nardell² ¹Infectious Diseases, Uniformed Services University of the Health Sciences, Bethesda, MD, ²Global Equity, Brigham and Women's Hospital, Boston, MA, USA.

An increasing number of students, physicians, researchers, other healthcare personnel, and humanitarian groups from areas of low risk travel to work in areas of the world where the incidence of TB (including MDR- and XDR-TB) is high. These workers are at risk for infection and disease from these resistant TB strains. Several studies and unpublished data indicate that TB infection risk for travelers to high burden countries is significant with estimates ranging from 4-8%. The primary objective of this proposed clinical trial is to test the hypothesis that BCG immunization can reduce the occurrence of *Mycobacterium tuberculosis* infection as measured by interferon gamma release assay (IGRA) conversion in BCG vaccinated recipients as compared to placebo recipients. This presentation will introduce the details of the TB Immunization to Prevent Infection (TIPI) clinical trial.

Implications for vaccine clinical trials

L Schrager Scientific Affairs, Aeras, Rockville, MD, USA.

Developing a vaccine capable of preventing established infection with *Mycobacterium tuberculosis* represents an intriguing and lofty goal among TB vaccine developers.

In addition to the significant challenges inherent in developing a vaccine capable of preventing established *M. tuberculosis* infection, designing clinical trials to actually prove vaccine efficacy for this endpoint presents an additional level of complexity. Currently, a Phase 2 'proof of concept' clinical trial assessing the potential of two *M. tuberculosis* vaccines to prevent *M. tuberculosis* infection is ongoing. This trial, however, is utilizing prevention of *M. tuberculosis* infection as an indicator of biological activity, intended to 'de-risk' future trials geared to assess the ability of vaccines to prevent active TB disease. A pivotal Phase 3 trial with the object of establishing prevention of *M. tuberculosis* infection as a licensable endpoint will necessitate far more regulatory scrutiny as compared to the prevention of disease endpoint. One critical issue that will have to be clarified before such an approach is likely to be viable from a regulatory perspective is the reliability of the currently available interferon gamma release assays (IGRAs) to accurately identify new *M. tuberculosis* infections among an uninfected population. Another likely regulatory concern is the uncertainty surrounding the actual effect a vaccine that is less than 100% efficacious in a prevention of infection study may have in preventing *M. tuberculosis* disease. While disease cannot occur absent infection, there is a theoretical concern that those in whom a vaccine prevents infection may be the approximately 90% of persons who would otherwise control *M. tuberculosis* for life, rather than the approximately 10% of individuals who will eventually develop disease, thereby having no real effect on TB disease outcomes. Unless these issues can be addressed, vaccines developed to prevent the establishment of *M. tuberculosis* infection may find their most efficient pathway to licensure via a Phase 3 clinical trial intended to prevent TB disease among persons initially uninfected with *M. tuberculosis*, considering that more than half of the persons who develop disease are likely to do so within the two years following initial infection. Sample size estimates that will provide insight as to the potential feasibility of this approach will be presented.

26. WHO/ERS initiative on e/mHealth in tuberculosis and tobacco control

The WHO/ERS initiative to improve e-/mHealth for TB and tobacco control: concepts and progress

D Falzon,¹ S Aliberti² ¹Global TB Programme, World Health Organization, Geneva, Switzerland; ²University of Milan Bicocca, Milan, Italy.

Tuberculosis (TB) remains a major global public health concern. Information and communication technologies (ICT) present new possibilities to address this challenge on different fronts. Various innovative digital health projects have been initiated by TB programmes and technical partners worldwide to support their TB care and prevention efforts. The fast rate with which ICT have

advanced and diversified in recent years creates increasing opportunities: by mid-2015 there were over 7.5 billion mobile phone connections globally, and about 40% of the world's population had an internet connection. The World Health Organization (WHO) and the European Respiratory Society (ERS) have joined forces to promote the broader use of state-of-the-art ICT to the benefit of TB patients. In line with WHO's post-2015 End TB Strategy, the two organisations are looking beyond traditional entry-points to support TB care and prevention. These include the use of e/mHealth interventions to improve the management of comorbidities (e.g. diabetes) and health risks (e.g. tobacco smoking) which frequently overlap in the TB patients. In February 2015, the two organisations jointly organised a technical consultation in Geneva on digital health for TB and tobacco control. As a result of this discussion, the participants identified priority digital health products for future focus and target product profiles (TPPs) were elaborated for these concepts (www.who.int/tb/areas-of-work/digital-health/). WHO appointed a 'Global Task Force on digital health for TB' and this group is now taking forward the continued development of the TPPs and country case studies to study these concepts at large scale. Case studies are now being mounted in Belarus, the Republic of Moldova, and elsewhere. It is envisaged that these studies will cover a diversity of products, including electronic tools for active TB drug safety management and monitoring, video observed therapy, connected diagnostics, and eLearning. The presentation will report on the early outcomes of the WHO/ERS collaboration, the rationale and content of the TPPs, the anticipated activities into 2016, and the 'Digital Health for the End TB Strategy: an agenda for action' which the two organizations have developed together.

Improving and increasing evidence: from pilot to clinical trials to scaled mHealth interventions

R Lester Medicine, University of British Columbia, Vancouver, BC, Canada.

Mobile and electronic health (mHealth and eHealth) provide exciting new opportunities to support tuberculosis (TB) and tobacco control efforts. Low cost cellular phones and improving internet access has made these innovations particularly attractive for overcoming barriers to prevention and care in resource-limited settings and among vulnerable populations worldwide. The evidence of effectiveness of these interventions for TB and tobacco control or related conditions is highly variable, but continues to rapidly emerge. Many initiatives are launched as pilot projects, raising fears among some as causing 'pilotitis' (health system inflammation from too many disconnected interventions that have been found successful without being brought to scale). Other projects are implemented broadly and at high cost with little evidence of health outcome effectiveness. In between, some high- (and poor-) quality evidence has emerged for both prevention (e.g., text2stop smoking cessation) and for treatment support (e.g., WelTel medication adherence support via SMS and video observed therapy (VOT)

monitoring). The quality evidence available is not all positive, but is necessary to inform what works and what doesn't so that the best investments in health systems can be made in an impactful and timely way. In this talk, we will briefly review the current evidence and discuss a system of developing evidence over the implementation spectrum - from formative research through pilot studies, efficacy and effectiveness studies, and ultimately program monitoring and evaluation at scale. Given the novelty of such systems in healthcare settings, issues such as technical capacity (e.g., cellular and wifi availability), privacy protection, policy and procedures in clinical environments, and resource / staff availability as well as stakeholder buy in and sustainable business models are critical evaluative considerations for adopting these innovations at scale. As such, 'implementation science' is increasingly recognized as a necessary research area to help bridge the evidence to practice gap for best practices and impact at scale.

Development of target product profiles for 'connected diagnostics' in TB

D M Cirillo,¹ C Denkinger² ¹San Raffaele Scientific Institute, Milano, Italy; ²FIND, Geneva, Switzerland.

eHealth solutions offer a unique opportunity in the operationalization of TB care to meet the EndTB strategy put forward by the WHO. Target product profiles (TPPs) can describe eHealth solutions that target priority needs of TB programmes in further detail and thus provide a strategic planning tool as well as a communication tool for investors and stakeholders. Diagnostic tests are a cornerstone of TB control in guiding appropriate therapy, infection control and surveillance. However, often the use of data generated by diagnostic tests is lost or reaches decision makers only with substantial delays particularly in decentralized settings. Decentralization of user-friendly, sophisticated diagnostics platforms has been started with GeneXpert and has shown that the benefit for patients and for the public health system in general. Even more decentralized platforms are on the horizon (e.g., Omni or Alere Q). These tests will on the hand facilitate direct patient management at the point of care; on the other hand the decentralization will pose challenges to ensure the appropriate data transfer for stock management, surveillance and reporting. Automated transfer of data generated by a diagnostic instrument using communication technology directly to the relevant individuals such as clinicians, public health officials and the patients themselves can overcome this. This enables shorter time to diagnosis, error reduction from data copy and transfer, collection of epidemiological data for analysis and planning interventions and also direct device and user management. A future TB test, independently from its size and location, should aim at having a simple way to report the results through connectivity-enabled diagnostics alongside appropriate data repository solutions and data presentation applications.

Diversifying approaches to eLearning for TB and tobacco control

M Dias,¹ C Gratziou² ¹World Health Organization, Geneva, Switzerland; ²European Respiratory Society, Athens, Greece.

Both TB and tobacco are major global public health concerns, causing millions of deaths each year. There is a strong association between smoking and TB, with each fuelling the other's impact. Information and communication technology could provide new solutions and avenues for joint action on both of these diseases. The World Health Organization (WHO) and the European Respiratory Society (ERS) have joined forces to support broader use of state-of-the-art information and communication technologies to the benefit of TB patients and tobacco users.¹ Following a joint WHO/ERS technical consultation on the role of digital health in TB care and prevention and tobacco control in February 2015, a number of e/mHealth eLearning products were identified as advantageously positioned to make an impact on global health efforts. These included: i) Comprehensive, e-Learning web-based courses on TB and smoking cessation approaches, optimized for mobile devices and equipped with visual instruction aids aims to help building capacity and skills of health professionals and ultimately facilitate the detection of TB among smokers as well as increase the number of people that stop smoking; ii) An online portal for patients to retrieve reliable information about their disease, treatment options and the risks of smoking; and iii) A clinical decision-support tool to facilitate the daily work of practitioners and reduce the number of sub-optimally treated patients. This presentation will highlight how new eLearning opportunities via the internet and mobile computing devices can be integrated into the work of TB programmes in line with WHO's End TB Strategy and the evidence-based strategies recommended by WHO's Framework Convention on Tobacco Control. Novel approaches such as gamification and peer-education will be reviewed. The potential impact and benefit of all these eLearning resources for people with TB and tobacco users will be presented.

Reference

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E-/mHealth initiatives for TB patients in Belarus and other European countries

A Skrahina,¹ D Klimuk,¹ D Falzon,² M Dara,³ P De Colombani,³ A Dadu,³ V Rusovich⁴ ¹Ministry of Health, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; ²Global TB Programme, World Health Organization (WHO), Geneva, Switzerland; ³WHO Regional Office for Europe, Copenhagen, Denmark; ⁴WHO Country Office, Minsk, Belarus.

Background: Information and communication technologies (ICT) could strengthen the fight against TB. However the potential of the ICT to combat TB/MDR-TB still remains largely untapped, particularly in high

TB/MDR-TB burden and Former Soviet Union (FSU) countries. Nevertheless, national TB programmes (NTPs) in many countries have embarked upon pilot projects to study how eHealth (electronic health) and mHealth (mobile health) can be used to help their efforts in the care and prevention of TB and multidrug-resistant TB (MDR-TB).

Methods: We describe achievements and challenges in integrating ICT for different aspects of the work of NTPs of some European FSU countries (Belarus, Moldova). Digital health products are considered under four functions: patient care, surveillance and monitoring, programme management and eLearning.

Results: In Belarus, the first steps in the development of electronic TB register were taken in 2006. In 2009, with the support of the Global Fund (GF) a module for the electronic registration of drug-susceptible TB cases was developed and implemented. This work was continued in 2012 when a component for drug-resistant TB was added and in 2013 with the addition of a TB laboratory informatics component. Since 2014, a drug management component has been under implementation. All register components comply with WHO requirements. An electronic database to evaluate safety and effectiveness of MDR-TB regimens which include new and repurposed drugs is also under development. Projects for the future include eLearning on PAL and video-observed therapy (VOT) for MDR-TB patients. TB/MDR-TB patients always face challenges to comply with the demands of daily long term treatment and many do not complete treatment as prescribed. mHealth could facilitate bidirectional exchange between patients and health care providers. Treatment interruption and loss to follow-up could be alleviated. Belarus NTP is on its way to the development of mobile digital health product and regulatory base for eDOT that are aligned to the challenges posed by TB to health care providers and patients. VOT/DOT RCT has been started in Moldova earlier this year, employing low-cost tablet computers to clinics.

Conclusion: The ICT shows promise in TB/MDR-TB care. The process for designing, building and rolling out a digital application needs to embrace a broad cross section of representative users and policy makers.

SYMPOSIA: SATURDAY 5 DECEMBER 2015

27. Building on emerging knowledge to develop novel regimens for paediatric drug-resistant TB

Global treatment outcomes in children with paediatric MDR-TB: systematic review and meta-analysis

E Harausz,^{1,2} A Garcia-Prats,¹ H S Schaaf,¹ A Hesselning,¹ J Furin,³ R Menzies,⁴ S Law,⁴ J Seddon⁵ ¹Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Desmond Tutu TB Centre, Cape Town, South Africa; ²Military HIV Research Program, Bethesda, MD, ³Harvard Medical School, Harvard Medical School Department of Global Health and Social Medicine, Boston, MA, USA; ⁴Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, QC, Canada; ⁵Department of Paediatrics, Imperial College London, London, UK.

Background: There is limited evidence on the optimal treatment of MDR-TB in children. Although outcomes in children are good (>80% treatment success), MDR-TB treatment duration is long, requiring the use of toxic drugs. We reviewed existing evidence on the treatment of MDR-TB in children to inform updated global treatment guidelines on paediatric MDR-TB.

Methods: This was a systematic review and individual patient data (IPD) meta-analysis of published and unpublished studies of MDR-TB treatment in children. We conducted a comprehensive search for articles and conference abstracts without language restriction. Experts and clinicians in the field were contacted to identify additional data. Cohorts were eligible regardless of study design if they included ≥ 3 children <15 years treated for MDR-TB and had treatment outcomes reported. Authors were contacted to provide IPD on key factors, including: HIV status, source case information, culture-confirmed vs. clinical diagnosis, disease severity, drug susceptibility, duration and use of drugs, sputum conversion and treatment outcomes.

Results: The majority of data came from directly contacting experts in the field; 28 authors and centers contributed IPD data. The literature search yielded 2673 articles or conference abstracts; 201 full-texts were reviewed; of these, 55 were eligible and from authors we had not yet contacted. They were contacted and 3 provided IPD. 997 children from 18 countries were included: median age 7 years; 40% were male. HIV status was documented in 850; 40% HIV-infected. 60% of cases were bacteriologically confirmed and 40% were clinically diagnosed. 250 children had extrapulmonary TB. Culture-confirmed extensively drug-resistant TB was documented in 35 children. Successful treatment outcomes (cured or treatment completed) were documented in 77%, while 1.5% failed treatment, 10% died, 6% were

lost to follow-up and 5.5% were not evaluated. Most regimens included pyrazinamide, prothionamide/ethionamide, a fluoroquinolone and a second-line injectable; 51% used cycloserine/terizidone and few used high-dose isoniazid, clofazimine and linezolid. Analysis of associations of outcomes with individual drugs and treatment durations, controlling for key covariates, is ongoing.

Conclusions: This IPD meta-analysis on MDR-TB treatment outcomes in children promises to be a rich source of information to help inform improved treatment of children with MDR-TB.

Emerging data on PK and safety of levofloxacin and amikacin informs care and design of new regimens

A Garcia-Prats,¹ H R Draper,¹ S Thee,^{1,3} A Hesselning,¹ H S Schaaf,¹ P Denti,² H McIlleron² ¹Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Desmond Tutu TB Centre, Tygerberg, ²Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa; ³Department of Paediatric Pneumology and Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany.

Levofloxacin is currently the most frequently used fluoroquinolone for multidrug-resistant tuberculosis (MDR-TB) treatment and prevention in young children; the current levofloxacin dose used in practice is 10-15 mg/kg once daily. The second-line injectable TB medications are used routinely in MDR-TB treatment regimens, at a recommended paediatric once daily dose of 15-30 mg/kg. However the pharmacokinetics of levofloxacin and the injectables have not been well-characterized in children with MDR-TB. The injectables are associated with permanent sensorineural hearing loss in up to 25% of children receiving them long-term, likely related to the total cumulative drug exposure. An ongoing observational study in Cape Town, South Africa, is evaluating the pharmacokinetics and safety of multiple second-line antituberculosis drugs in HIV-infected and uninfected children with MDR-TB. We have previously reported data from this study on the pharmacokinetics and short-term safety of levofloxacin at a dose of 15 mg/kg in a limited number of young children with MDR-TB ($n=22$), demonstrating a median maximum plasma concentration (C_{max}) of 6.79 mg/ml and a median area under the concentration time curve (AUC_{0-inf}) of 32.9 $\mu\text{g}\cdot\text{h}/\text{ml}$, which are well below those seen in adults following the currently recommended 750 mg once-daily dose (C_{max} 8.6 $\mu\text{g}/\text{ml}$, AUC_{0-24} 90.7 $\mu\text{g}\cdot\text{h}/\text{ml}$). Preliminary data on amikacin pharmacokinetics in 28 children with MDR-TB at an intramuscular dose of 20 mg/kg showed a median C_{max} of 47.1 $\mu\text{g}/\text{ml}$, which is above the currently proposed target C_{max} of 35-45 $\mu\text{g}/\text{ml}$ in a large proportion of children. Based on this data, we have now evaluated the pharmacokinetics and safety of a higher dose of levofloxacin (20 mg/kg) and a lower dose of amikacin (15 mg/kg). We present here emerging data from this study on the pharmacokinetics of levofloxacin in >100 children with MDR-TB at doses of 15 mg/kg and 20 mg/kg, using state of the art pharmacometric

modeling. We will also present data on the pharmacokinetics and safety of amikacin given at both the 20 mg/kg once daily and at a reduced dose of 15 mg/kg once daily. We will discuss the implications of this data for the design and evaluation of novel, more optimal, safer, and better-tolerated regimens for the treatment and prevention of MDR-TB in children.

Compassionate use of bedaquiline and delamanid in children with MDR-and XDR-TB: early experiences and challenges

M Tadolini,¹ L D'ambrosio,^{2,4} G B Migliori,^{2,3} R Centis,² S Esposito⁵ ¹Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Infectious Diseases Unit, Bologna, ²World Health Organization Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy; ³European Respiratory Society (ERS), Secretary General, Lausanne, ⁴Public Health Consulting Group, Lugano, Switzerland; ⁵Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Highly Intensive Care Unit, Milan, Italy.

Multidrug-resistant tuberculosis (MDR-TB) is a serious obstacle to TB control. Delamanid and bedaquiline are novel anti-TB agents recently approved for the management of MDR-TB patients. Both of them have been approved for adults only. Our group described a case of compassionate delamanid use in a 12 years old child (male, native Italian) who was diagnosed in October 2013 with laryngeal and pulmonary TB, with positive smear on gastric aspirate. When the drug susceptibility test (DST) results became available (showing resistance to all first- and second-line drugs except para-aminosalicylic acid (PAS) and linezolid), the initial regimen with ethambutol, pyrazinamide, high-dose isoniazid and moxifloxacin was re-designed (Figure). After an initial clinical and radiological improvement, the patient experienced gastric aspirate direct smear reversion to positive and progressive clinical deterioration. In order to select the most appropriate treatment regimen, the ERS/WHO TB Consilium platform was used and four different world experts in paediatric MDR/XDR-TB management were consulted. All of them recommended the inclusion of one of the newly approved TB drugs in a regimen including also meropenem and clofazimine. Following the experts' recommendations, delamanid was procured in 10 days via the manufacturer and treatment initiated, with close monitoring of the patient. After treatment revision and delamanid introduction (Figure), a rapid and sustained clinical and radiological improvement was observed, with gastric aspirate bacteriological conversion. The regimen was tolerated very well with no major side effects onset. This case shows that there is an urgent need of expanding the access to new drugs for children, through the development of a consensus-based roadmap to ensure new drugs rational use. In our experience, in the absence of a pre-existing national authorization process for the compassionate use of an unregistered drug (formally approved in Europe for

adults only), the TB Consilium experts' opinion played a crucial role in obtaining clearance from Italian regulatory bodies. Building on the newly published data on pharmacokinetics, safety and efficacy of delamanid in children, it is essential to stimulate similar clinical trials on bedaquiline in pediatric population. At the same time it is important to ensure rapid access to the new drugs through compassionate programmes in selected cases, to save patients' lives and to break the transmission cycle.

	Africa	Asia	Europe	Latin America
Isoniazid				
Rifampicin				
Ethambutol				
Clofazimine				
Bedaquiline				
Delamanid				
PAS				
Linezolid				
Moxifloxacin				
Fluoroquinolones				

28. End TB, end MDR-TB

Prioritisation: mapping the hotspots—fighting TB in urban settings

R Orejel ¹Programa Nacional Tuberculosis, México, DF, Mexico.

Background: It is widely known that there is a higher-burden of TB in urban areas than in rural areas. This is largely because of the living conditions in poor marginal neighborhoods. Various publications have pointed out that a 48% of high-burden TB is not attributed to health services, but rather to the social determinants of health. The reason for this that the options of intervention should be out of health services. However, it is necessary to build and create alliances with the other (The National Crusade against hunger 'Cruzada Nacional Contra el Hambre', Department of water 'CONAGUA' Housing sector, etc). **Design/Methods:** 31 municipalities were selected that have 100 or more cases of tuberculosis in all its forms. In Mexico these municipalities account for 48% of all cases in the country. An epidemiological mapping was carried out for each municipality to select are as to intervene in considering other epidemiological indicators such as low detection rates or curing, high percentages of dropouts or MDR-TB. From the selected municipalities, 31 coordinators in the TB Program were instructed to work on a different work plan where social determinants can be addressed and get existing health suppliers involved in each municipality using the model "Big Cities" by proposed PAHO/WHO. It was recommended to work with private pharmacies, private clinics, schools, textile factories and assembly plants, as well as Alcoholics Anonymous, midwives, churches and others. The National Program is monitoring that the work plans are being carried out. In the following September there will be results of this initiative.

Results: In a period of 4 months, 50 respiratory symptomatic have been detected along with 2 confirmed cases.

Conclusion: The alliances with other sectors can contribute to increasing case detection and bettering the quality of life for those affected by TB.

Making the case: TIME and One Health modelling the epidemic and the impact of interventions

M Lalli,¹ R Houben,¹ A Gebhard,² B H Nguyen,³ N V Nhung³ ¹London School of Hygiene & Tropical Medicine, London, UK; ²KNCV Tuberculosis Foundation, The Hague, Netherlands; ³National Tuberculosis Control Programme, Hanoi, Viet Nam.

Mathematical modelling is increasingly being used in the policy development cycle to generate evidence that can inform policy decisions. Modelling provides a rational framework in which assumptions can be made explicit and combined with data, which can be used to support an Investment Case for national and international funders. However, mathematical models are often not accessible for policy makers in low- and middle-income countries due to the complexity and required expertise. The TIME modelling suite was developed by The London School of Hygiene & Tropical Medicine in partnership with Avenir Health as a user-friendly modelling tool that can be used in-country. TIME works in conjunction with One Health, a costing and financing tool for strategic health planning. TIME and OneHealth have been used in Viet Nam to inform policy discussions and the development of the Concept Note to the Global Fund to Fight AIDS, Tuberculosis and Malaria. Through discussions with the Viet Nam National TB Control Programme, KNCV and LSHTM, local epidemiological and costing data were collected and used to populate the TIME and OneHealth models. The models were then used to generate projections of the TB epidemic and associated costs, with a focus on the potential impact of new MDR-TB policies. We will present the methods and results of this process, highlight achievements and lessons learned.

This work was initiated by the KNCV Tuberculosis Foundation and funded by WHO.

29. Pneumonia in children and adults beyond 2015

Pneumonia in adults in resource-limited settings: an update

C Feldman Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa.

A number of challenges exist with regard to the diagnosis and management of community-acquired pneumonia (CAP) in adults in resource-limited settings, not least of which are a lack of adequate local data on which to base important clinical decisions. Appropriate treatment recommendations and guidelines are therefore not usually available in these settings and patient management is often not standardized. In resource limited regions, human immunodeficiency virus (HIV) infections

and tuberculosis tend to be more common, so that CAP occurring in these patients is a more complex clinical problem, with a broader spectrum of possible pathogens, including unusual and/or opportunistic pathogens. There also tends to be a higher mortality, particularly in severely ill cases, and especially among those with advanced immunocompromise. Early diagnosis, assessment of disease severity and institution of appropriate empiric antibiotic therapy are all important means of decreasing the mortality from CAP; unfortunately each of these face potential challenges in resource-limited regions. With regard to likely microbial aetiology, a full range of diagnostic tests is often not available. While severity of illness scoring systems have been thoroughly studied in well-resourced areas, few have been validated in resource-limited settings. Furthermore a broad range of antibiotics are often not available in resource-limited situations. In contrast, studies have clearly indicated that collection of local epidemiological data and the development of locally appropriate guidelines based on the available information can go a long way to improving the outcome from CAP in resource-limited settings.

HIV-related pneumonia: towards elimination beyond 2015

M Kelly ¹Department of General Pediatrics, Duke University Medical Center, Durham, NC, USA.

More than 150 million episodes of pneumonia occur each year among children. Most child deaths from pneumonia occur in sub-Saharan Africa and South-East Asia. In these regions, HIV remains a major obstacle to reducing pneumonia-related mortality in children. Pneumonia is the leading cause of death among HIV-infected children, and the aetiologies and treatment outcomes in these children differ from HIV-negative children. HIV-infected children have a higher incidence of bacterial pneumonia, particularly caused by *Streptococcus pneumoniae*, and are at risk for pneumonia caused by the opportunistic pathogens *Pneumocystis jirovecii* and cytomegalovirus. HIV-infected children with pneumonia also have worse short-term outcomes and a higher case-fatality than HIV-negative children. In some highly endemic countries, the incorporation of antiretroviral therapy into antenatal services has markedly reduced mother-to-child HIV transmission and, in turn, led to rising numbers of infants who are exposed to HIV in utero but do not acquire the virus. Despite the absence of HIV infection, HIV-exposed, uninfected children have immune abnormalities and are also at higher risk of pneumonia and death during early childhood. The presenter will discuss the current global burden and diagnostic and treatment strategies for pneumonia among HIV-infected children as well as new data on the aetiologies and outcomes of pneumonia among HIV-exposed, uninfected children. Finally, strategies aimed at eliminating HIV-related pneumonia beyond 2015 will be reviewed, including the prevention or early identification of infant HIV infection, cotrimoxazole prophylaxis, and vaccination against respiratory pathogens.

30. Eliminating the burden of TB in indigenous populations

Latin America region disaggregates TB data on indigenous populations: progress in Mexico and Colombia

M Del Granado,¹ S Guessoum,¹ S Del Pino¹

¹Communicable Disease and Health Analysis Department; Gender and Life Course Department, Pan American Health Organization, Washington, DC, USA.

Despite progress in terms of economic and social development, Latin America continues to be one of the most inequitable and unequal regions in the world. The indigenous peoples of Latin America continue to face discrimination and are left to live in poverty. In Latin America there are 826 different indigenous groups with a total population of 45 million. The health conditions of the indigenous population indicate high levels of morbidity and mortality with regards to diseases of inequality such as tuberculosis (TB). TB remains a serious public health problem in Latin America. In 2013, WHO estimated that there were 270 600 new TB cases and 16 080 TB deaths. The Latin American countries reported 208 400 new TB cases (77% of estimated) for the same year. This specific analysis was possible only in Brazil, Colombia, Mexico and Venezuela. These countries possess TB information systems with nominal records, as well as the inclusion of the variable of ethnicity. The analysis was done for 2010-2014. By 2010, Brazil's indigenous population represented 0.5% of the total population and 1% of new TB cases with RR of 2.3; in Colombia 7% of all TB cases in the country are concentrated in 3.4% in the indigenous population with RR of 2; the TB incidence in Mexico in indigenous is lower than the national incidence with a RR of less than 1. In Venezuela the analysis was carried out for 2010 to 2014, during which we observed a decrease of the TB incidence in the country by 1.1% per year and 15.7% per year for the indigenous population. This analysis was limited, however by the lack of population projections of indigenous and the bias linked to their self-identification. This is possibly attributed to the double stigma of being identified as indigenous and a TB patient.

Explaining trends in TB rates in North American indigenous populations

K Dehghani,^{1,7} E Robinson,^{1,7} B Soborg,² J Picard,³ G Alvarez,⁴ M Cooper,⁵ R Long,⁶ Z Lan⁷ ¹Public Health Department, Cree Board of Health & Social Service of James Bay, Montreal, QC, Canada; ²Statens Serum Institut, Copenhagen, Denmark; ³Public Health Department, Nunavik Regional Board of Health & Social Services, Kuujuaq, QC, ⁴Divisions of Respiriology & Infectious Diseases, University of Ottawa, Ottawa, ON, Canada; ⁵Department of Health & Social Services, Government of Alaska, Anchorage, AK, USA; ⁶Department of Medicine, University of Alberta, Edmonton, AL, ⁷McGill University, Montreal, QC, Canada.

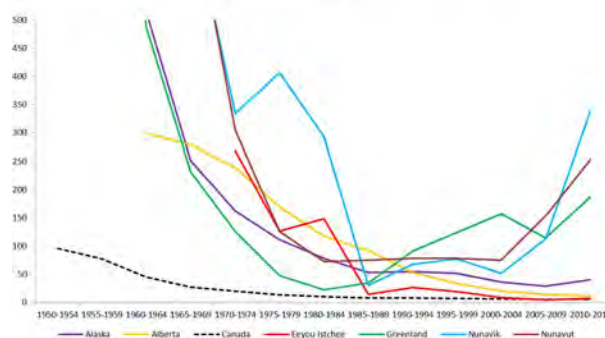
Introduction: The continued high incidence of TB in indigenous populations of North America and Greenland

represents a major public health challenge. It is unclear whether this should be addressed by intensifying TB control and prevention interventions, or by addressing the underlying social and economic disadvantages faced by these indigenous populations.

Methods: This ecological study examined the trends of tuberculosis notification rates from 1960 to 2014 in indigenous populations in Nunavut, Nunavik, Eeyou Istchee (Cree QC), Alberta, Alaska, and Greenland. The association of these trends with major historical landmarks, mass TB control and prevention strategies (mass radiographic screening, INH treatment and BCG vaccination of infants) other major health indicators (e.g. life expectancy) was examined. Furthermore, the trends of other health (e.g. diabetes), health system (e.g. health budget), lifestyle (e.g. smoking) and socioeconomic (e.g. crowded housing) indicators were examined from 1980's on, as these indicators became more available. The TB and other health and socioeconomic trends in these years were compared within and between these populations, and with the Canadian general population. This study used population data already in the public domain. The data collection included search of epidemiologic sources (for example, census and surveillance data), systematic search of scientific and medical literature (for example through PubMed, and Emb-Base), as well as publicly available grey or non-indexed literature (such as regional public health reports and conference proceedings). Regression analysis was used to estimate the change in slope of notification trends associated with changes in social and economic indicators as well as changes in TB control activities.

Results: All indigenous populations had very high TB notification rates in the 1950s and 1960s, which declined dramatically to a nadir between 1985 to 1995. In three Inuit populations - in Nunavut, Nunavik, and Greenland, there has been a substantial resurgence since 1995. Possible reasons for this parallel resurgence, not seen in the other three indigenous populations analyzed, will be presented.

TB notification rate (per 100,000 population) in 6 Indigenous Populations of North America (compared to the Canadian general population) 1960 to 2014



31. High burden, neglected patients: addressing the intersection of tuberculosis and mental disorders

Understanding and addressing the link between depression and TB treatment

A Pasha,¹ O Qureshi,¹ S Khowaja,¹ Z Hasnain,¹ N Baig-ansari,¹ A Khan¹ ¹Interactive Research and Development, Karachi, Pakistan.

Background: This study has added to the dearth of existing literature on the relationship between a TB patient's mental health and their treatment. The study aimed to measure the pattern of depression and anxiety in TB patients during the course of their treatment and to understand whether depression and anxiety increased, decreased or stayed constant over the course of treatment.

Design/Methods: This randomized, cross-sectional study was conducted at the TB clinic at Indus Hospital in Karachi. The treatment period for CAT 1 TB patients (6 months) was divided into five stages: Stage 1: Pre-diagnosis (before test results were attained); Stage 2: Month 0 (i.e. day of enrollment/first day of TB treatment); Stage 3: Month 2 of treatment; Stage 4: Month 4 of treatment and Stage 5: Month 6 of treatment. Fifty patients from each stage were screened using the Aga Khan University Anxiety and Depression Scale (AKUADS), resulting in a total sample size of 250 patients. All TB patients who screened positive for depression and/or anxiety were offered free mental health counseling immediately following their screening as well as on-going weekly sessions, as required.

Results: Our results show that 48% of patients in Stage 1 screened positive for depression and anxiety, 52% in Stage 2, 30% in Stage 3, 20% in Stage 4 and 24% in Stage 5. In other words, the prevalence of depression and anxiety in the pre-diagnosis and earlier stages of TB treatment are significantly higher than those in later stages. In all 5 stages, females were more likely to screen positive for depression and anxiety, particularly in Stage 2, with 76% of females screening positive for depression and anxiety as compared to only 28% of males.

Conclusion: Through this study, the impact of TB treatment on mental health and vice versa was explored, adding depth to the implications of possible interventions that can be developed to target the maladaptive effects and outcomes of this relationship. The interventions that can be developed from these results have the potential of strengthening mental health coping strategies for a TB patient's personal and environmental stressors during the length of the treatment. We hope the results from this study are utilized for the positive development and implementation of psychosocial support interventions that will improve the mental health of TB patients, and that will ultimately increase adherence to treatment and improve TB treatment outcomes.

Depression and other mental illnesses: silent drivers of the TB epidemic

S Annika,¹ M Wainberg,¹ D Boccia,² A Karpati³

¹Columbia University, New York, NY, USA; ²London School of Hygiene & Tropical Medicine, London, UK; ³International Union Against Tuberculosis and Lung Disease, North America Office, New York, NY, USA.

TB has long been considered as much a social as biological disease; the same socioeconomic conditions that increase risk for exposure contribute to both disease reactivation and poor treatment outcomes, posing a significant challenge to global TB control. Mental illnesses such as depression, substance addiction, and severe mental disorders, are also strongly associated with poverty, and have been linked to all negative TB outcomes including increased morbidity, mortality, drug-resistance, and community transmission. As with poverty, there may be a bi-directional association between TB and mental disorders due to inflammatory processes, psychiatric side-effects, and social stigma, which may partially mediate poor TB outcomes. Treating comorbid mental disorders may help to interrupt the vicious cycle of poverty, mental illness, and TB by increasing functional status and enhancing health behaviors that favor positive TB outcomes. This conceptual framework offers new insights into the complex interaction between social, psychological, and biological factors that challenge global TB control, with significant policy, research, and clinical implications.

Sustainability of motivational counseling: Integrated Management of Physician-delivered Alcohol Care for TB patients (IMPACT) trial, Tomsk, Russia

V Livchits,¹ A Solovyeva,¹ S Shin² ¹Department of TB Programs in Russia, Partners in Health, Boston, MA, ²Project COPE, Partners in Health, Albuquerque, New Mexico, USA.

Objective: To perform an assessment identifying the sustainability of brief counseling intervention (BCI) for excessive alcohol use among tuberculosis patients within the Tomsk TB service after the completion of the RCT 'Integrated Management of Physician-delivered Alcohol Care for Tuberculosis Patients' (IMPACT) research phase.

Methods: We conducted audio-taped individual interviews using semi-structured questionnaires after obtaining verbal informed consent with four TB practitioners from Tomsk TB Services out of six who had participated in the RCT. Interviews were transcribed, coded with a standardized framework, and analyzed to identify emergent domains. We used domain analysis to describe the TB doctors' perceptions of the multi-level factors that influence BCI practice in post-RCT phase and illustrate current situation in providing care to TB patients with alcohol use disorders (AUD).

Results: The study found that all participants discontinued BCI at some point and the motivational interview (MI) skills were not sustained after the completion of the research. TB doctors were unanimous in describing how

difficult it was to maintain alcohol interventions since the completion of the RCT working with TB patients with AUDs and to ensure compliance with the intervention. Although the doctors considered the doctor-patient relationship strong enough to sustain targeting of alcohol use, they often failed to follow up on an initial patient AUD assessment. They identified key barriers providing BCI systematically, including: high workload, low staff motivation, lack of booster trainings, and lack of interest from the administration. Doctors' suggestions for strategies that could address these barriers include: assign a counseling coordinator for: setting up each patient's management map at the hospital entry point, monitoring accomplishments, and coaching new medical staff; establish recognition and incentives for good counseling practices; provide intensive booster series of trainings.

Discussion: The improvement in the MI skills achieved during the research period is ceased after the research is phased out. Hence, the patients are barred from the beneficial effect of the intervention. Though the TB doctors believe that BCI is an effective and convenient strategy to work with TB patients with ADU, the intervention could not be continued, as it has not been incorporated in the formal standard of care.

32. Does MPOWER empower women?

Why women should be targeted for tobacco control

M Aghi ¹Healis Sekhsaria Institute for Public Health, New Delhi, India.

Background: The WHO estimates 80 000–100 000 people initiate tobacco use on daily basis; a significant number among them are females. In India, the increasing trend of tobacco use among females is indeed being seen. A secondary analysis of the Global Adult Tobacco Survey (GATS, India 2009–2010) data reported initiation of tobacco use among males and females at age of 12 years. More females (5%) started smoking at age 12 than men (3%) at the same age. Twelve percent of females started using smokeless tobacco products at age of 12 years, as opposed to 4% of males. Also, data shows that 44% females start dual tobacco use at same age compared to 32% of males. Additionally, on average, an Indian woman starts to smoke at 17.5 earlier than her male counterpart. A recent journal article shows tobacco prevalence among Indian women doubled during the period 1995 to 2009 from 10 to 20%. Smokeless tobacco use has also increased over time. This significant rise in tobacco use is to a great extent due to the relentless and unchecked work of the tobacco industry whose sole objective is making money. This is happening despite the Indian tobacco control legislation, which has provisions for smoke-free public places, bans on tobacco advertising, and prohibition on sale to minors. Women leaders in tobacco control have traced this worrying trend to the fact that tobacco control policy makers have not paid

sufficient attention to the unique problems of girls and women.

Conclusion: FCTC could be a critical tool for achieving the goal of reducing tobacco use among women, provided it keeps a clear commitment to gender with a focus on women's and girls' specific issues and makes it a basis for action in the 21st century.

What gender-specific research is needed to inform and evaluate the elements of MPOWER?

A Amos Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK.

Global female tobacco use is increasingly complex, involving diverse products and factors including tobacco marketing, globalisation, urbanisation and changes in women's social and economic status. In high income countries (HICs) female smoking is declining but increasingly concentrated among disadvantaged women. In low and middle income countries (LMICs) the pattern is more complex; in several regions the gap between girls' and boys' smoking is narrowing. The past twenty-five years have seen numerous calls for action on women and tobacco, and for considering the impact of tobacco on women's health and economic well-being. However, tobacco control research, policy and programmes have remained largely gender blind. There has been little recognition of the importance of understanding the context and challenges of girls' and women's smoking, their exposure to secondhand smoke, and the increase in women's smoking in LMICs. Thus many opportunities for knowledge generation and effective responses remain lost or overlooked. This presentation will consider what is meant by gender-specific research and why such research is needed to inform both the development and evaluation of the different elements of MPOWER. It will argue that tobacco control strategies aimed at addressing the female smoking epidemic need to be grounded in a multi-faceted understanding of women's smoking, in order to create a more robust research base for developing interventions for girls and women. This will help animate the WHO-FCTC's concern for gender specificity and women's leadership, and reduce the impact of tobacco on women.

Trends in global tobacco prevalence and use among women

J Tonsing,¹ A Pandey¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India.

Background: Globally, about 40% of men smoke compared with nearly 9% of women. However, the epidemic of tobacco use among women is increasing and there is growing concern among policy makers with respect to alarming smoking prevalence among women. The WHO Framework Convention on Tobacco Control has emphasized the need for gender specific tobacco control strategies in their tobacco control programs.

About 250 million women in the world are daily smokers. In developed countries 22 percent and in developing countries 9 percent of women smoke tobacco. Of the more than 5 million people who die every year from tobacco use, approximately 1.5 million are women. Most (75%) of these women live in low- and middle-income countries.

Methodology: Using secondary data available in public domain including survey reports, publications and peer reviewed papers trend among global tobacco prevalence and use among women has been analysed.

Results: Cigarette smoking among women is declining in many developed countries, notably in Australia, Canada, UK and USA. But this trend is not similar across all developed countries or in the developing countries. In several southern, central and eastern European countries cigarette smoking is either still increasing among women or has not shown any decline. In India female smoking has increased more than double (1.4 – 2.9%) during the period 2005–2009. Further survey of smoking trends in youths showed that in half of the 151 countries surveyed, similar numbers of girls and boys smoked. Evidence suggests that most of these girls and boys will continue to smoke into adulthood. Unless urgent action is taken, tobacco use could kill up to 8 million people every year by 2030, of which 2.5 million would be women.

Recommendation: There is an urgent need to institute gender based tobacco control policies to stop the rise in women's smoking rates. Tobacco prevention and cessation programmes should be integrated into maternal, child and reproductive health services.

33. Modelling to support TB control policy in the era of the End TB Strategy

TIME TB Model: a new publicly available TB model to support country-level TB control policy

R Houben,¹ D Pedrazzoli,¹ M Lalli,¹ R White,¹ M Hamilton,² C Pretorius² ¹London School of Hygiene & Tropical Medicine, London, UK; ²Avenir Health, Glastonbury, CT, USA.

Mathematical modelling can generate key inputs into developing rational TB policy decisions on the global, country or sub-national level. In addition, by providing a logical framework that brings together stakeholders (NTP, funder, community representatives, research community), the available data and necessary assumptions, modelling can improve communication and shared understanding of the local epidemiological situation. Through these discussions, gaps in data can be highlighted, driving local data collection and operational research. The TIME modelling suite was developed to provide this framework and support decision making at the local level. In addition, it has a user-friendly interface which allows for capacity building and increased local ownership of the model and result. TIME has been used as part of Global Fund applications for a number of

countries, and is also part of a number of long-term collaborations with countries, illustrating the value of TIME and modelling throughout the grant application and implementation cycle. The presentation will highlight the structure of the TIME models, the importance of data to inform the model, and illustrate the use of TIME through a number of case-studies.

Experience using models to support TB control policies in Viet Nam

R White,¹ M Lalli,¹ R Houben,¹ A Gebhard,² H T T Thuy,³ N V Nhung,³ B H Nguyen³ ¹London School of Hygiene & Tropical Medicine, London, UK; ²KNCV Tuberculosis Foundation, The Hague, Netherlands; ³National Tuberculosis Control Programme, Hanoi, Viet Nam.

Previously, the Viet Nam National TB control programme (VN NTP) set targets for the next years based on the historical case notification data and the amount of budget used in previous years only. Ambitious targets were needed to attract national and international funders. In order to develop a more comprehensive strategic plan to mobilize funding and achieve the set goals, Viet Nam needed a scientific sound assessment and projection for the TB control programme objectives, with clearly identified and justified activities. Without a model to create projection of TB epidemic in Viet Nam, it was not possible to anticipate what activities Viet Nam could achieve the set goal to decrease the TB prevalence to 131 per 100 000 population by 2020. In 2014, the TIME Impact and One Health tools were applied to inform the VN NTP strategy and funding applications, with support from KNCV. Epidemiological and costing data of the VN NTP were used to populate the TIME Impact and OneHealth models, generate projections of the TB epidemic and associated costs for the future plans. Two areas were focussed on: case finding and new MDR-TB policies. The baseline projections indicated that after a continuous decline in trend between 1990-2010, the TB burden was due to start increasing after 2020 if NTP activity levels remained stable. Furthermore, the model showed that, even with strongly increased efforts, notifications will continue to decline due to the background decrease in prevalence, and pushing with additional case finding is key to continue decline of TB burden. Accordingly, the VN NTP to increase case finding to find more TB cases in community with the set objective to increase case detection rate by 8% by 2017, to continue the ongoing decline in TB incidence, mortality and prevalence by 2%, 4% and 4% respectively. In addition, a scale-up of Drug Sensitivity testing and introduction of a new 9 month second line drug regimen could become cost-saving. These results have been used to develop the Concept Note to the Global Fund to Fight AIDS, Tuberculosis and Malaria. The Concept Note was highly appreciated and approved by the funders to provide additional support beyond the country allocation to scale up the programmatic management of drug resistant tuberculosis (PMDT).

Modelling to explore the cost-effectiveness and resource implications of reaching the post-2015 targets

N Menzies,¹ G Gomez,² A Vassall³ ¹Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ²Amsterdam Institute for Global Health and Development, University of Amsterdam, Amsterdam, Netherlands; ³Department of Global Health, London School of Hygiene & Tropical Medicine, London, UK.

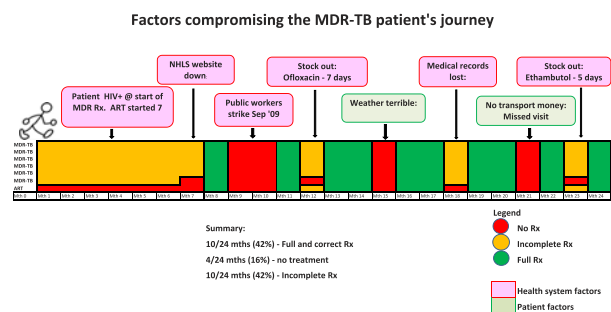
The post-2015 End TB Strategy formalizes goals for aggressive TB control. One outcome anticipated by the strategy is reduction in global TB incidence and prevalence by 50% and 75% respectively by 2025. A study organized by the TB Modelling and Analysis Consortium (TB-MAC) tested the feasibility of these goals when applied to three major high-burden countries – China, India, and South Africa. This study was implemented using computer models of TB epidemiology to project long-term policy outcomes. To address concerns that individual models may provide biased results we invited participation from multiple independent research groups. We developed cost projections to provide information on resource implications and cost-effectiveness. Eleven research groups participated in the study. We examined six discrete intervention approaches, assuming interventions would be scaled up to high (but feasible) coverage by 2025. Intervention scenarios were developed by country stakeholders, based on current technology. Implementation differed by country, considering local policy preferences / capacity. The costing approach, using country-specific cost models, was designed to accommodate differing capabilities of participating models and estimate results for multiple perspectives, using a synthesis of empirical cost data. Health impact (DALYs averted) and resource implications (total costs) were estimated for 2015-2035. We estimated resource needs, over time and by payer, as well as the cost-effectiveness of competing policy scenarios. Policies were compared against each other and against a 'status quo' policy that held TB control activities at current levels. Compared to the status quo, most interventions appeared cost-effective when evaluated against conventional willingness-to-pay thresholds. However, many interventions required substantially increased budgets, and the opportunity cost of increased spending (or reallocation within the TB budget) is likely higher than implied by conventional thresholds. Incremental costs were generally front-loaded, with rapid cost increases during scale-up. In contrast incremental health gains accumulated more slowly, and cost-savings due to interruption of transmission followed a similar pattern. Interventions had important implications for financial protection: while lower TB burden benefits households over the long-term, results suggested an initial increase in costs borne by TB patients and households as interventions were scaled up.

34. MDR-TB: a complex disease requiring a comprehensive health system response

A typical patient's journey: how the health system fails the patient

M Loveday,¹ A Voce,² N Padayatchi,³ J Brust,⁴ K Wallengren⁵ Health Systems Research Unit, South African Medical Research Council, Cape Town, ²Department of Public Health, University of KwaZulu-Natal, Durban, ³Department of CAPRISA, University of KwaZulu-Natal, Durban, South Africa; ⁴Department of Medicine, Montefiore Medical Center & Albert Einstein College of Medicine, Bronx, NY, USA; ⁵TB and HIV Investigative Network (Think), Durban, South Africa..

We describe hospital performance from the patient perspective by the use of a graphic which visually represents a patient's treatment journey. The graphic was used to report study findings to study sites and as a catalyst for a quality improvement process.



Patient and health care worker experiences of MDR-TB management

M P Mbiko¹ ¹Department of Health, Bizana, South Africa.

Although there has been an attempt to decentralise MDR-TB services by the South African Department of Health, access to services and the costs incurred in accessing services remain challenges for MDR-TB patients. And, even if a patient gets to the hospital, one of the many different components needed to provide an optimal service may be unavailable, compromising treatment. We share patient and healthcare worker experiences of MDR-TB services.

35. Controversies and critical issues in clinical trial design for TB

What are the meaningful endpoints in phase 2 and phase 3 trials?

S Dorman¹ ¹Johns Hopkins University School of Medicine, Baltimore, MD, USA.

The approaches used in recent years to assess new tuberculosis drug regimens are lengthy, inefficient, and expensive. This talk will set the stage by providing an

overview of commonly-used approaches, including potential strengths and weaknesses as well as gaps in scientific knowledge and implementation that limit progress. This talk will then focus in on Phase 2 and Phase 3 clinical trials and explore strategies that might be helpful in overcoming some of the challenges.

Pragmatic trials and other alternatives to standard RCTs

A Nunn¹ Medical Research Council Clinical Trials Unit, UCL, London, UK.

Late stage clinical trials are increasingly expensive and time consuming. This is particularly true when small differences in efficacy are being compared or non-inferiority trials are designed with relatively small margins of non-inferiority. If we do conduct a large scale trial how relevant are the results? Experience has shown that results in clinical trials may not be readily demonstrated in real life situations. The patient population in a clinical trial is invariably restricted and the settings under which trials are conducted are often far removed from every day experience. Is it possible for our trials to more closely reflect real life conditions? Can we be more efficient in our designs? Do we always need trials? Why not well conducted cohort studies? What are the limitations of alternative study designs? The opportunities and challenges presented by alternative approaches will be discussed.

Building clinical trial capacity in low-resource, high-burden settings

I D Rusen¹ ¹Department of Research, International Union Against Tuberculosis and Lung Disease, North America Office, New York, NY, USA.

High quality, programmatically-relevant research is increasingly recognized as an essential component to guide tuberculosis policy and program decisions in high-burden settings. Clinical trials, in particular, require a specialized site capacity to undertake scientifically sound research. The available sites with existing capacity for clinical trial implementation within the tuberculosis field is limited. As a result, STREAM Clinical Trial partners have worked with sites not previously engaged in MDR-TB clinical trials - or in some cases - any previous clinical trials. Through routine protocol training, additional GCP training and intensive monitoring and support, STREAM trial sites have performed well to date and will serve as a growing and necessary pool of clinical trial sites in low-resource, high-burden settings. Regulatory clinical trials may bring particular challenges in these settings compared to pragmatic clinical trials and require additional capacity building efforts. Attention to all aspects of trial implementation, including the laboratory component, data management and supply procurement have been important features of building clinical trial capacity within the STREAM trial.

Ethical challenges in TB research

J Denholm^{1,2} ¹Victorian Tuberculosis Program, Melbourne, VIC, ²Department of Microbiology and Immunology at the Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, VIC, Australia.

From the very beginning, ethical controversies have abounded in medical research. Likewise, the history of TB research includes a number of examples of ethically problematic episodes. Emerging clinical and public health challenges around TB demand new research and practice innovations, but rapid development can also bring with it unexpected ethical tensions. Rather than simply waiting for ethical problems to arise, the development of new research methodologies should include proactive consideration of potential moral tensions, and monitoring and evaluation of research should be alert for emerging ethical themes.

36. Innovations to improve the TB/HIV patient experience: from diagnosis to treatment

The potential and pitfalls of using Xpert MTB/RIF to detect TB in people living with HIV (PLHIV): what have we learned from the African experience?

M Casenghi,¹ C Jennifer (*check*),¹ H Huerga,² E Fajardo,³ E Goemere³ Access Campaign, Médecins Sans Frontières (MSF), Geneva, Switzerland; ²Department of Epicentre, MSF, Paris, France; Southern Africa Medical Unit, MSF, Cape Town, South Africa.

In 2013, an estimated 1.1 million HIV-positive new tuberculosis (TB) cases were reported globally, and sub-Saharan Africa carries about 78% of this dual epidemic. TB remains the leading cause of death among PLHIV but TB diagnosis is often missed or delayed in this patient population due to limitations of diagnostic tools available in resource limited settings. In December 2010, WHO recommended Xpert MTB/RIF (Xpert) as the initial test for people at risk of HIV-associated TB and MDR-TB. Xpert simultaneously detects TB and resistance to rifampicin and can be placed at intermediary level of laboratory networks. Primarily designed to work on sputum samples, Xpert pooled sensitivity for detection of TB amongst PLHIV and smear negative cases is 79% and 67%, respectively. Clinical trials assessing impact of Xpert used as initial test compared to routine diagnostic algorithms showed that use of this test increased the proportion of bacteriologically confirmed TB cases among people initiated on treatment and reduced the proportion of people with confirmed TB who did not start therapy. Xpert also reduced time to treatment initiation. However, no impact on the number of people initiated on treatment (suggesting that Xpert replaced rather than complemented empirical treatment) and on TB-related mortality was observed. Availability of chest X-Ray and high rate of empirical treatment in

most study settings might have undermined Xpert impact. More significant effect might be observed in settings where initiation of TB treatment on empirical basis is not common practice. In addition, the availability of HIV assays to be performed on GeneXpert platform offers potential to catalyze better integration of HIV and TB services. Despite these advantages, suboptimal sensitivity on smear negative cases and weak performance on extra-pulmonary TB (EPTB) samples remain key Xpert limitations and management of test negative cases is challenging. In conclusion, Xpert offers key advantages for the diagnosis of HIV-associated TB. Increased rates of bacteriological confirmation and upfront testing for drug resistance can facilitate rapid treatment initiation and selection of most effective regimen, with potential to reduce transmission. However, diagnostic tests with improved sensitivity on smear negative cases, better performance on EPTB and suitable for further decentralization are needed in order to further improve diagnosis and timely, effective treatment of TB in PLHIV.

Strengthening specimen referral and transport networks in resource-limited settings: a Nigerian pilot to improve diagnosis of TB in PLHIV

S Useni,¹ M Gidado,¹ J Onazi,¹ S Gande,¹ P Nwadike,¹ S Massaut,² S Kik,² G Akang³ ¹KNCV Nigeria/Challenge TB, Abuja, Nigeria; ²KNCV, The Hague, Netherlands; ³National TBL Program, Abuja, Nigeria.

Background: The use of Xpert MTB/RIF has proven to be effective in rapid diagnosis of *M. tuberculosis* and rifampicin resistance (RR); however the programmatic use, especially among PLHIV, requires specific programmatic/referral arrangements.

Objective: This pilot project aimed to develop a practical model for specimen referral and transportation thereby increasing the number of PLHIV screened, tested for TB and put on treatment.

Methodology: A 20-month project at two sites was implemented in six phases; rapid assessment and site selection; pilot model design; stakeholders' sensitization; pilot implementation; supervision; M&E, data collection, analysis and reporting. A hub and spoke approach was used to link a tertiary or secondary facility with an Xpert machine to at least 10 peripheral facilities. A specimen transportation system was supported to ensure sputum specimens were brought twice a week to the Xpert machine and hardcopies of the results returned to the referring facility.

Results: At baseline, only 9 PLHIVs were tested with Xpert and in pilot period 782. There was a 1.9 fold increase of notified bacteriological confirmed TB cases; at baseline 180 cases compared to pilot of 347 cases. In the pilot period 1232 TB cases were registered for treatment (including 497 PLHIV), 824 of these were bacteriologically confirmed cases (including 354 PLHIV). Overall, 60% (1066 out of 2665) of all sputum

specimens that were tested with Xpert were from referral sites.

Conclusion: A well-coordinated sputum transportation system to Xpert testing sites minimizes the movement of patients and increases access to diagnostic and care services; not only for TB but also HIV.

Are TB-HIV 'one-stop shops' effective for rapid TB diagnosis and treatment of PLHIV?

R Ncube,¹ C Zishiri,¹ M Nqobile,¹ K Charambira,¹ R Dlodlo,² S Hove,³ P Shiri,⁴ C Sandy⁴ ¹Department of TB-HIV, International Union Against Tuberculosis and Lung Disease, Harare, Zimbabwe; ²Department of TB-HIV, International Union Against Tuberculosis and Lung Disease, Paris, France; ³Health Department, Bulawayo City Council, Bulawayo, ⁴Department of AIDS and TB, Ministry of Health and Child Care, Harare, Zimbabwe.

Background: Tuberculosis (TB) remains a disease of public health importance in Zimbabwe. Despite gains in curtailing the scourge, the country still ranks among the top 22 high burdened countries. Estimated incidence in 2013 was 552 per 100 000, HIV predominantly driving the epidemic with co-infection rates as high as 69%. Integrated TB-HIV patient care has in the past remained constrained by centralized TB diagnostic services, with presumed TB patients accessing services from district and provincial referral facilities. In addition, provision of anti-retroviral services has predominantly been doctor led.

Intervention: In 2007, the Ministry of Health and Child Care, with funding from European Union and technical support from The Union piloted a nurse-led decentralized 'One Stop Shop' TB-HIV care model in three high volume urban clinics in Zimbabwe. Between 2012 and 2014, with additional funding from the United States Agency for International Development, this model was rolled out to 23 additional facilities in 17 urban communities. The scope of support included minor refurbishments to improve patient flow and infection control; training and post training mentorship of health care workers on Provider Initiated HIV Testing and counselling, co-trimoxazole preventive therapy; anti-retroviral treatment (ART) initiation and follow up for co-infected patients. A dedicated specimen transport system was established through a network of motorcycle transporting sputum and other HIV related specimens. All supported sites were equipped with Point of Care CD4 machines to improve timely treatment monitoring and recording and reporting were strengthened.

Results: There was a sustained increase in TB-HIV service uptake indicators across all sites supported. Notably, ART uptake among co-infected TB patients increased by 14% point from 70% in the January-March 2013 cohort to 84% in July-September 2014. Turn-around time for TB diagnostic results plummeted from more than a week before the support to the current 24-48 hours.

Conclusions: A Nurse-led 'One Stop Shop' TB-HIV diagnostic and treatment service is feasible in a resource limited primary health care setting. The country has since

mobilized additional funding for decentralization beyond the urban primary care setting.

Automated reporting of TB diagnostic results: progress, challenges and country experiences

A Habib ¹Interactive Health Solutions, Karachi, Pakistan.

Background: A key factor in successful treatment of TB is the early start of treatment. Not only does early treatment start improve chances of treatment success, but in the case of pulmonary TB, it also means that the index patient is likely to infect fewer people around them. Rapid diagnostic devices like the GeneXpert have reduced the time to diagnosis, but given that the results seen by a lab technician can still take a long time to be seen by someone who can take action; this rapid diagnosis has not always been accompanied by a rapid start of treatment

Intervention: Software to automatically transport GeneXpert results was developed as three independent open source initiatives. These applications were able to receive results from the GeneXpert as soon as the test was completed and transmit them to a central server over the Internet or SMS. They were also integrated with commonly used medical record systems to create a linkage to care. Alerts could be generated from the server and patients, caregivers, and program staff could be notified about test completion and the results. Additionally, the applications also captured cartridge information and error information allowing inventory and best practices to be remotely monitored.

Results: These applications have been deployed in more than 20 countries with several others in preparatory phases. Over the past three years these systems have been used to collect some 400 000 results. While a systematic impact assessment has not been conducted to date, those using the systems have claimed that their access to data and the ability to monitor all of the machines centrally and remotely are a huge advantage for TB programs. The independent developers of the three systems have converged onto a single open source platform to make it simpler for countries to deploy these systems. Other similar systems have also been developed by commercial vendors.

Conclusion: Systems to automatically report GeneXpert results have been widely deployed and generally well-received. These systems speed the rate at which test results are made available thereby allowing treatment to be started faster and allow remote monitoring of a country's network of GeneXpert machines.

37. Inhaled therapies for tuberculosis

Ways and means for inhaled drug delivery in TB

S Giovagnoli,¹ A Schoubben,¹ M Ricci¹ ¹Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy.

Inhalation is unarguably the best way to achieve local drug accumulation in the lungs. Such strategy is suitable

to treat lung infections, especially TB, being systemic TB therapy affected by high dosages and lengthy treatments with high risks of toxic effects and low patient adherence. Here we discuss some of the strategies to achieve anti-TB drug (ATD) pulmonary delivery useful for vaccination as well with a focus on their potential impact on TB therapy and market. Increased evidences support inhalation as the only way to obtain high lung concentrations of multiple ATD at the desired pharmacological ratio, otherwise impossible to achieve through systemic administration, with limited increased costs compared to the oral route, in light even of the availability of cheap disposable devices. Based on the evidence that the search for novel and more potent, but often more toxic, ATD cannot be the only solution to the TB problem, we believe that a shift in the approaches to TB treatment is needed and that such change relies on the development of effective inhalation protocols. In particular, we propose the hydrophobic strategy based on drug modification through ion pairing and complexation to improve inhalable drug penetration into tissues and intracellular activity. A few examples include metal complexes and ion pairs of second line peptide and aminoglycoside ATD (capreomycin, amikacin, kanamycin) obtained with palladium, dehydrocholic acid (DCA) and oleic acid. Moreover, vaccines and the microbiome strategy aimed at enhancing prevention and control of the infection and to limit the progression of the disease show some potential when delivered through inhalation in animal models. In addition, a few clinical trials are exploring safety and efficacy of such procedures. The proposed approaches provide multiple advantages. On the one side, the physical modification of the drugs is intrinsically advantageous compared to chemical synthesis of new compounds as it may grant shorter bench-to-market time and repurposing of old actives. On the other side, delivery of microbiomes and vaccines through inhalation can grant better control of TB infections and resistance development. The technology required to develop TB inhalation therapy is already available and the higher cost of production compared to oral systems is balanced by higher efficacy. A global and concerted effort is however required to speed up innovation in this field.

Clinical, epidemiological and patient compliance factors affecting deployment of inhaled therapies for TB in the field

B Fourie,¹ R Netter² ¹University of Pretoria, Pretoria, South Africa; ²Northwestern University, Chicago, IL, USA.

Background: Patient and system delays in low income countries are important determinants of success in TB control programmes. Curing patients after diagnosis is subject to rigid compliance with a treatment regimen that may last as long as 24 months. Simplification of regimens and treatment-shortening are high priorities. Inhaled therapies offer major opportunities for lower dose adjunctive therapy to existing regimens. Recent research provides strong evidence for enhanced efficacy at lower

dose of several anti-TB agents formulated in dry powder form. Our aim in this study was to gain some degree of understanding as to whether inhaled drugs delivered by a simple breath-activated inhaler instead of injections would be favoured by health care workers overseeing treatment of MDR-TB patients.

Methods: We developed and applied a short structured questionnaire to 48 health care service providers (doctors, nurses, or treatment supporters) who had current experience in managing TB patients and were familiar with administering injections to patients with multi-drug resistant TB in four South African provincial hospitals/clinics. This opinion-based survey focused largely on the provider's experience with administering injections for TB treatment. We introduced to them, in a descriptive manner using a Plastiap RS01 monodose dry powder inhaler, the concept of inhalation therapy. The questionnaire also solicited opinions about ease of use, product acceptability, predictors of obstacles to adoption, and suggestions for product improvement.

Results: Of the population of service providers surveyed, almost all respondents (92%) felt patients would be comfortable using the inhaler and most (84%) found the inhaler easy to use. Most of the respondents (88%) indicated that they would probably use inhaled therapies for TB in patients if it was available. There were some concerns about implementing the inhaler, with 22% finding its durability on repeated use somewhat questionable and 26% querying whether the device might pose a risk for cross-infection or recurrent self-infection if used repeatedly.

Conclusion: Dry powder inhaled agents delivered by simple devices, instead of injectable agents, might be feasible and acceptable to clinical staff managing TB patients. The educational gap that distinguishes the array of patients normally requiring injectable anti-TB agents in low-resource settings would need to be taken into consideration when such technologies are introduced.

38. Affordable solutions to indoor air pollution for one-third of the world's population

Indoor air pollution and the health of children under five in Bangladesh

M Khalequzzaman,¹ M Kamijima,² K Sakai,³ B A Hoque,⁴ N A Chowdhury,⁵ T Nakajima⁶ ¹Department of Public Health and Informatics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; ²Department of Occupational and Environmental Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, ³Department of Environmental Health, Nagoya City Public Health Research Institute, Nagoya, Japan; ⁴Environment and Population Research Centre, Dhaka, ; ⁵DFID, British High Commission, Dhaka, Bangladesh; ⁶Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Indoor air pollution levels are reported to be higher with biomass fuel, and a number of respiratory diseases in

children are associated with pollution from burning such fuel. For their domestic source of energy, 92% of Bangladesh's people depend on biomass fuel. Indoor air pollution is responsible for an estimated 3.6% of the overall disease burden in the country. About 25% of deaths among children under 5 years old in Bangladesh are associated with acute respiratory tract infection (ARTI). Switching from biomass to fossil fuel is thus encouraged in Bangladesh, as pollution levels are believed to be higher with biomass fuel. However, little is known about the situation in developing countries. In our studies we checked the indoor air concentrations of volatile organic compounds (VOCs), carbon monoxide (CO), carbon dioxide (CO₂), nitrogen dioxide (NO₂), and dust particles. The measured pollution concentrations shows that CO were found to be significantly higher in biomass fuel users, while concentrations of benzene, xylene, toluene, hexane, total VOCs, and NO₂ were significantly higher in the fossil fuel users. Considering the seasonal variation, levels of VOCs such as benzene, toluene, and xylene, were higher in winter than summer. On the other hand, levels of CO, CO₂ were found to be higher in summer than winter. We also checked the geographical distribution of the indoor air pollutants. The pollutant concentrations were higher in urban kitchen than rural ones. The health impacts of the mentioned indoor air pollutants were checked among the children under five years old in Bangladesh but could not attribute the occurrence of respiratory symptoms among children. Other factors may be involved.

39. Taking stock of TB epidemiological assessments: experience, lessons learned and the way forward

The NTP perspective: from recommendation to implementation and policy change

C Widaningrum Sub Directorate of TB Control Program, Ministry of Health Republic of Indonesia, Jakarta, Indonesia.

Background: Indonesia is one of the countries with the highest TB burden in the world. TB burden has been estimated from different sources: surveys, modeling estimates, and notification. Series of activities and discussion were conducted to evaluate TB epidemiological situation in Indonesia and to integrate them into TB control program policies

Methods: Joint External Monitoring Mission (JEMM) was conducted in February, 2013 to assess TB control situation in Indonesia. Assessment on the surveillance system and available data to measure the trend of incidence, prevalence, and mortality was part of the JEMM activities. TB NPS was conducted on 2013-2014. In 2014, National TB Control Program invited WHO technical advisors and National Institute of Health Research and Development (NIHRD) to update TB burden estimates based on NPS results, notification data, and available data on TB mortality from sample registration survey of cause of death. Indonesia was

developing National Strategy for TB Control at the end 2014.

Results: TB incidence, prevalence, and mortality and their trends were estimated in 2013 and updated with the analysis of TB NPS in 2014. TB prevalence, TB incidence, and TB mortality was estimated to be 660, 403, and 42 per 100 000 persons respectively. It was estimated that 1 600 000 TB cases existed in Indonesia in 2013. The updated estimates were much higher than the previous estimates. Gaps on case detection and case notification were identified. The updated estimates were utilized to develop the strategic plans of TB control. As it was higher than previously estimated, it posed important strategic and budget implication. Intensified case finding and TB mandatory notification were put as important strategies. Case based electronic registration was improved. Challenges remains that TB surveillance system has not covered most health facilities which manage TB cases, cause of death reporting was not routinely done, and under notification of TB-HIV, drug resistant TB, pediatrics TB is high.

Conclusion: TB epidemiological assessment in Indonesia is a dynamic process. Recommendations resulted from the assessment were taken into account for policy development. Efforts are needed to close the surveillance gaps so TB burden can be estimated from routine surveillance.

40. Reinforcing research for TB elimination at the country level: experiences from path-finding countries

Developing a national TB research strategy: an example from Kenya

M Muhwa Kenya Association for the Prevention of Tuberculosis and Lung Diseases, Nairobi, Kenya.

Tuberculosis remains a major public health concern in Kenya. Although Kenya has made tremendous progress in its war against TB many challenges remain. These include a persistent inability to find an estimated 15-20% incident cases of TB; delays in TB diagnosis; low treatment success rates in some parts of the country; inadequate uptake of interventions to identify and prevent TB in persons living with HIV and prevention, care and control of drug resistant TB. The solutions for many of these challenges demand the design and implementation of program based operations and implementation research to identify the most affordable, sustainable, effective and efficient approaches. To achieve this end Kenya formed a multi stakeholder national TB research task force in 2008 which was charged with several responsibilities including identifying the TB program's research priorities, guide the development of research proposals, organize forums for dissemination of research findings to all stakeholders and the integration of research findings into routine program activities, support the development of appropriate training programmes for operations research, maintain

an inventory of planned, on- going and completed TB research projects, coordinate research activities to ensure conformity with identified national research priorities and to avoid unnecessary and potentially costly duplicative research efforts and develop and implement a costed strategy for multi -year TB operations research. The task force has organized several meetings in which Kenya's TB research priorities were identified and results of completed research projects disseminated. Efforts have also been made to develop a mentorship program to support young TB researchers to start and complete the research cycle. This presentation will highlight the achievements that have been made so far, the persisting challenges and constraints and the opportunities that could be used to enhance TB research to support the full implementation of the End TB Strategy in Kenya.

Undertaking the full spectrum of research in a TB-endemic country: an example from South Africa

V Mizrahi¹ ¹Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.

South Africa is a TB-endemic country with significant scientific, technological and clinical research capabilities and infrastructure. Working at the interface of the laboratory, the clinic and the community, researchers in South Africa are playing an important role the discovery, development, evaluation and implementation new tools for the diagnosis, prevention and treatment of TB through research that spans the entire spectrum from basic through to clinical, operational, implementation, health services and health systems research. Within this context, the peculiarities of the TB epidemic in South Africa have driven the development of highly specialised research capacity and expertise in the areas of HIV-associated TB, paediatric TB and MDR/XDR-TB. These developments have, in turn, provided a platform for South African researchers to engage in collaborative, interdisciplinary TB research at the national, regional and international level, supported by novel funding instruments. They have also provided a mechanism for using research as a vehicle for training the next generation of scientists, clinicians and public health specialists for the country. In this talk, I will describe the key strengths of the TB research enterprise in South Africa, and use specific examples to illustrate how research is being used to address critical questions in TB control.

41. The Union/CDC Late-Breaker Session on TB

The mortality impact of point-of-care urine lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-infected hospitalised patients: a multi-country randomised controlled trial

J G Peter,¹⁻⁴ L S Zijenah,⁵ D Chanda,^{1,6,7} P Clowes,^{8,9} M Lesosky,¹ C J Lombard,¹⁰ G Kadzirange,¹¹ T Bandason,¹² A Chansa,^{6,7} N Liusha,^{6,7} C Mangu,⁸ B Mtshafya,⁸ H Msila,⁸ B Mtshafya,¹² A Rachow,^{8,9,13} M Hoelscher,^{8,9,13} P Mwaba,⁶ G Theron,^{1,14} K Dheda¹⁻⁴ ¹Lung Infection and Immunity Unit, Division of Pulmonology & UCT Lung Institute, Department of Medicine, University of Cape Town, Cape Town, ²Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, ³University of Cape Town Lung Institute, Cape Town, ⁴Division of Clinical Immunology and Allergology, Department of Medicine, University of Cape Town, Cape Town, South Africa; ⁵University of Zimbabwe College of Health Sciences, Department of Immunology Harare, Zimbabwe; ⁶University Teaching Hospital, Lusaka, ⁷Institute for Medical Research & Training (IMReT), Lusaka, Zambia; ⁸National Institute for Medical Research, Mbeya Medical Research Centre, Mbeya, Tanzania; ⁹Division of Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich, Munich, Germany; ¹⁰Biostatistics Unit, South African Medical Research Council & School of Public Health and Family Medicine, University of Cape Town Cape Town, South Africa; ¹¹University of Zimbabwe College of Health Sciences, Department of Medicine, Harare, ¹²Biomedical Research and Training Institute, Harare, Zimbabwe; ¹³German Centre for Infection Research, Munich, Germany; ¹⁴DST/NRF of Excellence for Biomedical Tuberculosis Research, and MRC Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa. Fax: (+27) 214 047 651. e-mail: keertan.dheda@uct.ac.za

Background: HIV-associated tuberculosis (TB) is difficult to diagnose and results in high mortality. Frequent extra-pulmonary presentation, inability to obtain sputum, and paucibacillary samples limits the usefulness of nucleic acid amplification tests and smear-microscopy. We assessed the diagnostic impact of a urine-based lateral flow point-of-care lipoarabinomannan assay (LAM) on the mortality of TB patients.

Methods: 2659 hospitalised adult HIV-infected patients with TB symptoms from South Africa, Tanzania, Zambia and Zimbabwe (median CD4 count = 86 cells/mm³) were randomly allocated to either routine diagnostics (smear-microscopy, Xpert MTB/RIF, and culture) or routine diagnostics plus adjunctive urine LAM testing. The primary endpoint was all-cause mortality at 8 weeks.

Findings: Urine LAM testing resulted in more patients starting anti-TB treatment (52% versus 47%, $P = 0.024$), a decrease in the median (IQR) days to treatment initiation [0(0-2) versus 1(0-3), $P < 0.001$], and less empiric treatment (48% versus 70%, $P < 0.001$). Overall, patients in the LAM study arm had reduced

mortality [adjusted HR (95%CI) 0.81 (0.69-0.95), $P = 0.009$]. The effect size varied by clinical characteristics with the greatest mortality reduction in those with CD4 ≤ 50 cells/mm³ [adjusted HR (95%CI) 0.68 (0.54-0.85)], sputum scarce or GeneXpert MTB/RIF/ smear negativity [adjusted HR (95%CI) 0.72 (0.55-0.95)], and at the Zambian site [adjusted HR (95%CI) 0.67 (0.49-0.90)] where patients were more likely to have poor prognostic features [stage 4 disease, low weight, haemoglobin and Karnofsky performance status, and high TBscore]. Overall 8 week TB-related morbidity (change in TBscore and Karnofsky Performance Scale) was similar in both arms.

Interpretation: Bedside LAM-guided rapid treatment initiation in hospitalised HIV-infected patients with suspected TB was associated with reduced 8-week mortality. The extent of the mortality benefit is likely to be greatest in those with poor prognostic features or who are rapid sputum test negative/ sputum scarce.

Funding: European Developing Clinical Trials Partnership (EDCTP; TB NEAT), and the South African MRC and NRF. ClinicalTrials.gov number: NCT01770730; <https://clinicaltrials.gov/ct2/show/NCT01770730>

Yield and impact of intensified case finding and isoniazid preventive therapy for tuberculosis among people living with HIV in Viet Nam

T Cowger,¹ L H Thai,¹ B D Duong,² N V Nhung,³ D T Nhan,² C K Thoa,² V T Khanh,⁴ T Thinh,⁵ N H Dung,⁶ N T B Yen,⁶ D V Ngoc,⁵ M McConnell,¹ S Whitehead,¹ E S Pevzner¹

¹US Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Viet Nam Authority for HIV/AIDS Control, Ministry of Health, Hanoi, ³National Lung Hospital, Hanoi, ⁴VAAC-U.S. CDC Co-agreement Project, Ministry of Health, Hanoi, ⁵Ho Chi Minh City Provincial AIDS Committee, Ho Chi Minh, ⁶Pham Ngoc Thach Hospital, Ho Chi Minh, Viet Nam

Introduction: In 2011, Viet Nam piloted an evidence-based algorithm to detect tuberculosis (TB) and provide isoniazid preventive therapy (IPT) among people living with HIV (PLHIV). We assessed the impact of antiretroviral therapy (ART) and IPT on TB incidence, and whether regular screening for TB reduced mortality.

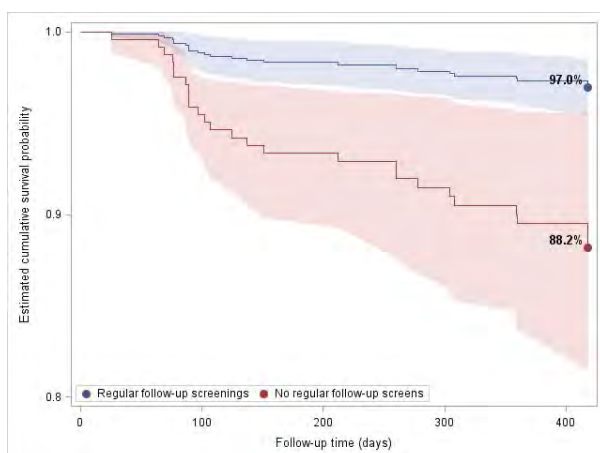
Methods: PLHIV aged >15 years at four HIV outpatient clinics in Viet Nam were screened for any cough, fever, or night sweats for >3 weeks and if positive, received sputum smear examination, chest radiography, and/or liquid culture per the diagnostic algorithm at each clinical encounter within 1 year of follow-up. We recorded timing of screening, ART and IPT uptake, TB diagnoses and deaths. We conducted two multivariable Cox regression analyses with ART and IPT as time-varying covariates and incident TB and death as endpoints.

Results: Of 789 participants enrolled, 64 (8.1%) were diagnosed with TB at enrollment and 36 (4.6%) were

excluded for missing data. Among the remaining 689 participants, TB incidence was 4966/100 000 person-years. TB incidence was 903 vs. 10 331 per 100 000 person-years, respectively, among participants prescribed and not prescribed IPT, adjusted hazard ratio (aHR) 0.13 (0.03–0.50); incidence was 4128/100 000 person-years among participants not yet on ART, aHR 12.1 (2.5–59.0) and 19 550/100 000 person-years among participants on ART <3 months' duration, aHR 16.9 (4.2–68.3) compared to 1256/100 000 person-years among those on ART $\geq$ 3 months. Survival was greater among participants screened regularly for TB (i.e., $\geq$ 1 screening every 4 months) (Figure). The impact of regular screening was greatest after 120 days of follow-up: mortality was 634/100 000 person-years among participants with regular screening versus 9439/100 000 person-years among those without regular screening, aHR: 0.07 (0.01–0.45).

Conclusions: Regular TB screening provided health care workers multiple opportunities to diagnose and treat TB, and likely contributed to reduced mortality among participants in this high TB prevalence population.

Figure Survival for patients with regular screening for TB compared with survival for those without regular screening for TB



A novel socioeconomic intervention improves TB cure and chemoprophylaxis completion in Peruvian shantytowns: a randomized controlled evaluation

T Wingfield,^{1–3} M A Tovar,^{2,4} D Huff,^{2,5} D Boccia,^{2,6} R Montoya,² E Ramos,⁴ S Datta,^{1,3} M J Saunders,^{1,2} J J Lewis,^{2,6} R H Gilman,⁷ C A Evans^{1,2,4}

¹IFHAD Innovation For Health And Development, Infectious Diseases & Immunity and Wellcome Trust Centre for Global Health Research, Imperial College London, UK; ²Innovación Por la Salud Y Desarrollo (IPSXD), Asociación Benéfica PRISMA, Lima, Peru; ³Monsall Infectious Diseases Unit, North Manchester General Hospital, Manchester, UK; ⁴IFHAD Innovation For Health And Development, Universidad Peruana Cayetano Heredia, Lima, Peru; ⁵Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA; ⁶Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; ⁷Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Socioeconomic support is part of the recently ratified post-2015 global End TB Strategy. However, evidence evaluating impact of TB-specific socioeconomic interventions is extremely limited.

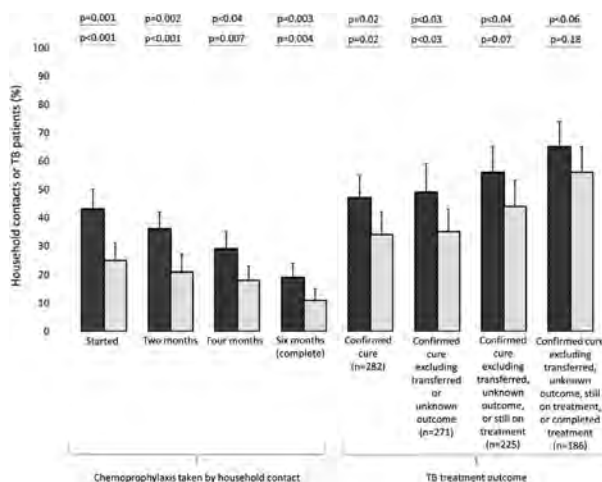
Objective: To evaluate the impact of a socioeconomic intervention on TB care and prevention.

Methods: Design: A household-randomized controlled study. Setting: 32 shantytown-communities, Callao, Peru. Participants: All TB patients treated by the Peruvian TB Program. Randomisation: Patient households were randomly assigned 1:1 to controls that received Peruvian TB program standard of care or intervention households that additionally received the socioeconomic intervention. Intervention consisted of socioeconomic support throughout TB treatment. Economic support constituted conditional cash transfers up to US\$230 (4.7% of average TB-affected household annual-income) to mitigate TB-related costs, incentivise and enable care. Social support constituted household-visits and TB club community-meetings aiming to inform and empower, reduce stigma, and facilitate mutual-support. Outcomes compared intervention with control households. The primary outcome was TB chemoprophylaxis completion in contacts aged <20 years. A priori analyses of contacts aged <5 and 5–19 years were also performed. Secondary outcome was confirmed TB patient cure.

Results: Seven months of recruitment achieved sample size to test for a 33% effect on the primary outcome. 90% (282/312) patients were recruited who had 518 eligible contacts. Patients were randomized to the intervention ($n = 135$) and control ($n = 147$) arms. Outcome (Figure): Intervention contacts were more likely to start (43% [95% confidence intervals, CI=36–49] versus 25% [95%CI=19–31], adjusted odds ratio, aOR = 2.0 [95%CI = 1.3–3.8], $P = 0.0001$) and more likely to complete (19%[95%CI = 14–25] versus 11%[95%CI = 7.0–15], aOR = 1.9 [95%CI=1.1–3.3, P

= 0.002) TB chemoprophylaxis than control contacts. This impact was also significant in sub-analyses of ages <5 and 5-19 years. Confirmed cure was more likely in intervention than control patients (47% [95%CI=39-56] versus (34% [95%CI=26-42], aOR-1.8 [95%CI = 1.1-2.9], $P = 0.02$).

Conclusions: The socioeconomic intervention improved TB cure rates and TB chemoprophylaxis uptake and completion in an impoverished setting. This evidence supports implementation of recent global policy changes. **Figure** Uptake, adherence to, and completion of six months of TB chemoprophylaxis in household contacts ($n = 518$) and confirmed TB cure in TB patients ($n = 282$). Error bars show 95% confidence intervals. P values on the lower lines are those derived from univariate logistic regression against the binary outcome variable of chemoprophylaxis completion or TB cure. P values on the upper lines are those derived from multiple logistic regression against the binary outcome variable of chemoprophylaxis completion or TB cure adjusting for food insecurity, age, gender, education level, employment status, crowding level, and monthly household income.



Electronic-cigarettes, nicotine and tobacco smoke impair human immune responses to virulent *Mycobacterium tuberculosis* infection

R Chang,¹ M Davids,¹ K Dheda,^{1,2} E Bateman,¹ R van Zyl-Smit¹

¹Division of Pulmonology & UCT Lung Institute, Department of Medicine, University of Cape Town, Cape Town, ²Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

Background: Electronic cigarettes (E-cig) are gaining widespread popularity as a 'safer alternative' to tobacco. There is a paucity of data evaluating their short-term impact on respiratory infections. Tobacco cigarettes impair human immune responses to mycobacterial infection and double the risk of developing tuberculosis.

Methodology: Adherent monocytes from healthy individuals were infected with BCG or virulent mycobacteria: H37Rv (laboratory strain) or CDC1551 (Clinical strain). Monocytes were co-cultured with E-cig liquid, E-cig vapour, cigarette smoke extract (CSE) or nicotine. E-cig liquid and vapour were obtained from nicotine containing Twisp® brand E-cigarettes. E-cigarette vapour was collected through RPMI during a 3 & 5 minute 'vape' in a similar published method used to generate tobacco smoke extract. Cell viability (trypan blue staining) and TNF responses (ELISA) were measured at 18 h.

Results: Toxicity experiments demonstrated a dose dependent toxicity of CSE, nicotine and E-Liquid. Using low concentrations of exposures, we demonstrated a consistent reduction in TNF- α production for all exposures: E-cig vapour (using a 50% concentration of 3 and 5 minute vape sessions) reduced TNF- α production by a mean 38% (SD 26) $P < 0.001$ and 78% (SD 20) $P < 0.001$, respectively. Nicotine 100 μ g/ml alone reduced TNF- α production by a mean 43% (SD 24) $P < 0.001$ and 1% E-cig liquid by 78% (SD 23) $P < 0.001$. 10% CSE reduced TNF- α by 67% (SD 23) $P < 0.001$ in response to virulent *Mycobacterium tuberculosis* infection.

Conclusions: Although electronic cigarettes are reported to be less harmful than tobacco, these data demonstrate impairment to a key mycobacterial immune response. Caution should be advocated – especially in TB endemic regions about using electronic cigarettes, until the full effect on mycobacterial immunity is clarified.

Early bactericidal activity of AZD5847 in pulmonary tuberculosis

J J Furin,¹ J Du Bois,² E van Brakel,² P Chheng,¹ A Venter,³ C A Peloquin,⁴ B Thiel,¹ S M Debanne,⁵ W H Boom,¹ A H Diacon,^{2,6} J L Johnson¹

¹Tuberculosis Research Unit, Department of Medicine, Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, OH, USA; ²TASK Applied Science, Bellville, ³Centre for Molecular and Cellular Biology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; ⁴Infectious Disease Pharmacokinetics Laboratory, University of Florida College of Pharmacy and Emerging Pathogens Institute, Gainesville, FL, ⁵Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, OH, USA; ⁶Division of Physiology, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

Background: New therapies are needed to treat patients with drug-resistant TB. We conducted a randomized, open label, phase 2a dose ranging trial to evaluate the 14-day bactericidal activity, safety and pharmacokinetics of AZD5847 (AstraZeneca, Wilmington, DE, USA), a new oxazolidinone antibiotic, in patients with pulmonary TB.

Methods: Seventy-five adults with newly-diagnosed, sputum smear-positive TB were randomly assigned to receive AZD5847 at different doses (500 mg once daily; 500 mg twice daily; 1200 mg once daily; and 800 mg twice daily) or standard treatment (Rifapirar; HRZE). The primary efficacy endpoint was the mean daily fall in MTB log₁₀ CFU per ml of sputum, analyzed with linear mixed modeling techniques for longitudinal data. Change in time to positivity (TTP) in MGIT culture over 14 days was a secondary endpoint. SAS 9.3 was used for statistical calculations. The trial was registered at www.clinicaltrials.gov (NCT01516203).

Results: The mean 14-day bactericidal activity of HRZE was consistent with previous studies (0.163 log₁₀ CFU/day). AZD5847 at a dose of 500 mg twice daily showed a decline in CFU over time that excluded zero (average change of -0.039 log₁₀ CFU/day, $P < 0.0048$). AZD5847 at doses of both 500 mg and 800 mg twice daily also showed an increase in TTP in MGIT. The 90%CI of the effects on TTP of both doses excluded zero, with an increase of 1.24 hours per day and 1.21 hours per day respectively ($P = 0.013$ and 0.018 , respectively). Over the exposure range tested, AZD5847 appeared to be generally well tolerated. The most frequent adverse events seen were hematologic, hepatic and gastrointestinal. The drug exhibited log-linear elimination with a half-life of 5 to 7 hours.

Conclusions: AZD5847 at the 500 mg and 800 mg twice daily doses showed an EBA that was different from zero. The drug merits further evaluation in patients with pulmonary TB.

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Unexpected high frequency of *Rv0678* mutations in MDR-TB patients without documented prior use of clofazimine or bedaquiline

N Coeck,¹ C Villellas,² C J Meehan,¹ N Lounis,² S Niemann,³ L Rigouts,¹ B de Jong,¹ K Andries²

¹Institute of Tropical Medicine, Antwerp, ²Janssen Research and Development, Beerse, Belgium; ³National Reference Centre for Mycobacteria, Borstel, Germany. e-mail: kandries@its.jnj.com

Background: Mutations in *Rv0678*, a gene regulating the expression of the MmpS5-MmpL5 efflux pump, have been shown to lead to 2- to 8- fold increases in bedaquiline (BDQ) MIC, and 2- to 4-fold increases in clofazimine (CFZ) MIC.¹ After the unexpected discovery of an *Rv0678* mutation in a baseline isolate from a patient without documented prior use of CFZ or BDQ, the prevalence of these mutations in clinical isolates was assessed.

Methods: Baseline isolates from two bedaquiline MDR-TB clinical trials were assessed for *Rv0678* mutations by Sanger sequencing; corresponding BDQ MICs were

determined on 7H11 agar. *Rv0678* mutations were also investigated in DS TB sequences of the Hamburg cohort,² using a modified version of the KvarQ software.³

Results: *Rv0678* mutations were identified in 21/345 (6.1%) of MDR-TB baseline isolates from the two clinical trials. BDQ MICs of these isolates were either normal (0.03 to 0.24 µg/ml, $n = 10$), high (0.48 to 1, $n = 8$), or low (0.004 to 0.015, $n = 4$). Mutations were also often identified in the intergenic region between *Rv0678* and *Rv0677c*. A mutation at position -11 in the intergenic region appeared to increase the sensitivity for BDQ (median MIC = 0.015). In DS TB isolates, the frequency of *Rv0678* mutations was lower (4/817 or 0.5%), but still higher than expected based on the theoretical mutation rate.

Conclusions: *Rv0678* mutations occur more frequently in MDR-TB patients than previously anticipated, and are not consistently associated with increased MICs for BDQ. Given the variety of mutations in *Rv0678* and their variable effects on the MIC, phenotypic DST methods are preferred to molecular methods to assess BDQ susceptibility. The origin of *Rv0678* mutations is unknown, but cannot be linked to prior use of BDQ or CFZ.

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TB type	<i>n</i>	<i>Rv0678</i> mutation	intergenic region position -8 to -9	Intergenic region position -11
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
MDR-TB	345	21 (6.1%)	2 (0.6%)	37 (10.7%)
DS TB	817	4 (0.5%)	0	0

TB = tuberculosis; MDR-TB = multi-drug resistant tuberculosis; DS TB = drug susceptible tuberculosis.

First results with a 9-month regimen for multidrug-resistant tuberculosis (MDR-TB) in francophone Africa

C Kuaban,¹ Z Kashongwe,² A Bakayoko,³ T Ndikumana,⁴ S Hassane,⁵ S Bassirou,⁵ V Fikouma,⁶ M Gninafon,⁷ M Ouedraogo,⁸ V Schwoebel,⁹ K G Koura,⁹ H Rieder,⁹ A Trébucq⁹

¹Bamenda University, Bamenda, Cameroon; ²Bukavu University, Bukavu, Democratic Republic of Congo; ³CHU Treichville, Abidjan, Ivory Coast; ⁴National Tuberculosis and Leprosy Program, Bujumbura, Burundi; ⁵Action Damien, Niamey, Niger; ⁶Bangui University, Bangui, Central African Republic; ⁷National Tuberculosis Program, Cotonou, Benin; ⁸CHU Yo, Ouagadougou, Burkina-Faso; ⁹International Union Against Tuberculosis and Lung Disease, Paris, France. e-mail: vschwoebel@theunion.org

Background: A 9-month regimen (4KmGfxPtoHCfzEZ/5GfxCfzEZ) for multidrug-resistant tuberculosis (MDR-TB) has been more than 80% effective in Bangladesh. We report results for the first cohort of patients included in an observational study coordinated by the International Union Against Tuberculosis and Lung Disease aiming to evaluate the effectiveness and tolerance of this regimen (moxifloxacin replacing gatifloxacin) in 9 countries of francophone Africa.

Methods: From January 2013 to March 2015, 1022 adult patients were recruited in Benin, Burkina Faso, Burundi, Cameroon, Ivory Coast, Niger, Central African Republic, Democratic Republic of Congo and Rwanda. The patients receive treatment under strict daily observation after standard clinical and laboratory examinations. Adverse drug events and clinical and bacteriological response to treatment are followed up monthly until treatment completion, and bacteriological status is monitored 6-monthly thereafter for 2 years. We describe the characteristics and analyzed the clinical and bacteriological response to treatment and the rate of adverse events of the first cohort of patients included before 1 July 2014.

Results: Among this cohort of 507 patients—37% female, median age 33 years, 88% previously treated for TB, 21% HIV-positive—80.9% had treatment success, 7.7% died, 6.5% were lost to follow-up and 4.9% were failures. The case fatality rate was higher in HIV-positive than in HIV-negative patients (17.1% vs. 5.0%, $P < 0.001$). The most frequent adverse event was mild gastric pain and vomiting during the 2 first months of the treatment. Hearing loss >70 dB was reported in 9.2% of the cohort. Severe (grade 4) adverse events occurred in 2.7%, and were significantly more frequent among HIV-positive than among HIV-negative patients (6.9% vs. 1.6%, $P = 0.003$).

Conclusions: Preliminary treatment results on the first enrolled patients are excellent. Implementing this short MDR-TB treatment regimen has proven feasible in the participating countries, with limited rates of adverse events except for hearing loss.

42. TB research and communities: ethical and practical considerations

Community engagement in descriptive studies

A Choko,¹ R Sambakunsi,¹ M Nliwasa,^{1,2} M Kumwenda,^{1,2} G Sinjani,¹ L Chiume,¹ L Corbett,^{1,3} N Desmond^{1,4} ¹Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, ²University of Malawi, College of Medicine, Blantyre, Malawi; ³London School of Hygiene & Tropical Medicine, London, ⁴Liverpool School of Tropical Medicine, Liverpool, UK.

Background: Ethical research requires reflective engagement between researchers and communities to maximise mutual benefits. Community engagement can be utilised to inform, consult or to enable local decision-making. Here we describe a community liaison system (CLS) established to facilitate consultation and dialogue during an HIV self-testing (HIVST) and TB screening trial in urban Malawi.

Methods: The trial setting was 28 small neighbourhoods, defined by community-health worker (CHW) catchment populations. Four cluster representatives (CRs) per neighbourhood (128 in total) were recruited using participatory methods (nominated and voted at residential meetings). Their primary mandate was to meet weekly as a neighbourhood team, to report all discussions (both positive and negative) relating to the trial, submitting their reports at monthly facilitated CR meetings where concerns were discussed and appropriate responses developed. CRs performed a secondary role reporting on all deaths for verbal autopsy ('dual representation'). Separately, a standard community advisory board (CAB) included 15 community members/leaders.

Results: Of 883 issues raised over the first 6 months from 416 residents, concerns most often related to lack of HIVST (41%) in control neighbourhoods. Additional common concerns included misunderstandings of HIV care pathways for people who self-tested positive. Women (49%) raised more concerns than men (27%) and mixed groups (24%). Benefits to the trial included CLS motivation to HIVST clients to fully participate with TB screening (sputum submission) and rapid tracing of participants with newly diagnosed TB. By sharing their collective lack of major adverse events (suicides, and gender-based violence) in real time, the CLS also supported rapid gains in community confidence around the safety of HIVST: a previously untried intervention. Furthermore, CRs assisted in QA activities and maintaining HIVST availability within defined neighbourhood boundaries despite very high demand (~84% population uptake).

Conclusions: A linked community liaison system was highly successful in facilitating dialogue between the research team and community, and dealing promptly with harmful rumours. Dual representation was highly beneficial to the trial team, although with potential to compromise the true 'community voice'. Initial feedback

on the community demand for HIVST was validated by subsequent update data.

Community engagement in TB vaccine studies

M Tameris¹ ¹South African Tuberculosis Vaccine Initiative, University of Cape Town, Cape Town, South Africa.

Background: The South African Tuberculosis Vaccine Initiative (SATVI) has been conducting clinical trials of novel tuberculosis (TB) vaccines in Worcester, Western Cape since 2005. Novel TB vaccines are targeted at infants as BCG replacements or at adolescents and adults as BCG boosters. Clinical researchers have a responsibility to the communities in which they work to engage with them in research activities and to build their capacity to understand and give input into the research. SATVI works closely with our community stakeholders in a variety of ways.

Methods: SATVI has established an active community advisory board (CAB) which has an adolescent CAB component. A comic book describing a young mother's decision to enrol her infant into a TB vaccine trial has been produced, distributed and dramatised. Two Wellcome Trust International Engagement grants have funded projects using drama to introduce the concepts of clinical research including participant rights, and TB vaccine research, to high school pupils and to the general population respectively.

Results: SATVI continues to have an excellent relationship with the community in which we work. Stakeholders include the local Departments of Health and Education, local business forum members, and most importantly the 'man in the street' who volunteers to participate in our trials.

Conclusion: Active and ongoing community engagement is essential when conducting clinical research.

43. Country experiences: enablers for community-based multi-drug resistant tuberculosis management programmes

The effects of Directly Observed Therapy (DOT) in MDR-TB treatment, a systematic review and field experience from China

X Wei,¹ **J Yin**¹ ¹JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China.

Background: Directly observed therapy (DOT) was recommended by WHO to improve adherence of Multidrug-resistant tuberculosis (MDR-TB). However, the effectiveness of DOT on medication adherence and treatment outcomes of MDR-TB was mixed in previous studies. Thus, with the aims of assessing medication adherence and treatment outcome among MDR-TB patients and their associations with provision of DOT, we systematically reviewed previous studies, and conducted a retrospective cohort study in two provinces of China.

Methods: We searched studies published in English between January 1970 and January 2015 in the major electronic databases. Two reviewers independently screened articles and extracted relevant information for the systematic review. The cohort study was conducted in Zhejiang (ZJ) and Shandong (SD) provinces. Culture confirmed MDR-TB patients who had begun their treatment between January 1 2009 and June 30 2012 in ZJ and between January 1 2009 and April 30 2012 in SD were included into the study. We reviewed clinical charts and conducted a questionnaire survey with the patients. Treatment interruption was defined as missing a dose for at least a day but less than eight consecutive weeks, while severe interruption was defined as missing doses between two to eight consecutive weeks.

Results: A total of 29 articles were included in the review. Studies adopting full DOT (68%, 95%CI 63-73%) had a significantly higher pooled treatment success rate than studies using self-administration treatment (47%, 95%CI 41-52%). Among the 330 patients (220 in ZJ and 110 in SD), 175 (53%) had a treatment interruption, while 62 (19%) reported severe interruption; 251 (76%) reported a culture conversion after six months treatment; 154 (47%) patients received DOT with 111 (72%) received from family members. Patients who were older (OR=2.14, 95%CI 1.12-4.10), did not receive DOT (OR=0.47, 95%CI 0.25-0.92), injected by health care workers (OR=0.28, 95%CI 0.08-0.98) had more severe interruptions than those who were younger, received DOT and injected by family members. Patients who had higher level of education (OR=1.95, 95%CI 1.09-3.50) and had no interruption (OR=0.54, 95%CI 0.31-0.95) were more likely to have six-month culture conversion.

Conclusions: Treatment interruptions are common in study sites. DOT was effective in improving adherence and successful treatment outcome among MDR-TB patients. Family members may act as treatment supporters after necessary training.

The role of health insurance schemes in managing community-based MDR-TB patients via designated hospitals in China

Q Sun Center for Health Management and Policy, Shandong University, Jinan, China.

Background: Poor MDR-TB patients' detection, low standard treatment rate of MDR-TB patients, lack of effective MDR-TB patients management and higher economic burden of MDR-TB treatment are the main challenges in the MDR-TB control of China. Under the support of the Bill and Melinda Gates Foundation, China initiated a comprehensive MDR-TB control project in four cities since the year 2011. One of the main interventions is increasing the reimbursement of health insurance to MDR-TB treatment for alleviating the economic burden of MDR-TB patients.

Methods: A field survey was conducted in the four pilot cities. The health insurance policies were collected; MDR-TB patients were surveyed using structured questionnaires to evaluate their economic disease burden

under the existed health insurance programs. Descriptive statistical methods were used to analyze the effects of health insurance program on decreasing the economic diseases burden of MDR-TB patients.

Results: The pilot projects regulated the health insurance schemes will cover at least 50% of MDR-TB treatment expenditure with the standard treatment protocol, the patients will cover 10% of medical expense, the left are covered by the projects. In the four pilot cities, we use the MDR-TB inpatient expenditure of the New Rural Cooperative Medical Scheme (NCMS) as example, it was found the proportion of MDR-TB inpatient reimbursement to total inpatients expenditure of NCMS in the four cities was very tiny varying from 0.02% to 0.05%. A total of 73 MDR-TB patients were investigated. Before the project reimbursement to MDR-TB patients, it was estimated that the total treatment cost of MDR-TB patients in the two years treatment period was 23 430 Yuan (18 966~30 894 Yuan) the total medical expenditure was 15 166 Yuan (12 811~17 898). Among the surveyed MDR-TB patients, 84% of them got the catastrophic medical expenditure in treating MDR-TB. After the reimbursement by the project, the total treatment costs decreased 67%, but 65.75% of MDR-TB patients still suffered the catastrophic medical expenditure.

Conclusions: The pilot projects decreased the economic burden of MDR-TB patients, but the effects and the sustainability of MDR-TB control is uncertainly without the subsidy of the project. So, a case-based payment by health insurance programs should be designed and implemented.

Expanding MDR-TB management through community health workers in Bangladesh and Nepal: NGO experiences

S Islam,¹ M Rana,¹ M Siddiqui,¹ M Akramul Islam,¹ M Husain² ¹Department of Health, BRAC, Dhaka, ²Department of Health, NTP, Dhaka, Bangladesh.

Background and challenges: Bangladesh ranks in 10th on the list of 27 high priority countries for MDR-TB. According to a recent drug resistance survey, MDR-TB burden is 1.4% among new cases and 28.5% among retreatment cases. However, considering the size of the population the absolute number of MDR-TB patients would be higher. National Tuberculosis Control Programme initiated Programmatic Management of DR-TB cases since 2008.

Intervention: Patients diagnosed in the National Institute of Diseases of the Chest and Hospital admitted for 6 to 8 months of intensive phase of treatment initially and 18 months ambulatory phase at community. Currently, sputum microscopy is done weekly for admitted patients. If two consecutive sputa become negative then the MDR-TB patients are shifted to the community for ambulatory care. Sputum follow up test like microscopy is done monthly at the field level and culture is done quarterly at TB Reference Laboratory throughout the treatment course. All the health care providers related to MDR-

TB management receive basic one day orientation before starting of MDR-TB management at community level. The community health workers play important role in educating MDR-TB patients and their family members for continuation the treatment and provide psychosocial support. They ensures daily intake of medicine during ambulatory phase of treatment and they also encourage patient to continue regular follow-up as per NTP guideline.

Results and lesson learnt: In 2008, a total of 70 confirmed patients were enrolled in BRAC covered TB areas and received standardized MDR-TB treatment. Out of 70 MDR-TB patients, 48 patients completed treatment successfully; the treatment success rate was 69%. The number of patients who were death and default was 6 (9%) and 16 (23%) respectively. In 2012, a total of 333 confirmed patients were enrolled and 238 patients completed treatment successfully, the treatment success rate was 71%. The number of patients who died or defaulted was 36 (11%) and 52 (16%), respectively.

Conclusion: Patients' adherence during hospital stay seems to be a difficulty in hospitalization treatment system as they had to stay for long time during intensive phase. The currently implemented community based MDR-TB treatment modality may contribute to minimize this challenge and ensure high treatment success rate for National Tuberculosis Control Programme in Bangladesh.

Expanding MDR-TB management through community health workers in Bangladesh and Nepal: NGO experiences

S C Baral,¹ S Khanal,¹ B Lamichhane,² K D Wagle²

¹Department of Research, Health Research and Social Development Forum (HERD), Kathmandu, ²Department of Programme, National Tuberculosis Centre, Bhaktapur, Nepal.

Background: TB is one of the major health problems in Nepal. More recently, the emergence of drug resistance (DR-TB) poses even a greater challenge to the NTP. In 2014, total of 349 DR-TB and 25 XDR-TB cases were enrolled for treatment. Treatment Success Rate of DR patients was 76.6%, however it was 11% for XDR.

Methods: Qualitative interviews held with DR-TB patients and their family members and group discussions with frontline health workers and stakeholders. We also reviewed NTP annual data.

Findings: Nepal initiated DR-TB management in 2005 with 5 treatment centres and 11 sub treatment centres. Since then there has been remarkable progress in the field of DR-TB control. The key achievements include expansion of DR-TB centres from 5 to 13 and DR-TB sub centres from 11 to 71 from 2005 to 2013, respectively, covering 42 of 75 districts, with increased involvement of community health workers. Ambulatory DR-TB treatment is now managed at the sub centre once patients have started their treatment at the centres. Similarly, 11 DR-TB hostels provide facility based treatment. Nepal's move to decentralised DR-TB treatment has led to improved DR-TB management. The

trend of DR case finding has been on rise from 94 (18.6%) in 2009 to 349 (22.3%) in 2013. The number of DR-TB patients registered for treatment was 87 in 2005 to 201 in 2010. Similarly, the treatment success rate has increased to 76.6% in 2010 as compared to 64.7% in 2007 with significant decrease in loss to follow up from 18.7% in 2007 to 7.3% in 2010. Major challenges include: poor adherence to the treatment, lack of community awareness, limited skilled human resources, limited provision of infection control measures in health facilities, relocation of patients for treatment resulting socioeconomic burden to patients.

Conclusion: Though the decentralised treatment services have been a major step forward in DR-TB management in Nepal, challenges remain: access to early diagnosis and treatment, quality care at the point of delivery, socioeconomic and psychological barriers to DR-TB patients and their family, skilled human resources at referral and periphery level facilities, continuation of DR-TB hostels, among others. Therefore, in order to achieve better outcomes with less burden on DR-TB patients and families, there is a need for further expansion and strengthening of patient centered decentralised DR-TB care tailored to the local context.

Developing and implementing an Internet-based information system, SITETB, to integrate services among health providers in Brazil for MDR-TB care

P Bartholomay Oliveira,¹ D Barreira,¹
S Barbosa Codenotti¹ ¹National Tuberculosis Programme,
BRASILIA, Distrito Federal, Brazil.

According to the World Health Organization (WHO), in 2014 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB) were estimated worldwide and approximately 210 000 deaths from the disease. When there is diagnosis of MDR-TB alternative treatment regimens are needed to control it, which usually have a lower cure rate, less favorable prognosis, more side effects and higher cost. The Brazil monitors cases of MDR-TB by Information System Tuberculosis Special Treatments (SITE-TB), is an online system available in all the federal units, and provides information for epidemiological surveillance, assists decision making, and the management of drugs. The SITE-TB allows the secondary and tertiary reference units notify, track and see the outcome the cases that require special treatment, including cases of mycobacteria non tuberculosis (MNT). The system was developed in partnership with Management Sciences for Health (MSH) aimed at to provide for the monitoring of cases with special schemes, clinical monitoring and rational use of medicines, essential strategies for the proper management and control of drug resistant tuberculosis (DR-TB). In 2012 a pilot study was conducted in three Federal Units, with different profiles, and after some adjustments, all the states were trained to use the system. Currently there are about 600 health professionals using the system for surveillance, clinical care, and the management of drugs. In addition, a group

of ten TB experts in DR-TB validate all cases to monitor the proper use of the national protocol, to do technical support and to provide better management of medicines. Currently, the SITE-TB is used by all the 27 states, for about 250 units that report and accompanying special cases. In 2014, 1738 cases of special tuberculosis treatments were followed in SITE-TB with indication for use of special schemes due to liver disease, severe intolerance, drug allergy or comorbidities, as well as 2416 cases of DR-TB and 548 cases of MNT.

44. Achieving quality Xpert MTB/RIF use for rapid case detection

The role of Xpert MTB/RIF testing in improving the clinical diagnosis of patients in Pakistan

E Qadeer,¹ S Tahseen,² F M Khanzada² ¹National Tuberculosis Control Program, Islamabad, ²Department of National Tuberculosis Reference Laboratory, National Tuberculosis Control Program, Islamabad, Pakistan.

Background: Pakistan is fourth among high burden countries for TB and DR-TB. 82% of cases notified are pulmonary TB and 50% of these are bacteriologically diagnosed; 9.9% of all incident cases notified are children. 75% of estimated MDR-TB burden is among new and only 25% among retreatment PTB cases. The capacity for conventional bacteriological diagnosis of TB cases among smear-negative PTB, childhood TB and EPTB is limited.

Intervention: GeneXpert was introduced in Pakistan in 2011 soon after its endorsement by WHO. It was implemented initially with focus to enhance DRTB case diagnosis but its use was soon expanded to improve bacteriological diagnosis of TB in vulnerable, at risk population (children and HIV +ve) and those having difficulty in diagnosis. The number of Xpert machines increased from eleven in 2011 to 67 in 2014 and patients tested increased from 482 In year 2011 to 56 252 in year 2014 and by mid-2015 a total of 101 242 patients had been tested across the country. We present the role of Xpert in clinical diagnosis of TB in 20 252 patients (19.8%) tested at the National TB Reference laboratory (NRL) during this period .

Results: Among patients tested (July 2011-2015), 50.8% had no history of previous treatment, 12.9% were under 15 yrs of age and 6.2% of patient had extra -pulmonary lesions. Number of adults and children tested with PTB or EPTB has increased from 116 (2011) to 7081 (2014) but proportion of paediatric cases has declined from 21.6% to 12.9% over time. In patients with no history of previous treatment, *Mycobacterium tuberculosis* was detected in 19.7% of patient s (22.6% in adults and 9.1% in <15yrs) and Rifampicin resistant (RR) was detected in 11.4% (11.6% in adults and 9.6% in < 15Yrs). In patients with history of previous treatment *M. tuberculosis* was detected in 37.4% (37.9% in adults and 27.7% in <15yrs) and RR was detected in 22.7% (22.5%in adults and 28.9% in <15yrs). Among extra-

pulmonary specimen, *M. tuberculosis* was detected in 20.0% and Rifampicin resistant in 12.8% of cases.

Conclusion: Introduction of Xpert along with enhancing diagnosis of DR-TB cases has played an important role in bacteriological diagnosis of tuberculosis in children, adults with difficulty in diagnosis as well as extra-pulmonary cases. There is need for sensitization of pediatricians and surgeons on role of diagnostic assay in bacteriological diagnosis of these difficult cases.

Table : Xpert MTB /Rif assay in diagnosis of TB and Rifampicin resistant in adults and <15yrs

PATIENT TYPE	No. Tested	No- MTB+	No- RR +	MTB%	RR %
All country (All Patients)	101242	39174	7228	38.7%	18.5%
NRL (All Patients)	20025	5698	1068	28.5%	18.7%
Adults	17441	5386	1016	30.9%	18.9%
Paeds	2584	312	52	12.1%	16.7%
Pulmonary TB case	18778	5448	1036	29.0%	19.0%
Adults	16412	5163	989	31.5%	19.2%
Paeds	2366	285	47	12.0%	16.5%
Extra Pulmonary TB	1247	250	32	20.0%	12.8%
Adults	1029	223	27	21.7%	12.1%
Paeds	218	27	5	12.4%	18.5%
No History of previous treatment	10165	2006	229	19.7%	11.4%
Adults	7993	1808	210	22.6%	11.6%
Paeds	2172	198	19	9.1%	9.6%
Previous History of ATT	9860	3692	839	37.4%	22.7%
Adults	9448	3578	806	37.9%	22.5%
Paeds	412	114	33	27.7%	28.9%

Yield of TB lymphadenitis with cytology vs. GeneXpert and culture in Ethiopia

T Gemechu,¹ M Aseresa Melese,² N Demmelash,² D Habte,² B Tessema,³ P G Suarez⁴ ¹Department of Pathology, College of Health Sciences, Addis Ababa University, Addis Ababa, ²Center for Health Services, HEAL TB Project, Management Sciences for Health, Addis Ababa, ³Department of Medical Microbiology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia; ⁴Center for Health Services, Management Sciences for Health, Arlington, VA, USA.

Background: GeneXpert MTB/RIF assay has been deployed close to the point of patient care in the fight against TB. The Ethiopian MOH has endorsed the test and there has been a wider installation of this technology into the existing TB diagnostic system. On the other hand, cytology microscopic reading, which has been the first line diagnostic tool for TB lymphadenitis is only conducted in centers staffed by Pathologists. The objective of this study was to compare the level of agreement between cytology readings and GeneXpert results for diagnosis of TB lymphadenitis.

Methods: A comparison was made between the cytology readings of two senior pathologists versus Xpert results of fine needle lymph node aspirates. A senior pathologist took a split sample of FNA from patients clinically suspected of TB lymphadenitis. The cytology smears were stained with Wright's stain and read by two senior pathologists. The cytology reading is considered TB if the two pathologists reported concordant TB diagnosis. A senior microbiologist runs the Xpert test following the standard procedure. Both the pathologist and the

microbiologist were blinded for the results of each other. We calculated the concordance rate of the two test results using Kappa statistics.

Results: A total of 150 TB lymphadenitis suspected patients were included in this study. From the total of 150 TB lymphadenitis suspects, 114 (76.0%) and 86 (57.3%) were diagnosed as TB by cytology reading and Xpert, respectively. Four (4.7%) of the TB patients diagnosed by Xpert were found to have Rifampicin Resistant Tuberculosis. Out of 114 patients diagnosed as TB lymphadenitis by cytology, 84 (73.7%) were also diagnosed as TB by Xpert. The cytology labeled 36 of the suspects as no TB of which 34 (94.4%) were also negative for TB by Xpert. The overall agreement level between the two tests was moderate (Kappa 0.54, $P < 0.001$). The agreement levels of Cytology and GeneXpert results in the caseous and pus aspirates were 0.58 ($P < 0.001$) and 0.49 ($P < 0.001$) respectively. Caseous aspirates yielded less TB positive result than pus aspirates: 69.2% versus 84.6% by cytology and 47.7% versus 67.9% by GeneXpert, respectively.

Conclusion: There is a good agreement between cytology reading and GeneXpert. GeneXpert is very helpful diagnostic tool for TB lymphadenitis in a country where there are few pathologists. We cannot conclude which method is superior because we do not have the gold standard, culture to compare with in this study.

Contribution of GeneXpert in MDR-TB case finding in Ethiopia

J Degu,¹ G Gudeto,¹ J Seid,¹ D Habte,¹ G Ayana² ¹HEAL TB Project, Management Sciences for Health, Addis Ababa, ²Regional Laboratories Capacity Building, Ethiopian Public Health Institute, Addis Ababa, Ethiopia.

Background: Ensuring adequate availability of rapid tuberculosis (TB) diagnostic tools such as GeneXpert is essential for early detection and prompt treatment of TB. Toward this end, the USAID-funded Help Ethiopia Address the Low TB Performance (HEAL TB) project supported the roll out of GeneXpert MTB/RIF in two large regions of Ethiopia. We present the experiences of GeneXpert implementation and its contribution in multi-drug resistant TB (MDR-TB) case finding in the two regions.

Interventions: In collaboration with the RHBs and the Ethiopian Public Health Institution (EPHI), HEAL TB trained laboratory personnel, developed standard operating procedures and reporting tools, provided site level mentoring, deployed short-term technical assistance through an international expert, and monitored progress through monthly reporting and feedback. Moreover HEAL TB oriented clinicians on the eligibility criteria for GeneXpert, facilitated sample transportation, and ensured adequate supply of cartridges. The trends in GeneXpert utilization and its contribution in the diagnosis of MDR-TB cases were evaluated on a quarterly basis, and the contribution was compared with that of conventional culture methods.

Results and lessons learnt: GeneXpert service started in the two regions as of January 2014 whereas the diagnosis of MDR-TB before January 2014 was only made by LPA culture. Of 108 MDR-TB cases reported in January-March 2014 when the project introduced Xpert use, 58% were diagnosed by Xpert while 42% were diagnosed by LPA culture. By the end of June 2015, a total of 41 GeneXpert machines were functional in the two regions. GeneXpert has progressively replaced culture in the diagnosis of MDR TB; it contributed for 74 (93%) of the 80 MDR-TB by June 2015. The number of new cases of MDR-TB enrolled to Second Line Drugs per quarter has doubled since the introduction of GeneXpert service in the HEAL TB supported regions. **Conclusion:** GeneXpert contributed to doubling of MDR-TB case finding and enrollment in care. More effort is needed to further strengthen the site level service utilization capacity.

The use of verification and external quality assessment panels to monitor the accuracy of Xpert MTB/RIF testing across 18 countries

A David,¹ V Magida,¹ W Stevens,^{1,2} L Scott,² V Deyde,³ A Adelekan,³ C Gilpin,⁴ R Coombs⁵ ¹National Priority Program, NHLS, Johannesburg, ²Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, ³Centres for Disease Control, Johannesburg, South Africa; ⁴Global TB Programme, World Health Organization, Geneva, Switzerland; ⁵Department of AIDS Clinical Trial Group, University of Washington, Seattle, WA, USA.

Background: More than 10 million Xpert® MTB/RIF (Cepheid) cartridges and 17 883 GeneXpert (Cepheid) instrument modules, used for diagnosing *Mycobacterium tuberculosis* have been procured globally (up to Q4 2014). Quality management of this molecular test encompasses verification, external quality assessment (EQA) and real time instrument/assay performance monitoring. Verification (determining an instrument [GeneXpert module] is 'fit for purpose') is recommended upon instrument installation or relocation, module replacement and module calibration. EQA (or proficiency testing) is performed to determine pre-analytical, analytical and post analytical 'user' performance and real time monitoring through cloud based software (such as RemoteXpert, Cepheid) can assist with daily instrument/site/country performance. The Dried Culture Spot (DCS) proficiency testing matrix endorsed by the WHO to verify GeneXpert instruments is also available as a global EQA program and both can be used to monitor performance.

Method: DCS material consists of inactivated *M. tuberculosis* (susceptible to Rifampicin (RIF) for verification). DCS for EQA is tested 3 times per year comprising 4 DCS (MTB with RIF susceptible, RIF resistant and non-TB mycobacteria). Submission and reporting of DCS results is managed through an in-house software program www.tbqmonitor.com.

Results: A total of 18 countries currently participate in the DCS EQA program. The Global participants (>1site)

include: South Africa's NHLS (207 sites), AIDS Clinical Trial Group (11 countries world-wide), Walter Reed Army Institute of Research (3 countries), and Namibia Institute of Pathology. Instruments verified with DCS material and registered on www.tbqmonitor.com have fluctuated from over the years since 2011 to 2015. EQA uptake increased from 17 participants in 2012 to 295 by second panel in 2015. By 30 April 2015, 4,377 verification DCS were performed globally. DCS used for EQA reported an overall 98.2% correct result. Incorrect results accounted for 0.7%, 0.6% and 0.8% for device error rates in 2013, 2014 and 2015 (up to Q1), respectively. **Conclusion:** The DCS quality program highlights the successful, rapid implementation of quality assured Xpert® MTB/RIF testing globally. The standardization of testing material and minimal variation of testing sites illustrates stability and robustness of instruments. High quality assay performance over time as well as consistency among sites and users was demonstrated.

Quality indicators and maintenance experience of Xpert MTB/RIF in South Africa

P Marokane,¹ S Molapo,¹ V Magida,¹ L Berrie,¹ W Stevens,^{1,2} L Scott² ¹NPP, National Health Laboratory Service, Johannesburg, ²Department of Haematology and Molecular Medicine, University of Witwatersrand, Johannesburg, South Africa.

Background: South Africa initiated the roll out of the Xpert® MTB/RIF assay across 221 laboratories performing smear microscopy. To ensure ongoing quality of services, the National Priority Programme (NPP) of National Health Laboratory Services (NHLS) developed and monitored quality measures for molecular testing that are consistent with good laboratory practices. **Method:** The performance of the 221 laboratories is reviewed on a monthly basis. All analysers ($n = 309$) deployed within the NHLS are connected and interfaced to the Laboratory information System (LIS) allowing for central collection of patient results. Data extracted from the Central Data Warehouse (CDW) is analysed to determine the national *Mycobacterium tuberculosis* complex (MTBC), Rifampicin (RIF) resistance and error rates. In addition, 211 devices were connected to the GeneXpert operational dashboard which allowed the NPP to receive data in real time and respond to potential laboratory, assay and analyser problems occurring in a more efficient, timely and targeted approach. The use and analysis of the 'real time' data enhanced the ability to respond to instrument failures that might result in module replacements and maintenance, operator training needs, potential laboratory contamination and assay related issues followed by root cause analysis.

Results: A total of 6 538 967 specimens have been processed as at 31 July 2015. The national TB positivity rate among individuals presumed to have MDR-TB or HIV-TB was found to be up to 16-18% in the first year and 13-14% in the second year, 10-11% in the third and fourth years and has reduced to 9% in the 5th year, after introduction of Xpert® MTB/RIF assay. Average Rifam-

picin resistance detection rates have remained around 7% since project inception with some geographical variations. Average error rate has ranged consistently below 3%. Over 3 million specimens were uploaded on the Xpert operational dashboard as at 31 July 2015. Comparisons of data from the RemoteXpert against LIS showed a 1% bias due to removal and repeat on error testing not extracted by the LIS. Since March 2011 to December 2014 South Africa replaced (33%) 1272 out of 4168 modules. Conclusion: The performance indicators have never been reported in real time and the implementation and utilization of these systems improved the overall programmatic monitoring and evaluation, which ultimately improved the quality of the laboratory processes and results.

46. Strengthening community systems: building the evidence for impact

Community-based monitoring and evaluation in Uganda: ensuring TB services delivered by public and private sectors are available and accessible

P Masembe¹ ¹African Young Positives Network, Kampala, Uganda.

One third of people estimated to have TB are either not reached for diagnosis and treatment by the current health systems. Even in patients who are identified, TB or MDR-TB is often diagnosed and treated late. In order to reach the unreached and to find TB patients early in the course of their illness, a wider range of stakeholders already involved in community-based activities needs to be engaged. Civil society organizations (CSOs) that are active in community-based development, particularly in primary health care, human immunodeficiency virus (HIV) infection and maternal and child health, but have not yet included TB in their priorities and activities. CBO membership consists entirely of the community members themselves, so these organizations can be considered to represent the community most directly. NGOs and other CSOs engage in activities that range from community mobilization, service delivery and technical assistance to research and advocacy. The strengths of CSOs active in health care interventions at the community level include their reach and spread and their ability to engage marginalized or remote groups. These organizations have a comparative advantage because of their understanding of the local context. Greater collaboration between CSOs and local and national governments could greatly enhance development outcomes. Reducing the complexity of transactions and increasing the speed of facilitation are key factors that improve the operating environment for community actors. NTPs or their equivalents have the responsibility of creating enabling national or local legal, policy and administrative environments to support the effective engagement of NGOs and other CSOs in TB activities. CSOs should also stimulate and support the development of an enabling

legal and policy environment through constructive dialogue and engagement with the NTPs or relevant legislative structures. The coalition should meet regularly and have mechanism for sharing information of common interest to improve contributions to national TB plans, discuss challenges and opportunities. The NTP, with inputs from the coalition and other stakeholders, should prepare a national policy to facilitate effective engagement of CSOs in TB prevention, diagnosis, treatment, patient care and support, and in research activities aligned with the national health strategy.

Contributions of communities in improving case detection in rural Ethiopia through TB REACH

M A Yassin,¹ D Gemechu,^{2,3} S Theobald,³ L Cuevas³ ¹The Global Fund, Geneva, Switzerland; ²REACH Ethiopia, Hawassa, Ethiopia; ³Liverpool School of Tropical Medicine, Liverpool, UK.

Introduction: In 2013, WHO estimated that three million cases of tuberculosis (TB) were missed. Ethiopia contributed to 3% of missed cases mainly due to health system and community factors. Different interventions were tried but with limited gain in case finding. We report successful implementation of TB REACH project in improving case finding in remote and rural communities in southern Ethiopia.

Methods: This is an innovative community-based collaborative project with the Ministry of Health of Ethiopia implemented in southern Ethiopia reaching a population of 7.5 million. The key interventions included familiarization, capacity strengthening, community-based intervention by engaging HEWs in TB diagnosis and treatment, mobile communication, slide referral and ensured sustained continuum of care including contact tracing, provision of Isoniazid Preventive Therapy (IPT) for asymptomatic under five years children. District supervisors were hired; motor bikes were provided training and contributed to diagnostic capacity building over four years.

Results: During this period, more than 180 000 presumptive TB cases were identified; sputum collected and slide fixed by HEWs in the community and slides were collected by district field supervisors for examination. Of these, more than 9000 smear-positive TB cases were diagnosed from the slides prepared and fixed by HEWs. Over all in the project area, more than 13 000 smear-positive TB cases and more than 29 000 all forms of TB were diagnosed and treated. The community-based intervention contributed to about 70% cases detected in the project area. More than 9000 household contact tracing was done and screened more than 35 000 contacts, identified more than 4000 symptomatic contacts, examined more than 3000 symptomatic and detected 243 smear-positive cases, about 2500 under five years asymptomatic children were put on IPT. About 6000 presumptive cases were examined using GeneXpert machine and detected 634 MTB+ cases.

Conclusions: Involvement of community people as DOTS provider and door step efforts in the community regarding TB control found to be effective in better treatment outcome among infectious cases over the years. Early diagnosis and prompt treatment initiation of TB cases from the community will reduce the spread of transmission.

Results: Data from 3307 persons receiving 39 530 doses were available for analysis. In this project, 2884/3307 (87%) persons completed 3HP; completion rates ranged from 81-100% across sites. Discontinuing treatment was associated with homelessness (ARR=1.65; 95%CI: 1.20-2.27), age >65 years (ARR=1.61; 95%CI: 1.21-2.13), and being non-Hispanic White (ARR=1.38; 95%CI: 1.14-1.68). Reporting at least one symptom before the 11th dose was associated with treatment discontinuation

Background and challenges to implementation: TB is a major public health concern in Bangladesh. BRAC, a development organization initiated community based tuberculosis control programme in 1984 in one sub-district to control TB. This model was gradually expanded since 1994 in collaboration with National Tuberculosis Control Programme (NTP) and currently covering two-third of the country with 93 million populations. Considering the long treatment duration, community based interventions intensified throughout BRAC implementing areas to increase TB case notification, to improve treatment success rate and to minimize unfavorable treatment outcome. Interventions: BRAC expanded peripheral laboratory facilities with solar system in very remote areas to increase the identification of smear positive TB cases. Outreach sputum collection centers are conducted to improve access to diagnosis. BRAC's frontline health workers known as Shasthya Sebika (SS) plays an important role in implementing community based DOT. They disseminate TB messages in the community during household visits and refer TB symptomatic for sputum examination at NTP designated laboratories. Treatment of all TB patients is initiated by graduate medical doctors and daily DOT is ensured by Shasthya Sebika (SS). BRAC's health workers give proper counseling and motivation to the TB patients for daily DOT and ensure follow up sputum examination timely

(OR 4.5, 95%CI: 3.6-5.6). Shortness of breath (OR 16.4; 95%CI 10.2-26.3) and fever/chills (OR 10.3; 95%CI 9.8 – 10.7) were most associated with treatment discontinuation, while nausea, the most commonly reported symptom, was least associated with treatment discontinuation if it was the only symptom reported (OR 0.4; 95%CI 0.2-0.7). In analyses of 2400 patients with medical information available, the additional risk factor of having ever smoked was associated with discontinuing 3HP (ARR=1.50; 95%CI: 1.21-1.85; $P < 0.001$). There were no deaths or permanent medical sequelae reported during treatment.

Conclusion: Completion of 3HP treatment in U.S. program settings is high, and similar to that seen in published trials. Isolated nausea, while commonly reported in patients, was not associated with treatment discontinuation. Persons who were homeless, age >65 years, non-Hispanic White, or smokers were more likely to discontinue treatment. The 3HP regimen is generally safe and well tolerated in these US program settings.

48. Beyond accelerated drug development: building successful partnerships and platforms as a critical path to TB drug regimens and PreDiCT-TB

Collaborative approaches to defining contribution of animal models

H Pertinez,¹ L Bonnett,¹ G R Davies¹ ¹University of Liverpool, Liverpool, UK.

Background: Mouse model data has played a central role in preclinical development of anti-tuberculosis drugs despite ongoing debate about representativeness and reproducibility. Within the PreDiCT-TB consortium, close collaboration between experimentalists and statistical modellers has been central to optimising designs and applying a common modelling approach to analysis of mouse experiments performed for a common set of drug combinations. Collaborating with external scientific partners, PreDiCT-TB has begun to assemble a more comprehensive database of mouse studies than previously, facilitating comparisons between such models and also with clinical outcomes on the basis of ranking of treatments and their effect sizes. This meta-analytic approach has been informative in other therapeutic areas and promises to lead to a deeper understanding of the strengths and weaknesses of this key step in preclinical development.

Methods: Timecourse profile datasets of *M. tuberculosis* load in mice under therapy, typically CFU plated on solid media from lung homogenate, were fitted with mathematical models describing bacterial elimination by nonlinear regression methods. Empirical models describing a monoexponential elimination of *M. tuberculosis* were generally applied and exponential elimination rate constants (k_{net}) estimated – this parameter is equivalent to the slope of elimination seen with log-transformed

CFU data. The relative efficacy of therapies was assessed by ranking them in order of their values for this parameter – faster elimination rates reflected in a more negative k_{net} parameter value.

Results: Ranking tables, according to k_{net} for various therapies in 3 mouse models are presented with correlation coefficients to compare parameter values and rankings in the separate models against each other, and a meta-analysis with accompanying Forrest plot was carried out to derive a general ranking of therapies in mice. Finally all mouse rankings were compared to rankings of therapies in a clinical setting, based on several endpoint measures of efficacy (e.g. EBA 0-x, TTP at 8 weeks etc.) derived by a separate meta-analysis also carried out under Predict-TB.

Conclusion: Of the models analysed so far, the Janssen mouse dataset showed the closest match to the ranking of therapies in human, with a general combined mouse model ranking showing some correlation with clinical rankings of EBA0-2 and 8 week TTP data. Ongoing work will analyse and incorporate further data from other mouse models.

Learning from clinical trial data

L Bonnett,^{1,2} G R Davies¹ ¹Department of Clinical Infection, Microbiology, and Immunology, University of Liverpool, Liverpool, ²Department of Biostatistics, University of Liverpool, Liverpool, UK.

Background: To understand and calibrate preclinical development of anti-tuberculosis (TB) drugs it is necessary to define their performance in real-life clinical trials. A systematic review and summary meta-analysis were undertaken to examine the existing evidence base, as well as historical and current development practices, particularly the progression of compounds from phase II to phase III studies.

Methods: Relevant studies evaluating key drugs in first-line treatment for drug-sensitive and isoniazid mono-resistant individuals with pulmonary TB were included. Early clinical outcomes of interest were EBA over 2, 7 and 14 days, and the proportion of patients with negative culture results at 8 weeks. Death, treatment failure, and relapse were the main later phase outcomes of interest.

Results: The review included more than 300 published trials comprising over 80 000 participants. 66 and 91 distinct drug combinations were identified in Phase II and III trials respectively, though few were common to both phases - only 9 distinct regimens were considered across multiple studies and early phase endpoints. In addition to the lack of consistency in the investigated treatments across studies, trial characteristics and reported outcomes were also highly variable. This suggests the need for a core outcome set for reporting in TB treatment trials – a minimum set of outcomes to be reported in all future TB trials. Individual participant data has been requested for all included studies with mixed success. Without this data it is currently difficult to evaluate outcomes consistently across trials, including analyses not performed by the original investigators.

Conclusions: The sparseness of the existing evidence base in trials of treatment for pulmonary TB is concerning – it makes comparison of results at different phases of development quite limited. It also suggests that historical and current development practices should be critically reviewed. In fact, the existing dataset which includes over 60 years' worth of data is too small to provide convincing support to the effectiveness of the current typical drug development pathway, particularly the progression of compounds from phase II to phase III studies. The lack of consistency in reporting of outcomes, and the lack of individual participant data are additional challenges which need addressing if the evidence base for treatments of TB is to be improved.

Improving TB clinical trial design through modeling and simulation

K Romero ¹Department of Clinical Pharmacology, Critical Path Institute, Tucson, AZ, USA.

Background: The Critical Path to TB Drug Regimens (CPTR) Regulatory Sciences programs are focused on de-risking the decision-making in the TB regimen development process. These efforts include the development of quantitative tools to optimize TB trial design through simulations. Each of these programs is enabled by the CPTR TB clinical trial data platform that includes critical data contributions from industry and academia. These clinical trials datasets have been mapped to a unified TB Data Standard, allowing the data to be integrated for more informed quantitative analyses.

Methods: A Physiologically-based pharmacokinetic (PBPK) model that captures the complex mechanistic drug distribution processes in the TB-infected, inflamed, and damaged lung has been developed, with the goal of improving treatment and regimen selection designed to optimize drug exposure across the heterogeneous sites of action in the lung. This model will optimize clinical trial design for first-in-human studies of anti-TB regimens. Additionally, there is a need for quantitative tools to more accurately evaluate efficacy in phase II clinical trials for combination regimens for TB and to reliably predict clinically-relevant endpoints for phase III clinical trials, based on early efficacy evaluations during phase II. Based on phase II and III patient-level data, a model of the longitudinal changes in time-to-positivity (TTP) is being developed, capturing relevant sources of variability. A subsequent model linking changes in TTP from liquid culture to durable cure will be developed. Simulations of longitudinal TTP data will be performed in sub-populations of interest and the resulting effect on durable cure will be determined.

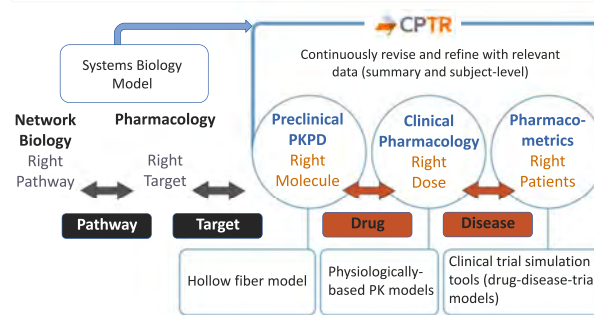
Results: A PBPK model for the TB-infected lung, a virtual South African population, and compound files for standard-of-care drugs has been developed and implemented on the Simcyp platform, and is fully available for drug developers. Preliminary results of the TTP model show that baseline pathogen burden is a significant predictor of the rate of TTP change over time, allowing the identification of distinct sub-populations.

Conclusion: The CPTR modeling and simulation efforts propose to develop quantitative tools to provide answers regarding how the interaction between pathogen dynamics, drug exposure and immune system interactions can be quantified and applied to inform TB drug development decisions.

Modeling and Simulation WG
Potential Expansion



Vision: More efficient translation between each stage of drug development



49. Sanatoria: back to the future?

The sanatoria movement: past and future

A Story ¹FIND & TREAT, London, UK.

Despite Koch's brilliant exposition of the mode by which tuberculosis spreads, its complex etiology continued to mask the facts of transmission for many years. The sanatorium movement was largely founded on the belief that it offered a promise of cure and much needed care as opposed to a means of limiting spread of infection. From the outset the movement was contentious and hotly debated. Insufficiency of beds to accommodate all sufferers created a class divide, with the poor largely reliant on 'home' care; segregation fuelled stigma; beds diverted scarce resources from ambulatory care; and even under the best conditions, over half of those admitted were dead within five years. With the advent of effective treatment and declining cases the movement was largely disbanded. The reality of untreatable tuberculosis has come full circle. Today there is an urgent necessity to re-examine the rationale that underpinned the sanatoria movement and its potential contribution to tuberculosis control. The need for facilities to offer long term hospitalisation and care for patients with M/XDR disease and for patients whose complex social circumstances render ambulatory care a near impossibility is a global public health priority. While the ethical, moral and public health arguments remain complex and contentious, there is now a need to move beyond debate to action. This first talk will set the scene for a symposium which is long overdue.

Netherlands: high-income, low-incidence, high programme budget

W De Lange ¹Department of Pulmonary Diseases and Tuberculosis, Tuberculosis Center Beatrixoord University Medical Center Groningen, Groningen, Netherlands.

The Netherlands has two national tertiary TB referral and expertise centers. Apart from 10 beds for non-infectious TB patients, e.g. with compliance, addiction or psychiatric problems, modern sanatorium Beatrixoord is equipped with state-of-the-art isolation rooms for twenty persons. These are suitable for admitting infectious XDR patients as well as severe immunocompromised, normal sensitive, TB-patients, in separate rooms on the same ward, for a price competitive with a general hospital. TB in the Netherlands is predominantly an imported disease. In 2014, thirty-four different nationalities stayed on the TB ward. The team is specialized in the transcultural approach of individual patient providing medical, nursing, nutritional, physiotherapy, psychiatric, social, rehabilitation and activity related support. Beatrixoord is also the designated centre in the Netherlands for mandatory isolation, when infectious TB patients ignore all advice for voluntary isolation. It is also located close to the national reception centre for asylum seekers in the Netherlands, where radiographic TB screening is performed within 24 hours of arrival, allowing for immediate admission and isolation or further examination, e.g., by bronchoscopy. The Netherlands is a country in the TB pre-elimination phase, with only 823 TB patients diagnosed in 2014. Maintaining TB expertise is difficult among physicians, even among pulmonologists and infectiologists. The treatment of MDR/XDR-TB patients is the responsibility of the national TB consultants for clinical TB working in the tertiary TB referral centers, with a successful outcome in 86% of the cases. Therapeutic drug monitoring, especially for second- and third line TB drugs, is a focus of research at Beatrixoord. The two tertiary pulmonologists of Beatrixoord annually perform approximately 800 consultations by telephone and work very close with the public health TB-professionals. In the Netherlands, a low-incidence country, two highly specialized tertiary TB referral centers complement primary and secondary medically and socially complicated TB care, preserving TB expertise and promoting research.

Barcelona: high-income, low-incidence, low programme budget

I Monedero ¹International Union Against Tuberculosis and Lung Disease, Paris, France.

Barcelona is one of the most touristic and cosmopolitan cities in Europe. Like in any other big city, TB thrives, hitting the most vulnerable populations hard. This inconvenient truth is frequently denied by politicians and institutions, leading to low investment in outreach and socially excluded populations. Barcelona was badly hit in the 1980s by TB at the hand of two other increasing epidemics: HIV and intravenous drug use. Mortality rates were so high that there was no excuse not to build a

specific system to manage TB in the city. Following the lessons learned from New York MDR-TB-HIV epidemic, a multi-stakeholder system was created. It was fine-tuned during years, lessons and errors. It would finally be known as the 'Barcelona model for TB control'. One of the pillars of this model is the existence of what we could call a modern sanatorium where TB patients are admitted when presenting difficult clinical and also social conditions. The use of such a facility has proved to increase the cure rates among those more difficult to be cured: TB-HIV, MDR and XDR-TB and also TB patients presenting alcoholism, multidrug addictions and other mental or social conditions that jeopardize patient adherence. The overall Barcelona model and the relevance of a sanatorium in Barcelona city center will be reviewed during the lecture.

Dominican Republic: middle-income, high-incidence, low programme budget

M Rodriguez ¹MDR-TB Unit, National Tuberculosis Control Program, Santo Domingo, Dominican Republic.

The Dominican Republic (DR) is a Caribbean country with an estimated tuberculosis incidence of 59.6. The only surveillance study performed in 1994-1995, showed initial MDR of 6.6% and 19.7% among previously treated patient. In 2006 with financial aid from the Global Fund and the technical assistance of The Union and PAHO/WHO, 24 MDR patients started second line drugs (SLD) treatment at a special unit in Juan Pablo Pina Hospital (HJPP), San Cristóbal, where 18 beds were assigned distributed in 3 rooms. The DOT-plus project protocol was accepted with a mixed model of care: a hospitalized phase, initially thought to be the intensive phase, and an ambulatory phase at centers near the patient's home. To increase the accessed to treatment, the hospitalization stage was reduced from 6 months in the original project to 90 days. It has been reduced to 45-60 days. In 2008, 9 more beds were assigned for patients from the north-central part of the country in Luis Morillo King Hospital, La Vega. Rooms in the hospital units are not individualized nor have negative pressure. There are located in the second and third level of old hospitals with a strong natural ventilation. By 2010, a complete ambulatory treatment model started in selected health centers, including primary care centers. Actually 22 centers have started SLD ambulatory treatments and there are 20 more under evaluation. Three rooms for separation were accommodated in HJPP in 2013. Until 2014, a total of 845 cases have initiated SLD treatment: 719 MDR/RR, 6 XDR, 48 poly-resistant, 72 presumed MDR cases. Eighty-six percent (86%) initiated with the mix model of care. All XDR patients started treatment hospitalized. The hospitalization period lasted between 6 to 8 months. Reviewing all cases from 2010 until 2012 (331 cases): 73% of those who started in mixed model had a successful outcome and 71% of the complete ambulatory care. The default rate was high in both but greater among those in the complete ambulatory model (26% versus 19%). Death was reported in 6% of the mix

model. The 2012 MDR cohort success rate was 72%, Of 2 XDR patients that initiated at 2011: 1 died and 1 failure. After having access to Group 5 SLDs, of the 4 patients in 2013, 3 are cured and 1 had failure, after irregular adherence. Patients with XDR had a hospitalization period of at least 6 months. For the Dominican Republic, the mixed model of care has showed good results in the management of drug-resistant TB.

South Africa: low-income, high-incidence, high programme budget

J Ferreira ¹North West Department of Health, MDR/XDR-TB Unit, Tshepong Hospital, Klerksdorp, South Africa.

In South Africa, tuberculosis is still the number one cause of morbidity and mortality, with 350 000 cases diagnosed annually. In 2013 cases diagnosed as Rifampicin resistant were 21 000, and confirmed MDR just less than 7000. There are 2500 beds available for DR-TB in the country, so we have decentralised care to a large extent. Well patients are managed as out-patients, with injection teams travelling to their homes to administer injections, and only sick patients are admitted. Patients with susceptible TB are managed at primary health care level. We have a population of 50 000 people in 9 provinces. The prevalence of HIV is estimated to be 15-20%, but among DR-TB patients it is as high as 75-80%. Susceptible TB has an 80% treatment success rate, but for MDR it drops to a country average of 40%, with a 20% defaulter rate, and a 20% mortality rate, for both HIV co-infected and non-infected patients. I work in the MDR/XDR-TB Unit at Tshepong Hospital in Klerksdorp, in the North West Province of South Africa. We provide services to 4000 people, as the Centre of Excellence in the province. The unit has 76 MDR and 22 XDR beds. Since the introduction of GeneXpert in 2011, the number of patients diagnosed with drug-resistant TB in our province has more than doubled (720 in 2014). Patients who are admitted in the unit have varied demographics: a) All smear positive patients – for isolation purposes, until smear negative; b) Smear negative patients who are weak and sick; c) Patients who cannot get to the clinic for injections/no injection team is available; d) Patients with poor social circumstances, and lack of support at home; e) Children with insufficient adult supervision at home; f) Chronic defaulters, who are repeatedly admitted in a poor condition; g) XDR and Pre-XDR patients until culture conversion. Since the opening of our unit in 2000, we have had successful outcomes for MDR-TB in 60% of cases, but since the necessary advent of decentralisation, we have noticed a significant increase in the number of defaulters in our province, as we have always strived to create a culture of adherence while patients are admitted in the unit. Conclusion: In South Africa there is a definite place for In-patient Units for management of DR TB, when taking into consideration the length of treatment, against the background of poor social circumstances.

50. Smokeless tobacco: a silent killer

Smokeless tobacco, cancers and cardiovascular diseases: a systematic review and meta-analysis

S Shah,¹ A L Vidyasagaran,¹ K Siddiqi,¹ M Jawad²

¹Department of Health Sciences, University of York, York,
²Imperial College, London, UK.

Background: Smokeless tobacco (ST) has long been recognised as a carcinogen in humans. Other potential health effects associated with its use include adverse cardiovascular outcomes such as myocardial infarction and stroke. A previous meta-analysis reporting the risk of cancers and cardiovascular diseases (CVD) among users of ST was restricted to studies from Sweden and North America. Recognising that ST consists of diverse products, and the products consumed in Asia are different from those consumed in Europe and North America, we aimed to update the existing review and expand on it by including studies from all geographical areas. We aimed to determine whether the ST products in Asia showed differences in their cancer and CVD risks as compared to products consumed in Sweden and North America.

Design/Methods: A systematic search of the literature was conducted by combining an exhaustive list of terms for ST with terms for specific cancers and CVD outcomes. The search was not restricted by language, search period, geographical areas or population characteristics. Studies included in the meta-analysis were identified after initial screening of abstracts, followed by full-text screening of short-listed papers. Both screenings were carried out independently by two reviewers. The meta-analysis was carried out using RevMan version 5.3.

Results: 39 studies reporting risk estimates for cancers of mouth, pharynx, oesophagus, larynx, pancreas and lungs were included. The pooled relative risk (RR) for mouth cancers was 3.43 (95%CI 2.26–5.19), pharynx 2.23 (95%CI 1.55–3.20), and oesophagus 2.17 (95%CI 1.70–2.78). 14 studies were included in the meta-analysis for CVD outcomes. While the pooled estimates did not show a significantly increased risk for CVDs, the RR for MI from studies in Asia was 1.40 (95%CI 1.01–1.95), and 1.57 (95%CI 1.24–1.99) from one large case-control study conducted in 52 countries.

Conclusion: ST is widely consumed worldwide and its use results in substantial morbidity and mortality. However, there are marked differences in the type of ST products available, patterns of consumption and associated risks in different regions and countries. Studies from Asia indicate an increased risk of cancers and CVDs for ST use, whereas results of studies from Europe and Americas do not support such an association.

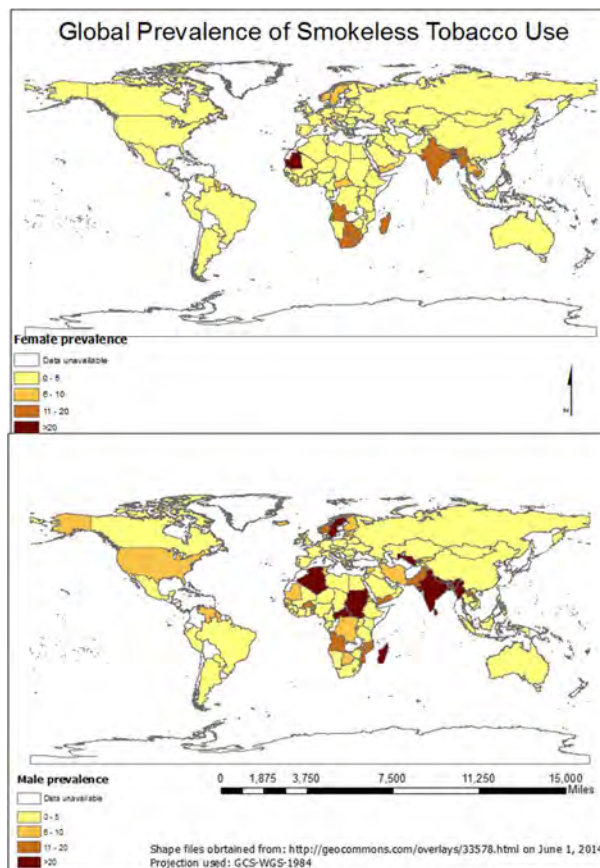
Global burden of disease due to smokeless tobacco consumption in adults: analysis of data from 113 countries

K Siddiqi,¹ S Shah,¹ A Vidyasagar¹ ¹University of York, York, UK.

Background: Smokeless tobacco is consumed in most countries in the world. In view of its widespread use and increasing awareness of the associated risks, there is a need for a detailed assessment of its impact on health. We present the first global estimates of the burden of disease due to consumption of smokeless tobacco by adults.

Methods The burden attributable to smokeless tobacco use in adults was estimated as a proportion of the disability-adjusted life-years (DALYs) lost and deaths reported in the 2010 Global Burden of Disease study. We used the comparative risk assessment method, which evaluates changes in population health that result from modifying a population's exposure to a risk factor. Population exposure was extrapolated from country-specific prevalence of smokeless tobacco consumption, and changes in population health were estimated using disease-specific risk estimates (relative risks/odds ratios) associated with it. Country-specific prevalence estimates were obtained through systematically searching for all relevant studies. Disease-specific risks were estimated by conducting systematic reviews and meta-analyses based on epidemiological studies. Results We found adult smokeless tobacco consumption figures for 115 countries and estimated burden of disease figures for 113 of these countries. Our estimates indicate that in 2010, smokeless tobacco use led to 1.7 million DALYs lost and 62 283 deaths due to cancers of mouth, pharynx and oesophagus and, based on data from the benchmark 52 country INTERHEART study, 4.7 million DALYs lost and 204 309 deaths from ischaemic heart disease. Over 85 % of this burden was in South-East Asia.

Conclusions: Smokeless tobacco results in considerable, potentially preventable, global morbidity and mortality from cancer; estimates in relation to ischaemic heart disease need to be interpreted with more caution, but nonetheless suggest that the likely burden of disease is also substantial. The World Health Organization needs to consider incorporating regulation of smokeless tobacco into its Framework Convention for Tobacco Control.



Smokeless tobacco consumption among adolescents: a global epidemiological perspective

I Agaku,¹ O Ayo-Yusuf² ¹Department of Office on Smoking and Health, Epidemiology branch, National Center for Chronic Disease Prevention and Health Promotion, U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Department of Office of the Director, School of Oral Health Sciences, University of Limpopo, Medunsa Campus, Pretoria, South Africa.

Background: Smokeless tobacco (ST) products can lead to tobacco addiction, disease, and death. The cultural differences in global adult tobacco use suggest that adolescents' tobacco use may also vary across cultures. We assessed ST use among adolescents in 57 countries during 2007-2010 using school-based surveys.

Methods: Data were analyzed for 57 countries for which nationally representative data were available, using the 2007-2010 Global Youth Tobacco Surveys (for 55 countries); the 2009 US National Youth Tobacco Survey, and the 2008-2009 Canada Youth Smoking Survey. Number of countries by World Health Organization (WHO) region were: Africa, AFRO ($n = 11$); Eastern Mediterranean, EMRO ($n = 9$); Europe, EURO ($n = 11$); the Americas, AMRO ($n = 14$); South-East Asia, SEAR ($n = 8$), and Western Pacific, WPRO ($n = 4$). Analyses were restricted to persons aged 13-15 years in each country. Current ST use was defined as past 30-day use of chewing

tobacco, pinch, snuff, dip, or snus. Data were weighted and analyzed by sex, WHO region and World Bank national income categories. Cross-country dispersion in ST use was assessed with the Coefficient of variation (CV).

Results: ST use varied widely among countries (CV=0.62); overall prevalence ranged from 1.1% in Montenegro to 16.4% in Congo. Prevalence by WHO region was: AFRO (median = 7.4%; range=5.4% to 16.4%); EMRO (median = 5.1%; range=1.6% to 12.6%); EURO (median = 2.0%; range=1.1% to 6.9%); AMRO (median = 5.3%; range=1.8% to 9.8%); SEAR (median = 6.3%; range=2.8% to 9.4%), and WPRO (median = 5.1%; range=2.1% to 8.7%). Prevalence by national income category was: low-income countries (median = 6.2%; range=2.5% to 16.4%), lower-middle-income countries (median = 6.2%; range=2.0% to 14.4%), upper-middle-income countries (median = 4.7%; range=1.1% to 11.3%), and high-income countries (median = 3.4%; range=1.8% to 9.8%). Overall ST prevalence exceeded 10% in 5 countries – 4 in AFRO and 1 in EMRO regions. Girls' ST use equaled or exceeded that of boys' in 10 low and middle income countries.

Conclusions: These findings suggest that region-specific patterns of ST use exist, with higher ST use observed in low and middle income countries, particularly in the AFRO and SEAR regions. Evidence-based interventions outlined in the WHO MPOWER package, such as raising tobacco taxes, and warning about the dangers of tobacco use, may prevent and reduce ST use among adolescents.

Smokeless tobacco addiction: an evaluation of ST dependence measures in Bangladeshi consumers

R Huque,¹ K Siddiqi,² S Shah² ¹University of Dhaka, Dhaka, Bangladesh; ²University of York, York, UK;

Background: Smokeless tobacco (ST) is an emerging public health issue in Bangladesh where adult ST use prevalence is more than 20% and in certain subgroups of population its prevalence is more than 40%. ST products contain high nicotine content which is highly addictive. With scarcity in research related to ST dependence, we have conducted a validation study to assess whether and to what extent the psychometric properties of existing tobacco dependency measures are a reliable and valid measure of tobacco dependence among Bangladeshi ST users. We also explored the underlying constructs and processes that explain dependence among ST users in Bangladesh.

Design/Methods: We recruited 200 ST users (50 male and 50 female) from Dhaka city through convenience sampling techniques. Target respondents for this study were adult (age greater than 18 years at the time of study enrolment) smokeless tobacco users with a history of >1 tin/pouch ST use per week for at least one year, and non smokers. An existing questionnaire to measure dependence had been used to study participants and its psychometric properties were assessed using quantitative

methods. Saliva samples were collected from participants and tested to measure their cotinine concentration.

Results: The findings suggest that majority of the users used Zarda (68.5%) followed by betel quid with tobacco (6%). On an average, a user takes ST 11.7 times per day. Around 9% users take ST daily and 42% users felt the urge to use ST all the time while 27% had the urge almost all the time. Only 19% users attempted to quit ST use in last 12 months and only 21.5% users tried to cut down the ST use. The findings show that 50% of the users had very high dependency on ST and 41% had high dependency. The mean cotinine concentration among ST users was 462.7 (SD 270.9). Beta coefficient presents increase in cotinine concentration with decrease in time to place first dip after waking up.

Conclusion: Bangladeshi ST consumers are highly dependent on ST and their cotinine concentration is also very high, which needs attention of policy makers.

Developing and evaluating a behavioural support intervention for smokeless tobacco cessation in Pakistan and the UK

O Dogar,¹ K Siddiqi,¹ C Jackson,¹ R Bibi,¹ H Thomson,² I Kellar³ ¹Department of Health Sciences, University of York, York, ²Department of Health, Leeds City Council, Leeds, ³Institute of Psychological Sciences, University of Leeds, Leeds, UK.

Background: Around 300 million people worldwide consume smokeless tobacco (SLT). Considered to be a part of the culture, its use is particularly common in people of South Asian-origin. A recent Cochrane review suggests that behavioural support interventions (BSIs) are likely to be effective in SLT cessation. However, studies in this review were mainly conducted in the US and European populations who, compared to South Asians, use less addictive and less hazardous products (e.g. moist snuff). Moreover, its consumption among South Asians has strong socio-cultural dimensions, which need to be considered in BSIs. We aim to evaluate the acceptability, feasibility and fidelity of a new BSI for South Asians trying to quit using SLT.

Methods: This is a two-country, multi-method pilot study, using qualitative and quantitative methods develop a solid theoretical framework for development of a SLT cessation intervention that is culturally appropriate for use with the South-Asian population. The BSI was developed, tested and refined in three iterative phases: Development phase (6 months): Two expert panel workshops were conducted to, first, select the behavioural determinants of SLT use and related behaviour change techniques (BCTs) based on their importance and relevance and second, to inform the structure and key messages for the intervention. Feasibility assessment phase (8 months): The BSI was tested at five sites in the UK and Pakistan, delivered by trained cessation advisors to 32 SLT users. All BSI sessions (pre-quit, quit and post-quit) will be audiotaped and analysed for fidelity, 16 participants and four advisors will be interviewed in depth to assess the feasibility and acceptability. All study

participants will be tested for SLT use status via urine/salivary cotinine testing at 6 months. Refinement phase (4 months): The BSI will be refined in light of the results from feasibility testing.

Results: Findings from the qualitative interviews, the audio-taped sessions' and participant SLT use status at 6 months will inform any further modifications needed in the content, structure or format of the BSI.

Conclusion: The refined BSI will be the first behavioural intervention of its kind developed specifically for SLT users of the South Asian-origin, with a comprehensive methodology involving the use of BCTs proven effective for tobacco cessation, ready for effectiveness testing in a randomised controlled trial.

51. e/m-Health as a transformational tool in TB control in high-burden countries

Setting up eHealth for TB at scale: lessons learned

D Falzon Global TB Programme, World Health Organization, Geneva, Switzerland.

In the last decades, advances in information and communication technologies (ICT) have stimulated many innovative e/mHealth interventions targeting various components of TB care and prevention in both high and low resource settings. The population-level impact of these efforts remains nonetheless unclear to a large degree and the evidence incomplete or at times conflicting. This is a result of two basic weaknesses: firstly, that only a relative minority of digital health interventions has succeeded in moving beyond the piloting phase; and secondly because implementation research on scalability has been relatively rare. The presentation will touch upon i) the definitional issues of what 'scale' signifies to different users and which elements could be scaled (project, strategy or technology); ii) the implementation concerns such as the importance of identifying and aligning the motives of different constituencies to increase long-term project viability; what resources and components are required to grow a project from pilot to large scale; and handling the rapidly-evolving landscape of ICT, and iii) the evaluation of effect, the documentation of unintended consequences and how measurement may change according to the technology and as the intervention moves to scale. The logistics of scalability differs substantially across the broad array of digital products which exist or which are expected in a near future. For instance, multilingual eLearning material could swiftly reach across huge geographic space when it takes advantage of an ever-expanding internet penetration. Other approaches, such as SMS-mediated interventions to improve patient treatment adherence; video observed therapy; and the management of surveillance data through online networks, are also relatively well positioned for rapid scale-up. The contents of the 'Digital Health for the End TB Strategy : an agenda for action', which was elaborated by

WHO's Global TB Programme, the European Respiratory Society and other partners in 2015, will be used to discuss potential digital health approaches for TB care and prevention under four rubrics: patient care, surveillance and monitoring, programme management and eLearning. Published literature and results from selected projects - including experiences from outside the TB field but which are reasonably applicable - will be used to illustrate issues relevant to the scalability of the digital health products prioritised by the strategic agenda for TB.

Challenges and opportunities for implementing e/m-Health for TB in resource-limited settings: experience from Georgia

T Gabunia ¹University Research Co. LLC Branch Office, Tbilisi, Georgia.

Background: Tuberculosis and especially drug resistant TB are critical public health threats in Georgia. In 2014, MDR-TB was found in 11.2% of new and 38.6% of previously treated cases. In response to TB challenges the Government of Georgia (GoG) has identified effective governance and monitoring of TB response as strategic priorities, including development of a well-designed health management information system (HMIS) which is critical for effective program monitoring, and evidence-based policy making. **Intervention:** The USAID Georgia Tuberculosis Prevention Project has assisted the National TB program in introducing innovative m/ eHealth tools using mobile phones, tablets, and web-based systems to enable optimization of communication and the exchange of information, and data among healthcare professionals and with patients. The e-TB system is composed of TB case registration, laboratory, prescription and treatment monitoring components. All indicators and data collection tools are aligned to the latest WHO standards. The e-TB module works by allowing providers to upload data to the system quickly for each patient with TB and presumptive TB. The Ministry of Health uses the module for generating case-based financial reports and simplifying transactions via electronic reporting. The mHealth component is also functional that facilitates patient counselling using a tablet based education module (which time- and geo-tags sessions) and allows electronic recording of patient attendance to directly observed therapy sessions via SMS. **Results:** After a successful pilot, a Government Decree has mandated electronic recording and reporting of TB related data from May 1st, 2015 onward. Within the first quarter of the implementation more than 80% of TB providers countrywide started using the eTB module on a daily basis. There were 2947 TB cases currently on treatment registered and daily DOT attendance reported for 92% of cases.

Conclusion: Availability of real time data on TB is of critical importance for timely risk analysis and providing adequate resources to high-risk TB patients. The high-level political commitment, donor support and private sector involvement have been the critical factors ensuring

the implementation of the new HMIS module. The political will and collaboration of many stakeholders promoted the system's sustainability by overcoming the initial barriers such as low computer literacy and lack of IT infrastructure and limited access to the Internet.

Using geographic information systems and patient mapping tools to improve follow up and support for MDR-TB patients in Swaziland

M Calnan,¹ T Zanamwe¹ ¹University Research Co. LLC, Mbabane, Swaziland.

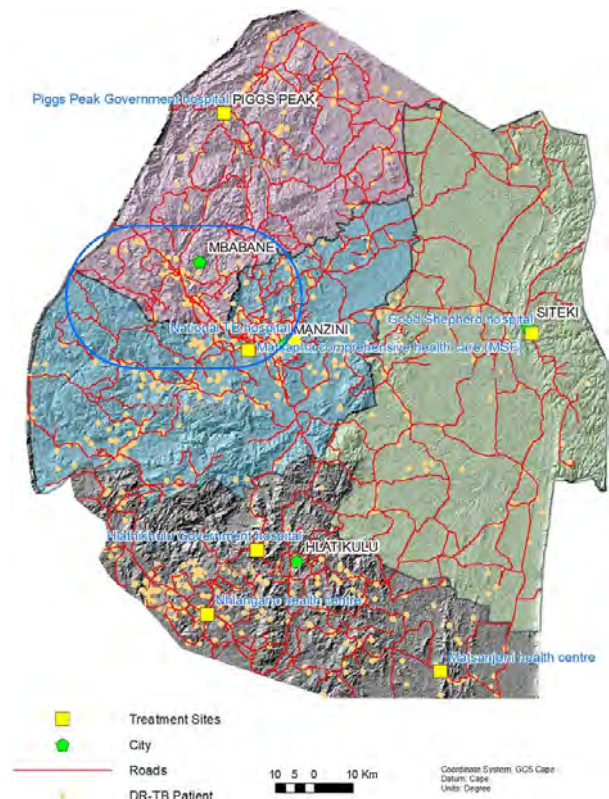
Background: Swaziland is challenged by dual epidemics of Multi-Drug Resistant TB and HIV. A TB drug resistance survey conducted in 2010 reported MDR-TB prevalence of 7.7% in new patients and 33.8% in previously treated patients, with an estimated 200 cases occurring annually. Mobile populations, reluctance to take long and difficult treatment for MDR-TB and limited country resources makes it difficult to keep patients engaged in care. Systems to track and follow up patients have not been effective unless patient can be traced physically and treatment provided nearer their homes.

Intervention: Geographical information systems (GIS) introduced in 2010 have been used to locate MDR-TB patients in the community and contribute to the national surveillance. Once registered in care, MDR-TB patients are visited at home: geo-coordinates of the homestead are obtained and uploaded. Active cell phone numbers for the patient and treatment supporter are also obtained and clinic contacts shared should patient have any concerns. Once patient misses a clinic appointment, the follow up tracking system is effected; patients receive a phone call to enquire the reason for missing the appointment and a home visit is scheduled. Location of the home is guided by the coordinates earlier captured. Patient coordinates are transposed into a map which is used to: determine location and distribution of the patients, distance to nearest health facility, monitor for hotspots or clustering of the disease and plan for decentralization of MDR-TB treatment services.

Results: Between 2010 and 2015, 1050 MDR-TB patients have been mapped; majority of the patients being situated along the Manzini-Mbabane corridor and the border with South Africa. Four hotspots have been identified over this period and outbreak investigation reports reveal that slums, seasonal workers and highly industrialized areas characterize these hotspots. With phone call follow up and home visits, the lost to follow up has declined from 35% in 2012 to 18% in 2015. The distribution of the patients has informed the decentralization of MDR-TB services to 2 more facilities. Client satisfaction surveys reveal that patients feel connected to their care givers and are satisfied with the services provided.

Conclusion: M-Health has informed the service delivery for MDR-TB patients in Swaziland and has the potential to be used for other chronic diseases that require patients

to remain engaged in care such as Diabetes Mellitus and HIV.



52. Developing a rights-based approach to prevention and treatment of tuberculosis

Empowering women and children through a rights-based approach to TB

P Mahesh ¹ALERT-INDIA, Mumbai, India.

A human rights-based approach to TB that ensures fundamental human entitlements – social, economic and political promote the well-being and empowerment of women and girls. However, a human rights-based approach to TB prevention and care, while aiming to realize equal human rights for women and girls. Empowerment lies in developing their awareness, as human rights cannot be given, but must be actively claimed by those who hold them. Barriers to the realization of human rights for women and children increase their vulnerability to TB and restrict their access to diagnostic and treatment services. The need of the hour is to address the socioeconomic and other health determinants. My first-hand experience as a TB patient of how devastating TB is, not only threatens people's bodies, but also economic livelihoods and closest relationships'. The primary barriers women and girls face is a lack of autonomy, financial and physical dependency and no or relatively low TB-related literacy,

which impacts negatively and perpetuates stigma. Interventions to address these barriers include legal literacy campaigns, inclusion of women with TB in program development, advocacy, lobbying and implementation of laws and policies that prohibit discrimination. Interventions to expand access to quality TB prevention and care should aim to establish an enabling legal and policy environment. Empowerment of women and girls through right health education about TB and their rights during intensive case detection enable them to fight the disease without discrimination. A rights-based approach to TB will compel governments to take responsibility to ensure women with TB are empowered enough to engage in policy making through representation in public institutions and other bodies so that they can contribute to decisions that affect them and their communities as this recognizes the need for women and girls to actively claim rights in order to achieve better prevention and treatment outcomes. It also promotes the knowledge and understanding of legal instruments and institutional machinery to seek protection and redress for rights violations. And crucially, it demands the; participation of women in standard setting and in formulating, implementing, and monitoring laws, policies, and programmes to combat TB by promoting a gender response approach to TB prevention and care.

SYMPOSIA: SUNDAY 6 DECEMBER 2015

53. Fighting TB in the post-2015 era: paradigm shift in strategies and plans to put an end to TB

New approaches in financing health and development: implications for the fight against TB

P L Osewe ¹World Bank Group, Washington, DC, USA

In the last 25 years, countries have made great strides in reducing maternal and child mortality: since 1990 there has been a 47% reduction in maternal mortality and a 49% reduction in child mortality.¹ Despite these tremendous gains, much more needs to be done. The child mortality rate in low-income countries is more than 15 times higher than in high-income countries and maternal mortality is nearly 30 times higher. Yet, there is an opportunity for a 'grand convergence' in mortality between low-income countries and the best-performing middle-income countries. To achieve this convergence, however, countries will need to significantly ramp up investments in reproductive maternal, newborn, child and adolescent health. Such increased investment has the potential to help prevent a total of 4 million maternal deaths, 101 million child deaths, and 22 million births between 2015 and 2030 in 74 of the highest burden countries.² On July 13, 2015, the United Nations, the World Bank Group, and the Governments of Canada, Norway and the United States joined country and global health leaders to launch the groundbreaking Global Financing Facility (GFF) in support of *Every Woman Every Child*. The GFF is a key financing platform of the United Nations Secretary-General's Global Strategy for Women's, Children's and Adolescents' Health. It aims to mobilize private sector resources that, in addition to public sector resources, help close the \$33.3 billion annual funding gap in the financing of essential interventions required to improve the health of women, children and adolescents.³ The GFF is an essential part of the paradigm shift in development financing, emphasizing the essential but changing role of official development assistance in unlocking domestic resources and private flows and focusing on results. It also has the potential to act as a pathfinder for financing the SDGs in the post-2015 era. This session will discuss the creation of the GFF, key lessons learnt for innovative financing of health sector priorities, and the implications for the fight against TB. The target audience includes policy makers; TB programme managers and health services providers; civil society and non-governmental organisation representatives; development partners.

References

¹ The Global Strategy for Women's, Children's and Adolescents Health

² Global Financing Facility in Support of Every Woman Every Child. Concept Note. September 2014.

³World Bank Press Release. July 13, 2015. *Global Financing Facility Launched with Billions Already Mobilized to End Maternal and Child Mortality by 2030*

Community-led planning and implementation of TB initiatives in the post-2015 era

T Abdullaev ¹Stop TB Partnership, Geneva, Switzerland

Communities of people affected by TB may be instrumental in various activities, from raising awareness and counseling to active case finding, psychosocial support and service provision. The voices of patient community, their unique experiences are crucial in programme planning, implementation, monitoring and evaluation. However, the principle 'Nothing For Us Without Us', so common in HIV world, continues to be largely neglected in the TB community. Patients are still seen by many as recipients of services rather than a helpful resource. The change in the attitude towards patients has been consistently promoted by the Stop TB Partnership. In its new Global Plan to Stop TB, the Stop TB Partnership stresses that, 'If countries are to move away from this passive approach to one where they seek to find and treat all the TB existing in their population, a radical shift in mindset is needed. Innovative changes to health delivery systems are required to navigate that roadmap. This is where civil society and communities have a critical role to play. These stakeholders [...] have already been identified as fundamental in the drive towards better access to health and universal health coverage'. But even with recognition of the importance of engagement of the patient community, little can be changed without consistent support to the process of community mobilization and strengthening. The development of communities of PLHIV often became possible due to the community mobilization, capacity building, institutional, technical and financial support efforts by UNAIDS, the Global Fund and other partners. If similar efforts are taken to strengthen the community of people affected by TB, they will be able to become important partners in ending TB epidemic. For the post-2015 era to be a turning point in the fight against TB, patient community has to be engaged meaningfully in programme development, implementation and assessment. The Global Fund's funding model envisages involvement of community representatives in the country dialogue. This participatory approach should be replicated beyond the Global Fund. It is also important for existing community networks, such as the Global Coalition of TB Activists, regional and local TB coalitions, to continue their work aimed at supporting the development of capacity and leadership potential of patient activists, networking of patients and their groups, inclusion of patient representatives in policy and decision making at all levels.

54. Critical updates on the treatment of TB-HIV co-infected children

Morbidity and mortality in TB-HIV co-infected children on TB treatment initiated on ART in the PAANTHER cohort in Asia and West Africa

O Marcy,¹ L Borand,¹ M Tejiokem,² F Ateba Ndongo,³ B Nacro,⁴ P Msellati,⁵ K Truong Huu,⁶ V Ung⁷ ¹Institut Pasteur du Cambodge, Epidemiology and Public Health Unit, Phnom Penh, Cambodia; ²Centre Pasteur du Cameroun, Service d'Epidémiologie et de Santé Publique, Yaounde, ³Centre Mère et Enfant de la Fondation Chantal Biya, Yaounde, Cameroon; ⁴Centre Hospitalier Universitaire Sourou Sanou, Bobo Dioulasso, Burkina Faso; ⁵UMI 233- U1175 TransVIHMI, IRD, Université de Montpellier, Montpellier, France; ⁶Pediatric Hospital Number One, Ho Chi Minh City, Viet Nam; ⁷University of Health Sciences, Phnom Penh, Cambodia,

Background:: Despite expanded access to antiretroviral treatment (ART) which has modified HIV-TB co-infection epidemic and had a great impact on TB disease incidence, TB remains a frequent opportunistic infection in HIV-infected children with major treatment challenges. Data is scarce on pediatric mortality and morbidity under joint TB and ART.

Methods: HIV-infected children aged ≤ 13 years with a suspicion of intra-thoracic TB were enrolled in the PAANTHER cohort after parental informed consent in pediatric HIV clinics in Burkina Faso, Cambodia, Cameroon, and Viet Nam. Children underwent TB diagnostic procedures and were initiated on ART and TB following national recommendations. We assessed mortality and morbidity over a follow-up period of 6 months.

Results: A total of 438 children were enrolled in the cohort, including 171 (39%) on ART at inclusion. In the 267 children without ART at inclusion, 138 (51.7%) were male, the median age was 6.2 (IQR 2.3-9.1) years, the median CD4% was 9.0% (IQR 2.0 – 18.0), and the median viral load was 5.9 (IQR 5.4 – 6.4) log₁₀ copies/ml. Of these 267 children, 139 (52.1%) were initiated on TB treatment within a median time of 7 days (IQR: 4 – 10) with 119 (85.6%) subsequently initiating ART, and 128 children were not treated as TB with 97 (76.7%) initiating ART. Overall, ART was started at a median time of 0.8 (IQR: 0.5 – 1.4) months after inclusion and the median duration of follow-up was 5.9 months (95%CI: 5.5-6.3). Mortality rates dropped from 92.5 per 100 PY (95%CI: 62.8 - 131.7) to 29.6 (53.4 - 118.8) after ART introduction: 28 children died before ART initiation and 24 while on ART, with 16 deaths occurring in children on TB drugs and ART. Of 119 children treated for TB who secondarily initiated ART, 12 (10.0%) died, 5 (4.2%) had a paradoxical TB-associated IRIS reported, and 16 (13.4%) had non-tuberculosis mycobacteria (NTM) diagnosed secondarily. NTM infection was not associated with mortality ($P = 1.0$). In the 97 children without initial TB diagnosis who initiated ART, 13 (13.4%) were subsequently treated for

TB, which was associated with a higher risk of mortality (adjusted OR 6.0, 95%CI 1.3-28.1).

Conclusion: Mortality remains high in the first 6 months following suspicion of TB in ART-naïve children, despite prompt TB treatment and access to ART. Shorter time to ART initiation, improved

Understanding the contribution of HIV to the risk of developing tuberculosis in children: a systematic review and meta-analysis

P Dodd,¹ J Seddon² ¹University of Sheffield, Sheffield, ²Imperial College London, London, UK

Following infection, children are at elevated risk of progression to active tuberculosis (TB), and are more prone to severe manifestations of disease. In adults, infection with the human immunodeficiency virus (HIV) is well established as a potent risk factor for TB progression the protective effect of anti-retroviral therapy (ART) has been quantified. A similar quantitative understanding of the effects of HIV and ART on TB progression in children is lacking. We sought to address this gap by a systematic review of the literature. Two classes of study were identified: 1) 'TB cohorts' - children with TB where HIV prevalence had been measured; 2) 'HIV cohorts' - children with HIV infection where the incidence of TB had been measured. Our literature search identified 3197 potentially relevant records. After screening, full text articles were assessed for 271 of these. This resulted in 38 TB cohorts and 31 HIV cohorts. Data on HIV infection were extracted from TB cohorts, a subset of which included data on HIV infection prevalence in children without TB. A random effects meta-analysis was applied to synthesise an odds ratio for HIV infection given TB disease, which can be transformed into an incidence rate ratio for TB disease given HIV infection. A confirmatory analysis was performed on all TB cohorts, using UNAIDS HIV prevalence estimates as controls. We found that, as with adults, HIV in children is a strong risk factor for progression to TB disease, and ART strongly protective. This emphasizes the importance of prevention of mother-to-child HIV transmission in averting paediatric TB in high HIV-prevalence settings.

TB screening and IPT delivery in HIV-infected children: programmatic uptake and challenges in Mozambique

WC Buck,¹ P Gudo,¹ H N Raman,¹ K Jobarteh,¹ F Bata,² A Couto,² K Alberto,³ I Manhiça³ ¹Centers for Disease Control and Prevention, Maputo, Mozambique, ²Department of HIV and STIs, Mozambique Ministry of Health, Maputo, Mozambique, ³National TB Control Program, Mozambique Ministry of Health, Maputo, Mozambique

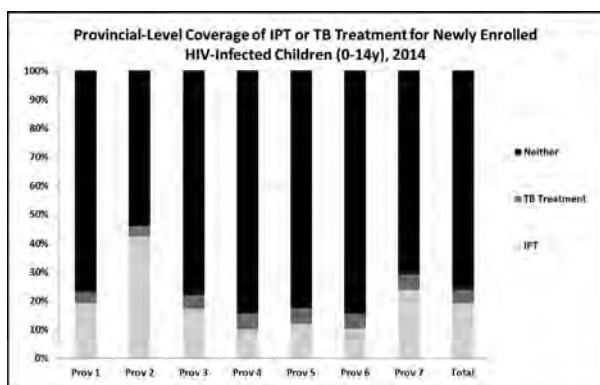
Background: TB is a leading cause of morbidity and mortality in HIV-infected children. Early diagnosis of both TB and HIV can improve outcomes, and Mozambique guidelines recommend active case-finding through

routine opt-out testing (ROOT) for HIV in children with TB and routine screening for TB at all HIV consultations. The burden of TB in HIV-infected children can be reduced with isoniazid preventive therapy (IPT), and national guidelines call for its use in newly enrolled children without active TB.

Methods: The Centers for Disease Control and Prevention (CDC) supports the Mozambique Ministry of Health HIV and TB programs and PEPFAR-funded clinical partners report routine data from both programs. Facilities serving 72.4% of children in HIV care in the seven CDC-supported provinces use electronic patient tracking systems (EPTS). This was a retrospective review of site-level TB-HIV indicators for children 0-14 years from EPTS sites over three program years (2012-2014) to assess compliance with guidelines and identify areas for improvement.

Results: From the TB sector, ROOT for patients of all ages (disaggregated data not available) improved from 92% to 98% (2012, 2014). From the HIV sector, TB screening for HIV-infected children at the last visit increased from 50% to 77% (2012, 2014). This correlated with an increase in the percentage of HIV-infected children in care receiving TB treatment each year from 1.4% to 2.9% (2012, 2014). And for newly enrolled children, the percentage receiving either IPT or TB treatment increased from 8.4% to 24.0% (2012, 2014), with provincial results in the Figure.

Discussion: Active HIV case-finding in the TB sector is programmatically strong with ROOT approaching 100% coverage. Results for intensified TB case finding in the HIV sector are below targets, but improving. While it is not possible to definitively link the increase in pediatric TB treatment to more frequent screening, it is encouraging to see these indicators trend together, and monitoring them as a pair may be a way to assess the quality of TB screening. IPT for newly enrolled children remains a significant challenge with only about 25% of eligible patients being reached in 2014. Further research is needed to identify barriers which may include provider training and comfort ruling out active TB in settings with limited diagnostics, medication availability, or patient factors, so that targeted activities can be designed to accelerate scale-up this evidence-based intervention.



Pharmacokinetics of the first-line TB drugs in West African children with and without HIV co-infection

A Kwara,^{1,2} F Gallani,^{1,2} A Enimil,^{3,4} A Sarfo,³ A Orstin,³ S Antwi,^{3,4} H Yang,⁵ L Wiesner⁶ ¹Medicine, Warren Alpert Medical School of Brown University, Providence, RI, ²Medicine, The Miriam Hospital, Providence, RI, USA; ³Child Health, Komfo Anokye Teaching Hospital, Kumasi, ⁴Child Health, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; ⁵Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; ⁶Medicine, University of Cape Town, Cape Town, South Africa.

Background: Pharmacokinetic data on the first-line antituberculosis drugs in children is limited. We investigated the pharmacokinetics of these drugs in children who were mostly treated with World Health Organization (WHO) revised dosages for children.

Methods: Ghanaian children with tuberculosis on first-line therapy for at least 4 weeks had blood samples collected at pre-dose, 1, 2, 4, and 8 hours post-dose. Drug concentrations were determined by validated liquid chromatography mass spectrometry methods and pharmacokinetic parameters calculated using noncompartmental analysis. Factors associated with plasma peak concentration (C_{max}) and the area under the time-concentration curve 0-8h (AUC_{0-8hr}) of each drug were examined using univariate and multivariate analysis.

Results: Of the 62 children, 32 (51.6%) were male, 29 (46.8%) were younger than 5 years old and 28 (45.2%) had HIV coinfection. Three patients had undetectable pyrazinamide and ethambutol concentrations. The median (IQR) AUC_{0-8hr} for isoniazid was 17.7 (10.2 – 23.4) µg.hr/mL, rifampin was 26.0 (15.3 – 36.1) µg.hr/mL, pyrazinamide was 144.6 (111.5 – 201.2) µg.hr/mL, ethambutol was 6.7 (3.8 – 10.4) µg.hr/mL. Of the children who received recommended weight-band dosages, 44/51 (86.3%), 46/56 (82.1%), 27/56 (48.2%) and 21/51 (41.2%) achieved target C_{max} for isoniazid, pyrazinamide, ethambutol and rifampin, respectively. In multivariate analysis, age, Sex, HIV coinfection status, and drug dosage in mg/kg were associated with the drugs plasma drug C_{max} or AUC_{0-8hr}.

Conclusions: The WHO revised dosages appeared to be adequate for isoniazid and pyrazinamide, but not for rifampin or ethambutol in this population. Higher dosages of rifampin and ethambutol than currently recommended may be required in most children. Children with HIV coinfection had lower plasma exposure of the first-line antituberculosis drugs.

55. Why are DR-TB patients lost by TB programmes? Patients' perspective on how to address DR-TB treatment adherence

Why are patients not adherent to DR-TB treatment? Patients' testimony

J Furin ¹Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA,

Discussions on adherence tend to exclude the voices of individuals with DR-TB and those of survivors. These leads to adherence strategies that may not be of greatest benefit to the affected community. This presentation will focus on actual experiences of persons who have survived DR-TB or who are currently undergoing therapy. Such insights and experiences are the only way to truly build 'patient-centered care.'

Addressing LTFU in high-burden MDR-TB countries: example from Belarus

A Skrahina,¹ G Gurevich,¹ D Klimuk,¹ L Zhilevich,² A Tkacheva,³ P De Colombani,⁴ M Dara,⁴ D Falzon⁵
¹Ministry of Health, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, ²Ministry of Health, General Directorate of Medical Care, Minsk, ³Ministry of Health, Directorate of Economic Analysis and Development of Health, Minsk, Belarus; ⁴World Health Organization (WHO), Regional Office for Europe, Copenhagen, Denmark; ⁵Global TB Programme, WHO, Geneva, Switzerland.

Background: Notification of TB new cases and deaths in Belarus has been progressively falling respectively from 54 to 41 and from 12.1 to 6.8 per 100 000 population during the last 7 years. Nevertheless, MDR-TB was found in 32% of the newly-diagnosed and in 76% of the previously-treated TB cases (2011 nationwide drug resistance survey). Treatment outcomes of MDR-TB are far from satisfactory (51% treatment success, 11% deaths, 24% failures and 10% loss to follow up). Outpatient care can reduce the risk of cross contaminations in health facilities, the cost of MDR-TB treatment and disruption of their social and working life. Nevertheless, evidence shows that strengthening outpatient care is very important to prevent treatment failure and loss to follow up, particularly among those patients at higher risk such as the unemployed, homeless, alcohol and drug users, former prisoners.

Method: A pilot project started in January 2014 in Mogilev region with WHO support. In this project, the Ministry of Health provided additional remuneration to primary health care providers them with for every TB patient visited from cost savings by reducing the number of TB hospital beds.

Results: Two operational research studies were conducted during the implementation of the project. One showed that MDR-TB treatment cost can be reduced by more than 5200 US\$ per patient by decreasing inpatient care with outpatient care and social support. The other study

showed that MDR-TB patients with social support had better treatment outcomes compared with those without it: treatment success 70% vs. 53%; mortality 2% vs. 6%; treatment failure 27% vs. 40%.

Conclusion: Reallocation of funds from TB hospitals to primary health care is an essential element for improving MDR-TB treatment outcomes and effective and sustainable patient support.

Reaching zero LTFU through community-based care for DR-TB and HIV co-infected patients: example from South Africa and Lesotho

L Ramangoela-Molatlhohle ¹Health Department, Dr J S Moroka, Free State, South Africa

Background: South Africa is one of the countries in the world highly burdened with DR TB with poor overall treatment outcomes especially notable for high rates of loss to follow-up. The Free State province has approximately 480 DR TB patients and faces serious challenges keeping patients in therapy. Free State is located at a National and International crossroads in Southern Africa and it is home to a large migrant population. This population is faced with serious challenges when it comes to successfully completing therapy. Of note different rates of lost to follow up occur at different stages of treatment 6, 12, 18, 24 months of treatment and different barriers have been noticed and established at these different stages. Based on the statistics of these lost to follow up patients the plan is to look retrospectively at the records to identify these factors and to plan for interventions and to improve retention in care.

Methodology: Retrospective review of records and trends of patients seen at the Drug resistant Tuberculosis units in the Free State as well as information gathered from TEBA Free State and Lesotho.

Results: Preliminary review of the information shows that more than 25% are lost to follow up after enrolling in care and treatment. These would be patients who interrupt, default, relocate, die, or leave the facility after initiation on treatment. The review analysis also shows that these patients face multiple barriers in completing therapy including, socio-economic, transportation and adverse events to treatment. Some of these patients are traced back to treatment, others were not found, others had died.

Interpretation and conclusion: New strategies are needed. Preliminary data suggests that community based models of care that bring services closer to the patients and provide ongoing monitoring and early interventions to adverse events and other social problems facing the patient population are urgently needed. These strategies will also help retain patients in care. Also it is important to look at strategies that that will assist the households and implement preventive therapy for those households exposed.

Study results: LTFU among MDR-TB patients in the Philippines and what other countries can learn

E Kurbatova,¹ T Tupasi² ¹The US Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA; ²Tropical Disease Foundation, Inc, Makati City, Philippines.

Background: In the Philippines, the number and proportion of patients lost to follow-up (LTFU) in the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) has steadily increased each year since 2007. This study was undertaken to identify factors associated with LTFU from multidrug-resistant (MDR) tuberculosis (TB) treatment.

Methods: A case-control study included adult (≥ 18 years old) patients with rifampicin-resistant TB who initiated MDR TB treatment between July 1-December 31, 2012 in the Philippines. Cases were patients lost to follow-up from MDR TB treatment. Controls were patients who were continuing MDR TB treatment or had a treatment outcome of cured, completed, or failed. In-depth interviews were conducted with both cases and controls, and their medical records were reviewed. Independent predictors of LTFU were identified using multivariable logistic regression analysis.

Results: A total of 91 cases and 182 controls were enrolled. Among cases, the mean age was 41+13 years, 66% were males, and 1.7% were HIV positive. Among controls, the mean age was 37+12 years, 57% were males, and 1.7% were HIV positive. Independent predictors of LTFU included: patients' rating of their vomiting as more severe following medication doses (OR=1.10 per one point in cumulative score, 95% CI 1.01-1.21), and alcohol abuse (OR=2.84, 95% CI 1.39-5.80), while protective factors included: receiving any type of assistance from the TB Program (OR=0.08, 95% CI 0.03-0.25), better general TB knowledge (OR=0.97 per point in cumulative score, 95% CI 0.95-0.99), and higher levels of trust in, rapport with, and support from physicians and nursing staff (OR=0.93 per one point in cumulative score, 95% CI 0.90-0.96). The most common patient-reported reason for LTFU was adverse drug reaction (ADR) or the fear of ADR (58%).

Conclusion: Interventions aimed at reducing treatment LTFU should include prevention and effective management of ADRs, patient education, enhancing provider-patient relationships, and improving program assistance for patients.

56. The relationship between gender and specific tobacco products, tobacco consumption and inequalities

Inequalities, gender and tobacco consumption

A Amos ¹Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK.

Smoking is the leading preventable cause of premature mortality and socioeconomic inequalities in health in women in many high income countries (HICs) that are at

Stage 4 of the tobacco epidemic. This includes countries such as the US, Canada and several countries in the European Union including the UK. While female smoking prevalence in these countries is declining, the social gradient in smoking is not. Indeed, female smoking is increasingly concentrated among disadvantaged groups. In HICs girls from disadvantaged backgrounds are more likely to start smoking and less likely to quit when adults. In low and middle income countries (LMICs) the pattern is more complex, but there is also evidence that smoking by girls and women is linked to disadvantage. This presentation will give an overview of inequalities in smoking in girls and women around the world. It will then draw on the findings of three recent systematic reviews on social inequalities and smoking to identify those policies which have a positive equity impact ie reduce inequalities in smoking. The reviews covered: population and individual level interventions/policies on youth smoking prevention; population level interventions/policies on adult smoking cessation; and individual level adult cessation support interventions. The presentation will highlight the lack of studies which have assessed the equity impact of tobacco control policies, and the even greater lack of studies that have looked at their equity impact from a gender perspective. Finally, it will consider the implications of these findings for developing effective gender-sensitive equity-orientated tobacco control strategies.

Use of water-pipe and oral tobacco among women

D Aslan ¹Public Health, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Currently there are 200 million women using tobacco products globally and there is an increasing trend in use of non-cigarette tobacco products among women due to the recent marketing strategies of the tobacco industry. Culture, geography, gender-based roles, price policies, advertisements, etc are among influencing factors. Scientific reports highlight different tactics used by tobacco industry on women and younger generations since decades. Without gender sensitive approaches, it may not be possible to overcome the problem as the problem includes many different dynamics. World Health Organization urges on the rising tobacco consumption trend in women and alerted its partner countries twice via 31st of May, World No Tobacco Day messages since 1988 (Women and tobacco: the female smoker: at added risk; 1989 and Gender and tobacco with an emphasis on marketing to women; 2010). Since 2005, with the strong contribution of the World Health Organization-Framework Convention on Tobacco Control (WHO-FCTC), comprehensive tobacco control policies started to be implemented all over the world. Although WHO-FCTC addresses all tobacco products, all partner countries expectedly starts the struggle with cigarette smoking as it is the most frequently used tobacco products in the country. The industry saves time to extend its tactics on its new products while the state

bodies organizes additional legal regulations/inspections on other tobacco products like water pipe, oral tobacco, etc. Although there are a number of non-cigarette tobacco products, this speech's content is limited to water pipe and oral tobacco among women. Water pipe is a frequently used tobacco product in the Middle East and Eastern Mediterranean countries. Many health risks of water pipe use like cancer, infectious diseases, respiratory threats are not well known influences in the community. Oral tobacco use is another type of non-cigarette tobacco consumption like chewing, etc. Oral squamous cell carcinoma is the main threat of such consumption which is also not a well-known effect in the society. Such information lacking may mislead the people to use non-cigarette tobacco products. In order to achieve the goal of TOBACCO FREE WORLD, struggle methods should be strengthened on all tobacco products without any distinction based on the WHO-FCTC including the M-POWER strategies in gender sensitive perspective.

E-cigarettes: tobacco industry and non-tobacco industry strategies

M De Andrade ¹School of Health in Social Science, University of Edinburgh, Edinburgh, UK

The need to understand tobacco industry (TI) tactics with regard to e-cigarettes is well documented. To date, however, our understanding of the TI's business strategies in this area has largely been based on speculation informed by the TI's deceptive past, ad hoc inquiries and isolated examples reported in commentaries, editorials and opinion pieces. This work does suggest cause for concern. All the tobacco multinational companies (MNCs) have now heavily invested in the e-cigarette market raising uneasiness for tobacco control that the focus for these companies will be on their core tobacco business, with e-cigarettes being used primarily to bolster this. There are clear indicators, for example, that for industry this is about business not public health. Similarly, the TI's 'low tar lie' and failed attempts at promoting a 'safe' cigarette have added weight to concerns that e-cigarettes may be industry's latest 'Trojan horse'. E-cigarettes, however, are distinctly different from traditional cigarettes and could significantly improve public health because of their extensive appeal as smoking cessation devices. In another echo of past misdemeanours, the promotion of these products as lifestyle accessories – using a combination of evocative advertising on television and in traditional, digital and social media outlets, sponsorship and celebrity endorsements – has an appeal to young people and women in particular. E-cigarette marketing has also been identified as a source of misleading product information for consumers. This presentation will systematically examine the business strategies being deployed in the e-cigarette market by both tobacco MNCs and independents. Specifically, it will compare and contrast their respective: (i) business approaches. (ii) targeting strategies. (iii) positions on harm reduction and health claims.

(iv) marketing plans (including product development, pricing, distribution, packaging and promotion). The implications for tobacco control will then be discussed, with particular reference to existing regulation and whether or not this needs to be strengthened to protect young people and non-smokers. Specifically, it will consider potential threats for inequalities and women.

How to counteract the changing industry tactics

M Haglund ¹ThinkTank Tobaksfakta, Stockholm, Sweden

Tobacco use among women is a 21st century global epidemic. The smoking trends of women and men change over time and across populations as do gender norms and roles. Today men is moving out of the tobacco pandemic and women moving in, a trend that has been clearly understood by the tobacco industry. Currently 250 million women are daily smokers. In industrialized countries, 22% women are smokers and in developing countries, 12%. The number of female tobacco users is predicted to continue to rise over the next several decades as a result of increased prevalence, and population growth in particular in low and middle income countries. Although the roots of tobacco uptake for women and girls often include cultural, psychosocial, and socioeconomic factors, including body image and peer pressure the most important factor influencing women to start smoking is the tobacco industry's marketing campaigns aggressively target women. Since the 1920's tobacco companies have been imposing women with their seducing messages in country after country with increased smoking among women as the result. This presentation will discuss different actions on how to counteract the tobacco epidemic among women incl. the tobacco industry's tactics e.g. the need to implement comprehensive bans on tobacco promotion and marketing and to use a gender approach whereby sex-and age-differentiated data are systematically taking into consideration. It is also vital to acknowledge women's tobacco use as a major health problem and to build international as well as national consensus around this issue.

57. The role of cost-effectiveness in achieving the End TB Strategy

Overview of TB control costs and financing issues

C Owunna, ¹**D Collins** ² ¹SIAPS Program, Management Sciences for Health, Arlington, VA, ²Management Sciences for Health, Medford, MA, USA.

An analysis of the TB treatment targets needed to achieve the goal of eradicating TB in many high-burden countries indicates that significant increases in resources will be needed to achieve those targets. Much of these additional resources are needed urgently over the next few years to get the incidence rate to fall sufficiently to eradicate TB by 2035. This resources will need to come from increased

domestic spending since donor funding is likely to decrease, especially in countries whose economies are improving, albeit slowly. This increased domestic funding will have to come from government budgets and from national health insurance. How much of the government financing should and can come from national, provincial or district budgets is open to question, but that should probably be based on the role of each level of government in TB control. In terms of national health insurance, there is already pressure on premiums, on the expected contents of the benefits coverage, and affordability will remain an issue. What is clear is that substantial evidence-based advocacy will be needed to persuade the government and the national health insurance scheme to increase and sustain the investment in TB control to achieve the goal of TB eradication. What is also clear is that cost-effectiveness and efficiency will be crucial to maximize detection, especially as regards reaching the poor and vulnerable. Improved screening will be essential to ensure that no opportunities are missed to identify cases. This presentation draws on the analysis and lessons learned in Indonesia, where considerable assessment has been conducted on the cost of scaling-up TB control services, on financing options and on cost-effectiveness.

The cost-effectiveness of different screening and diagnostic methods: lessons from several countries

D Dowdy¹ John Hopkins University School of Medicine, Baltimore, MD, USA

The cost-effectiveness of diagnostic testing for tuberculosis (TB) depends on a number of factors beyond just the cost of the diagnostic test. These factors include the intended role of the test (symptomatic testing, systematic screening, drug susceptibility testing, etc.), the population in which the test is employed (probability of TB, HIV prevalence, drug resistance profiles), existing diagnostic and empiric treatment patterns, and integration of the test into current healthcare systems. In areas of high prevalence of HIV and drug-resistant TB, cost and cost-effectiveness considerations of TB diagnosis are overshadowed by the cost of treating these conditions. A determination of 'cost-effectiveness' may not equate to affordability or an appropriate decision to scale up a diagnostic test. Major areas of data uncertainty also exist - including the timing of TB transmission and the accuracy of diagnostic tests across settings and study designs. While most published cost-effectiveness analyses of TB screening and diagnosis have found those activities to be highly cost-effective, the assumptions underlying those analyses may not reflect actual implementation. Case studies from Africa and Southeast Asia are illustrative of these principles. For example, Xpert MTB/RIF was found to be highly cost-effective in southern Africa, but early evaluations considered levels of empiric treatment to be low, and did not account for costs of antiretroviral therapy. Incorporating costs of HIV care and the high probability of empiric therapy (as

later demonstrated in randomized trials) dramatically attenuates the cost-effectiveness of Xpert. Evidence from Uganda and Tanzania also suggests that the cost-effectiveness of Xpert as implemented in the field may be substantially lower than estimates from idealized settings. In Southeast Asia, the cost-effectiveness of novel diagnostic tools has been shown to reflect tradeoffs between accuracy and ability to implement each test, in both diagnostic and screening settings. These case studies demonstrate that the cost-effectiveness of TB diagnosis represents a complex interplay between diagnostic test characteristics, healthcare systems, patients, providers, ancillary conditions (e.g., HIV), and implementation.

Economic evaluation of new TB diagnostics in South Africa: an analysis of differences found in early trial and 'real world' cost-effectiveness

N Foster,¹ S Cleary,¹ L Cunnamo,¹ A Vassall,²

G Churchyard³ ¹University of Cape Town, Cape Town, South Africa; ²London School of Hygiene and Tropical Medicine, London, UK; ³Aurum Institute, Johannesburg, South Africa

Background: Given limited resources, policy makers have to make decisions regarding where investments in health systems are likely to have the greatest impact on reducing the burden of TB. Since social protection against the cost of illness is a key policy objective of the post-2015 Global strategy for TB, the costs incurred by patients and their households is an important consideration in targeting TB interventions. However, the evidence base on these costs is limited, as is their application to prioritisation within TB control.

Methods: A longitudinal patient cost survey was conducted, sampling patients from 10 health facilities in four provinces in South Africa. A total of 351 patients with symptoms suggestive of TB were interviewed at time of receiving a TB diagnostic and again 6 months later. A separate cohort of 168 TB patients was interviewed at 2 and 5 months on treatment.

Results and discussion: Those who started TB treatment reported a mean monthly individual income (prior to symptoms) of \$76.05 per month. During the TB episode, the greatest cost was incurred in the pre-treatment period (\$85.72 out of a total of \$209.97 per TB episode). Direct out-of-pocket costs were approximately 12% of annual individual income. The primary economic loss was income loss prior to starting treatment, which accounted for almost half pre-treatment costs. Interventions focussed on shortening the pre-treatment period - and relieving the cost of illness, such as increased case finding efforts, have a relatively high potential in terms of averting the economic burden of TB on patients and households. These interventions should be considered as part of the package, alongside social support to those diagnosed with TB, to address the poverty impact of TB in South Africa.

Modeling the economic impact of TB treatment interruption

D Collins,¹ E Rutta¹ ¹Management Sciences for Health, Medford, MA, USA

The interruption of treatment by TB patients has a significant impact on their health and recovery. Whether interruption is caused by patient challenges or by stock-outs of accessible medicines, it results in increased transmission and can result in drug-resistance and can cause additional costs for health providers and governments who are often already underfunded. Interruption can also increase patient costs which can further contribute to loss to follow-up. This presentation describes a costing tool that has been developed to calculate the costs of treatment interruption and the savings from preventing them. The results are intended for advocating with managers, policy makers and donors for greater investment in preventing treatment interruption and for budgeting for the resources needed.

The economic costs of TB medicine stock-outs in the Philippines

H Lam,¹ T Sy,¹ A Rivera,¹ K Cheng,¹ P Chua,¹ M Lamayra,¹ E Rutta,² D Collins³ ¹Institute of Health Policy and Development Studies, National Institute of Health, University of the Philippines, Manila, Philippines; ²Systems for Improved Access for Pharmaceuticals and Services, Management Sciences for Health, Arlington, VA; ³Health Programs Group, Management sciences for Health, Medford, MA, USA

Having a reliable supply of TB medicines is necessary element of a TB control program. Stock-outs of medicines result in delays and interruptions in treatment which can impact outcomes, increase transmission and can result in drug-resistance. They can also increase patient costs which can further contribute to loss to follow-up. Stock-outs of TB drugs is an important reason for treatment interruption but is often not sufficiently taken into account. More attention is generally paid to patient issues (demand) than the availability of medicines (supply issues). There are many sunk costs in TB control that are wasted if there are no medicines for the patients. Case finding, diagnosis, contact tracing, dedicated TB staff and facilities are all worthless if there are no medicines. Without medicines the patient will continue to infect other people and will not be cured. With intermittent supplies of medicines the results may be the same but there is also the risk of developing MDR-TB or XDR-TB which is more costly to treat and more difficult to cure. The SIAPS project in The Philippines, through a national survey of 200 facilities with the IHPDS, determined that 27.1% of sampled rural health units and 54.2% of sampled warehouses experienced stock-outs with a mean durations of between 0 and 95 days for drugs and between 0 and 181 days for laboratory supplies. An intervention mix that would cost USD 13 per day of reduced stockout was identified. This presentation describes the steps that were followed to reduce stock-outs and the costs of those steps. It also describes that economic costs that were saved for

providers, patients and society of reducing stock-outs and makes a compelling argument for further investment in improving supply chain.

58. Universal health coverage and insurance: how TB fits into the health financing picture

A framework for analysing TB and insurance, and assigning TB financing to either insurance or government budgets

D Collins,¹ F Hafidz² ¹Management Sciences for Health, Medford, MA, USA; ²Gadja Madah University, Yogyakarta, Indonesia

In order to end the TB epidemic by 2035 in the high-burden countries the vast majority of TB cases will have to be detected and successfully treated by 2019 so that incidence rates are to start to fall in time. This will be a major challenge, especially for Multi-Drug Resistant Tuberculosis (MDR-TB) where the numbers of cases detected and treated are often low. Increased case detection and treatment will require significant additional resources and with reducing donor funding in some countries, more and more of the costs will have to be funded from domestic sources. To ensure equitable access to services, the bulk of the financing will have to come from government budgets and social health insurance. And in some countries government funding can come from local, provincial or national levels. One of the challenges for a country where the financing comes from these different sources is to ensure that there is adequate funding from each source and that none of the inter-related areas of a TB program are neglected. In Indonesia, a financing framework was developed based on the expected role of each level of government in TB control as well as the role and likely coverage under the social health insurance system. Detailed costs were projected for each program element (e.g., detection, case finding, diagnosis and treatment) and for each resource (e.g., salaries, laboratory reagents and medicines). Using a new costing and financing model, the projected costs were then allocated to the various funding sources. This provided a valuable basis for advocacy to the government and the insurance agency and for developing cost and financing expectations for both public and private sector providers. This presentation will describe the framework used to project the costs of the TB program in Indonesia and the assignment of roles and funding to the three levels of government and to social health insurance.

Challenges and solutions for reaching more TB providers with insurance schemes in the Philippines

AMC Garfin ¹Department of Health, Manila, Philippines

Social Health Insurance in the Philippines started from the Government's desire to provide its people with access

to effective medical care services at an affordable price. This started in 1972 when the law creating the Medicare Program was enacted. That was the country's first attempt at universal social health insurance. After twenty-five years, the program covered only the employed sector and paid for a very small fraction of the country's health expenditures and this paved the way for PhilHealth. In 1995, Republic Act 7875 was signed and established the National Health Insurance Program. With this, PhilHealth was created to administer the program with the mandate of providing universal social health insurance coverage. For tuberculosis, an out-patient benefit package was formulated as a response to the need to provide accessible and quality health care services to its members and their qualified dependents who are suffering from TB. For the TB program this is a mechanism to ensure quality of TB services and an additional financing source. The package covers all drug susceptible TB patients. All certified and accredited health care providers can participate. A reimbursement of about 90US\$ will be provided to the facility for each TB patient that has completed treatment. A referring physician will also be provided with about 23US\$ for each referred patient. This initiative started in 2003 and there are several challenges and actions to be taken to improve the system. Here are some of the challenges and actions to be made. 1. Low utilization rate due to non-disclosure of patients of PhilHealth membership. Enhanced health care institution portal will be provided to address this issue. 2. Problems in the process of claims and reimbursement for file cases. A trust fund will be created and a circular will be provided to include the allocation of the package as a guide to the facility. 3. Low number of certified and accredited DOTS facilities. Funds will be provided to for facility improvement and review of the certification and accreditation process will be done. 4. Limited number of staff to do certification due to the rationalization at the regional level. Trainings for regional staff will be done supported by partners.

Maintaining NTP functions in the context of national health insurance

S Jittimane, ¹ S Somthong, ¹ C Nampeng, ¹ J Vorasingha, ¹ C Namwat ¹ ¹Disease Control, MOPH, National TB Program, Bangkok, Thailand

The burden of tuberculosis (TB) (mortality, prevalence and incidence) in Thailand is gradually reducing, according to the World Health Organization (WHO). An important contribution to this reduction is likely to be free access to TB diagnosis, treatment and care due to the vertical program before 2002 and the decentralized program through the universal health care scheme since 2002 and the high standard of clinical care available in hospitals, both public and private. The health system in Thailand is the link with three insurance schemes, which cover 99% of the Thai population. Most important is the Universal Coverage Scheme (UCS), established in 2001 and run through the National Health Security Office (NHSO). The others are the Civil Servants Medical

Benefits Scheme (CSMBS) and the Social Security Scheme (SSS), which go back to the 1980s and 1990s, respectively. However, these insurance packages are not harmonized, leading to some inequity – a problem that is recognized and being addressed. The CSMBS and UCS are financed by general taxation whereas the SSS is financed by a payroll tax with a tripartite contribution shared by employer, employee and the government, with 1.5 % of the salary as premium. These schemes cover the costs of basic care for almost all the population, and have nearly eliminated the risk of catastrophic health expenditure for families. Bureau of TB (BTB), the center unit of NTP is responsible for policy development, supervision, monitoring and evaluation, training, surveillance, laboratory reference issues and research. The BTB has only a technical support function towards the NHSO and provincial health offices. Hospital practice is driven by the reimbursement amount agreed upon with the insurance schemes and, as a consequence, adherence to national technical standards, such as those set by the BTB, is sometimes compromised. However, the NHSO is open to discussion on the package of care that should be remunerated. Private providers and academic centres are not accountable to the BTB and generally do not report to them. This limits the coordination between program staff to provide support for treatment practice, recording, reporting, supervision and monitoring. However there are multiple health care providers. The private sector is large and not fully regulated. Migrants and prisoners are challenging groups when it comes to providing health services. Both these groups are particularly vulnerable to TB.

59. HIV-TB Late-Breaker Session

Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored tablets are bioequivalent to individual products and are acceptable to patients with advanced HIV infection in the REALITY trial

D M Gibb, ¹ M Bwakura-Dangarembizi, ² D Abhyankar, ³ A J Szubert, ¹ C Agutu, ⁴ A Lugemwa, ⁵ J Abach, ⁶ M Kemigisa, ⁷ J Mallewa, ⁸ A Siika, ⁹ A Mukuye, ¹⁰ V Mehta, ³ G Malhotra, ³ E Nambi, ⁹ M Thomason, ¹ S Pett, ¹ J Berkley, ⁴ B Meli, ⁹ C Kityo, ¹⁰ K Nathoo, ² V Musiime, ¹¹

A S Walker, ¹ J Gogtay, ³ REALITY Trial Team ¹MRC Clinical Trials Unit at University College London, London, UK;

²University of Zimbabwe, Harare, Zimbabwe; ³Cipla Ltd., Mumbai, India; ⁴KEMRI Wellcome Trust Research

Programme, Kilifi, Kenya; ⁵Joint Clinical Research Centre, Mbarara, ⁶Joint Clinical Research Centre, Gulu, ⁷Joint Clinical Research Centre, Fort Portal, Uganda; ⁸University of Malawi, Blantyre, Malawi; ⁹Moi University Clinical Research Centre, Eldoret, Kenya; ¹⁰Joint Clinical Research Centre, Mbale,

¹¹Joint Clinical Research Centre, Kampala, and Makerere University College of Health Sciences, Kampala, Uganda.

Background: Human immunodeficiency virus (HIV) infected patients initiating antiretroviral therapy (ART)

with low CD4 counts particularly benefit from opportunistic infection (OI) and anti-tuberculosis prophylaxis. However, individual drug formulations of isoniazid and cotrimoxazole add to the pill burden of ART and adherence difficulties early in treatment when mortality is highest. Stockouts are also frequent in low-resource settings.

Methods: Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine (800/160/300/25 mg) fixed-dose combination (FDC) scored tablets, made by Cipla, India, were evaluated for bioequivalence vs. separate tablets of Septrin®Forte (sulfamethoxazole 800 mg/trimethoprim 160 mg [GlaxoWellcome]) and isoniazid 300 mg (Sandoz) in an open-label, randomized, single-dose, two-treatment, two-period, 26-sample crossover pharmacokinetic study. Acceptability and adherence questionnaire data were collected in the ongoing, 2x2x2 factorial, REALITY randomised trial evaluating 12-week enhanced OI prophylaxis, 4-drug ART and enhanced nutrition in 1805 African adults/children (≥ 5 years) with CD4 < 100 cells/mm³. Within-individual data on FDC (weeks 12–24) vs. cotrimoxazole alone (weeks 0–12) were compared in 319 patients; and in weeks 0–12 among those receiving FDC+fluconazole (for prophylaxis against cryptococcal disease) ($n = 543$) vs. cotrimoxazole ($n = 604$).

Results: Among 28 fasting healthy subjects (18 male; 10 female; mean (range) age 31 (18–45) years; BMI 25.1 $\pm$ 2.9), geometric mean test-to-reference ratios for sulfamethoxazole (AUC 99.8%, 90%CI 96.2–103.5 and C_{max} 103.2%, 90%CI 99.5–107.0), trimethoprim (97.2%, 90%CI 93.7–100.9; 98.2%, 90%CI 93.4–103.3) and isoniazid 103.8% (90%CI 99.5–108.3; 104.3%, 90%CI 95.1–114.4) were well within required 80–125% range. In REALITY, no within-individual differences in acceptability were reported between FDC (12–24 weeks) vs. cotrimoxazole (0–12 weeks): 99.7% vs 99.4% reported none/not much interference with everyday life and 95.6% vs. 96.6% reported that drugs were very easy/easy to take. Comparing groups over 0–12 weeks gave similar results: 500/543 (92.1%) vs. 565/604 (93.5%) ($P = 0.8$) reported taking medication was very easy/easy; 4.0% vs. 3.9% reported missing ≥ 1 dose.

Conclusions: Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored FDC tablets are bioequivalent to individual drugs; data have been submitted for World Health Organization prequalification. They are acceptable, reduce pill burden and could improve adherence for adults/children ≥ 5 years, in addition to simplifying drug distribution for HIV programmes.

Household point-of-care CD4 testing and IPT initiation in a TB contact tracing programme: feasibility, uptake and linkage to care

L Page-Shipp,¹ J J Lewis,² V Kavindhran,^{1,3} S Senoge,¹ E Zishiri,¹ F Popane,¹ V N Chihota,^{1,3} D Clark,¹

G J Churchyard,^{1,3} S Charalambous^{1,3} ¹Aurum Institute, Johannesburg, South Africa; ²Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; ³School of Public Health, University of Witwatersrand, Johannesburg, South Africa.

Background: Household TB contact tracing provides an opportunity for HIV and Point-of-Care CD4 (PoCCD4) testing and home-based IPT initiation. Feasibility, HIV uptake, linkage-to-care, IPT initiation and completion were assessed.

Methods: A pragmatic cluster-randomised trial among household contacts of index TB patients in two districts in South Africa. Households were randomised into three arms: 1) Standard of Care (SoC): TB symptom screening, TB testing if symptomatic and HCT offer; 2) SoC plus PoCCD4 for newly diagnosed HIV+ (PoCCD4 arm); 3) SoC, PoCCD4 and household-initiated IPT (HH-IPT arm) if CD4 > 350 and clinically eligible. Follow-up was at 10 weeks and 6 months to determine linkage-to-care (SoC/PoCCD4 arms) and IPT initiation and continuation (PoCCD4/ HH-IPT).

Results: 2243 index TB patients enrolled between November 2012 and August 2014; 63.2% female, median age 30 years. HCT uptake was 34.7% in SoC; increasing to 40.2% in the PoCCD4 arm (RR = 1.16; 95%CI: 0.99, 1.36) and to 39.9% in the HH-IPT arm (RR = 1.15; 95%CI 0.99, 1.35), ($P = 0.06$ and 0.08 respectively). 98 new HIV+ were evaluated for linkage-to-care within 3 months. Linkage-to-care was recorded for 30.8% in the SoC arm and 42.1% in the PoCCD4 arm (RR=1.37; 95%CI 0.68, 2.76, $P = 0.38$). In the PoCCD4 arm, 3/20 (15.0%) reported initiating IPT. In the HH-IPT arm, 20/21 (95.2%) initiated IPT in the household (RR = 8.20; 95%CI 1.98, 33.95, $P = 0.004$). Receipt of at least four months of IPT was reported for 3/20 (15.0%) in the PoCCD4 arm, and 12/21 contacts (57.1%) in the PoCCD4+HH-IPT arm ($P = 0.009$).

Conclusions: Household PoCCD4 testing and IPT initiation is feasible. PoCCD4 increased HCT uptake but did not significantly increase linkage-to-care. IPT initiation and completion was significantly increased in the household intervention but numbers were small due to low numbers of new HIV+ household contacts. Although feasible, these interventions had low impact due to the low uptake of HIV testing in households.

Cell phone ringtone intervention to improve adherence to antiretroviral therapy in Yaounde, Cameroon: a randomized controlled trial

E W Pefura-Yone,^{1,2} Z Nzina-Toupendi,³ A D Balkissou,^{1,2} A P Kengne,⁴ E Afane-Ze^{1,2} ¹Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, ²Yaounde Jamot Hospital, Yaounde, ³Institut Supérieur de Technologie Médicale, Yaounde, Cameroon; ⁴South Africa Medical Research Council, Cape Town, South Africa.

Background: Despite continuing education of people living with HIV infection (PLWHIV), up to one third still have poor adherence to antiretroviral therapy (ART). We assessed the effect of cell phone-based reminders (ring-tones) on adherence to ART among PLWHIV receiving care at the Approved Treatment Centre for HIV infection (ATC) of Yaounde Jamot Hospital (YJH), Cameroon.

Methods: This single-center, single-blinded randomized controlled trial was conducted from December 2014 to May 2015 (6 months). PLWHIV aged >18 years were randomly assigned to intervention (ringtones group) or control group (routine care group) on a 1:1 allocation ratio. Adherence to ART was assessed using the Center Adherence Support for Evaluation self-reported adherence index (CASE), with an index score >10 indicating high adherence. The primary endpoint was the proportion of patients achieving high adherence to ART in both groups after 4 months of follow-up (M4). Secondary endpoints included adherence rate at month 2 and retention in care.

Results: A total of 199 participants were allocated to the ringtones group and 201 to the usual care group. The positive history of tuberculosis was found in 48.2% and 37.3% of the patients in the ringtones and control groups respectively. The adherence rate at M4 was 68.8% in the ringtones group and 54.2% in the control group, corresponding to a relative 27% (95%CI 8-49%; $P = 0.003$) higher adherence in the intervention group. Adherence rate to ART after 2 months of follow-up intervention vs. control group was 80.4% vs. 54.7%, $P < 0.001$. No statistical significant difference was found between the two groups regarding the retention in care during follow-up.

Conclusions: Programming ringtone alarms on mobile phones of HIV-infected patients improved the short and medium terms adherence to ART. Extended follow-up of a larger cohort is needed to assess the effects on the outcomes of care.

Adherence to antiretroviral therapy is associated with retention in care for extensively drug-resistant tuberculosis HIV co-infected patients undergoing treatment in South Africa

M R O'Donnell,¹⁻³ A Daftary,^{3,4} K R Amico,⁵ A Wolf,¹ G Friedland,⁶ D Bangsberg,⁷ N Padayatchi³ ¹Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA; ²Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY, USA; ³Centre for AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa; ⁴Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; ⁵School of Public Health, University of Michigan, Ann Arbor, MI, ⁶Yale University School of Medicine, New Haven, CT, ⁷Harvard Medical School, Boston, MA, USA.

Background: There are critical gaps in our understanding of the linkage between medication adherence and retention in care for patients with drug-resistant tuberculosis (TB) and HIV, which may contribute to low treatment success.

Methods: XDR-TB patients in KwaZulu-Natal, South Africa, were prospectively enrolled at start of treatment and followed monthly for >2 years (PROX study). Adherence was assessed monthly by study staff by 7-day recall. Missing patients were followed up in person or by telephone. Optimal adherence was defined as self-report of taking all pills in the previous 7 days; missing any pills was defined as suboptimal adherence. Loss of retention in care was defined as missing >2 consecutive monthly clinic visits without known transfer or death.

Results: From October 2009 through July 2011, 104 XDR-TB patients (79% HIV co-infected, 82.5% on antiretroviral therapy [ART]) were enrolled. At 24 months 16% of patients defaulted (loss of retention in care), while 41% died, 26% cured, 6% completed treatment and 11% failed treatment. HIV co-infection did not affect retention (Panel A) nor did ART (data not shown). For XDR-TB HIV patients on ART ($n = 64$), cumulative optimal adherence to ART at 6 months predicted higher levels of retention in care at 24 months compared to suboptimal ART adherence (86% vs. 57%, $P < 0.01$) (Panel B). This difference was significant on univariate and on multivariate analysis (OR 6.08 1.05–43.92, $P = 0.04$).

Conclusion: Although default rates were high, XDR-TB HIV patients reporting optimal ART adherence were significantly more likely to be retained in care through 24 months. This finding may be due to enhanced ART counseling, behavioral links between optimal adherence and retention, or other factors. We speculate that interventions to improve adherence may also improve retention in care. Further studies to understand and improve adherence and retention in care for drug-resistant TB-HIV are critically needed.

Acquired drug resistance in rifampicin susceptible pulmonary tuberculosis a programmatic setting with a high prevalence of HIV co-infection

N Rockwood,^{1,2} F Sirgel,³ G Meintjes,^{1,2,4}
R J Wilkinson,^{1,2,5} ¹Department of Medicine, Imperial College, London, UK; ²Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, ³DST/NRF Centre of Excellence for Biomedical Tuberculosis Research/SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Health Sciences, Stellenbosch University, Tygerberg, ⁴Department of Medicine, University of Cape Town, Cape Town, South Africa; ⁵MRC Francis Crick Institute, Mill Hill Laboratory, London, UK.

Background: The incidence of acquired drug resistance (ADR) in patients treated for rifampicin susceptible (RS) tuberculosis (TB) has been reported to be as high as 5-10%. We prospectively studied the incidence and risk factors of ADR in Khayelitsha township, Western Cape, South Africa, where HIV co-infection is present in 50-70% of TB patients.

Methods: Consecutive cases of Xpert MTB/RIF confirmed RS pulmonary TB were recruited at diagnosis and followed up at 2 and 5 months when sputum TB cultures (MGIT) and adherence assessment (urine acetylisoniazid; pill counts; self-report) were done. Treatment followed local TB program guidelines. MTBDR_{plus} was performed on positive cultures at 2 and 5 months to screen for ADR, with spoligotyping carried out on suspected cases of ADR. We retrospectively tested for isoniazid monoresistance (IMR) in stored baseline isolates. Minimum inhibitory concentrations (MIC) were determined in a sub-cohort at baseline ($n = 109$) and 2 months ($n = 25$) using BACTEC MGIT 960 system.

Results: 308 participants (33% retreatment) were recruited and followed up between March 2013 and December 2014. 62% were HIV co-infected [median CD4 count 233cells/mm³, (IQR 101-389), 39% on antiretroviral therapy at baseline]. Poor adherence was documented in 8-12% of patients. 32% of male participants were ex-prisoners. 2 cases of ADR were detected at 5 months, incidence 0.7% (95%CI 0.09 to 2.5%). MIC at baseline was similar when analysed according to HIV, retreatment and culture converter status. In paired isolates, there was no significant change in MIC by 2 months for any patient for rifampicin/isoniazid/pyrazinamide (defined as $\times 4$ change). 6% (95%CI 3.6-9.6%) of baseline isolates had IMR (13/17 had low level IMR-*inhA* mutation or MIC $\leq 0.4\mu\text{g/ml}$). Despite being on the standard first-line regimen, no participants with IMR amplified resistance.

Conclusions: After roll out of Xpert in this well-functioning programmatic setting, ADR arising in baseline RS TB is rare (0.7%) with acquired resistance to isoniazid and rifampicin each in 1 patient, both with evidence of poor adherence.

60. Moving past clinic-based care: practical steps to improve TB care through community engagement

Mobilising communities to fight TB in remote islands of Indonesia

E Siahaan,¹ S Ruschak,² J Ake² ¹Program Dept, Yayasan Menara Agung Pengharapan Internasional, Medan Johor, Indonesia; ²Global Program, MAP International, Brunswick, GA, USA

Background: South Nias Regency is one of the most under-developed areas in Sumatera Province. It contains over 100 islands, many of which are inhabited by indigenous people. TB prevalence in the Regency is higher than the revised national estimate, but due to the lack of human resources and the high transportation costs between these remote islands, many TB patients do not access care. **Interventions:** Indigenous community volunteers were recruited and trained to screen for symptoms of TB. Individuals suspected of having TB were then referred to a health facility to smear microscopy. Community volunteers facilitated transportation to ensure testing occurred. When a patient was detected, the volunteers helped to initiate and follow up treatment on the remote islands. In addition to these community-based activities, laboratory technicians were trained and monitored to improve the quality of diagnostic services offered through government health facilities.



Results: In a span of just 9 months, 1536 community volunteers screened over 50 000 people for symptoms of TB across 112 villages. These activities resulted in the detection of 579 suspected TB patients who were referred for testing. Over 225 smear-positive TB patients were diagnosed and 44 of these newly detected patients were among children aged less than 14 years. These active case

finding activities resulted in +86% increase in new smear-positive case notifications compared with the same quarters in the prior year, indicating that the TB patients detected among people living on remote islands would likely not have been treated in the absence of the project.

Conclusion: This project demonstrates that community health volunteers can be a highly effective solution for expanding TB care services into remote and underserved populations in conjunction with strengthening existing government laboratory services. In light of the significant upward revision Indonesia's prevalence estimate and subsequent decline in its case detection rate, initiatives which are able to expand services and demonstrate increases in anti-TB treatment uptake should be prioritized for scale-up.

Improving state-wide TB case notifications through engaging leaders in nomadic pastoralist communities in Nigeria

S John,¹ M Gidado,² T Dahiru,³ A Fanning,⁴ A Codlin,⁵ J Creswell,⁵ AD Belal⁶ (*check S John???*) ¹Adamawa State Tuberculosis and Leprosy Control Programme, Yola, ²KNCV Nigeria/Challenge TB, Abuja, ³Netherlands Leprosy Relief, Jos, Nigeria; ⁴Health, University of Alberta, Edmonton, Alberta, Canada; ⁵STOP TB Partnership, Geneva, Switzerland; ⁶Adamawa State Primary Health Care Development Agency, Yola, Nigeria,

Background: With an estimated population of 4.1 million, Adamawa, one of the 36 States of Nigeria has an estimated 450 000 Nomadic pastoralists. Poor access to health services, low immunization coverage, poor housing and overcrowding, high rates of bovine TB infection and consumption of unpasteurized milk are known to contribute to high rates of TB among Nomads. Although Nigeria has one of the highest tuberculosis (TB) burdens in Africa, case detection rates remain relatively low. With support from Nomadic Community Leaders (CL) and the Stop TB Partnership through its Wave 2 TB Reach grant in 2011, TB control service was launched within Nomadic Communities of Adamawa State.

Objective: To demonstrate results of 2 years Active TB Case Finding (ACF) among Nomadic Pastoralists through engagement of Nomadic Community Leaders in Adamawa State of Nigeria.

Methods: ACF among nomadic populations was implemented from 1st January 2012 to 31st December 2013 in Adamawa State. The process involved mapping of cattle routes, Nomadic settlements and Health Facilities, advocacy and engagement of identified Nomadic CLs, identification of Community Volunteers (CVs), reorientation of General Health Workers (GHWs) and training of the CVs on sputum collection, transportation and documentation. The CLs took responsibility for identification of CVs and provided leadership in the organization and conduct of the training & screening days among community settlers. The CLs also accepted all processes involved. Sputa were tested by AFB microscopy and smear negative samples examined by GeneXpert

MTB/Rif (Gx). A total of 378 community screening days was organised.

Results: 680 CVs, 435 GHWs, 85 laboratory staff and 21 TB supervisors were trained on TB screening, diagnosis and treatment. 96 376 nomads were verbally screened, sputa from 9890 (10.3%) presumptive TB cases were collected and examined while 1150 (11.6%) smear positive TB cases were detected. Of 8740 nomads with smear-negative microscopy results, 1685 (19.3%) were tested using Gx, yielding an additional 160 TB cases. An increase of 112% in number of patients submitting sputum for smear microscopy State-wide compared with the 2 years before the intervention was observed. New smear-positive notifications increased by 49.5%, while notifications of all forms of TB increased by 24.5% compared with expected notifications based on historical trends.

Conclusion: Engaging Nomadic CLs to be the face of the project was key to its success.

61. Progress in clinical trials for TB treatment: 2015

High-dose rifapentine: preparation and design of a four-month regimen trial

S Dorman ¹Johns Hopkins University School of Medicine, Baltimore, MD, USA

Optimizing the activity of individual components of a tuberculosis regimen is part of a strategy to shorten overall treatment duration. Rifamycins have inimitable anti-tuberculosis activity, and evidence from animal and clinical studies shows that the currently-recommended 10 mg/kg dosage of rifampicin is at the low end of the dose-response curve. For drug-susceptible tuberculosis, we and others have performed a sequence of research studies with the goal of understanding how to optimize rifamycin activity. Rifapentine is a cyclopentyl ring-substituted rifamycin that, compared with rifampicin, has a longer half-life and lower minimum inhibitory concentration against *M. tuberculosis*. This talk will provide an overview of pre-clinical, phase 1, and phase 2 data using daily rifapentine as a component of tuberculosis treatment. This talk will focus on the design and implementation of a phase 3 multicenter, randomized, controlled clinical trial to determine whether 4-month regimens that contain daily rifapentine can cure drug-susceptible smear-positive pulmonary tuberculosis. The investigational regimens in this phase 3 trial are A) 2 months of daily RPT/INH/PZA/EMB followed by 2 months of daily RPT/INH and B) 2 months of daily RPT/INH/PZA/MOX followed by 2 months of daily RPT/INH/MOX.

Tuberculosis trials from the AIDS Clinical Trials Group

S Swindells¹ University of Nebraska Medical Center, Omaha, NE, USA

The AIDS Clinical Trials Group (ACTG) was initially established in 1987 to support the research efforts of the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health. The ACTG established and supports the largest Network of expert clinical and translational investigators and therapeutic clinical trials units in the world, including sites in resource-limited countries. These investigators and units serve as the major resource for HIV/AIDS research, treatment, care, and training/education in their communities. The Tuberculosis Transformative Science Group of the ACTG is responsible for development, implementation, and oversight of the ACTG research agenda related to the treatment and prevention of tuberculosis with and without HIV co-infection. We collaborate and coordinate with multiple partners internationally, and contribute to global policy. Mentoring and training of new investigators, particularly those in high burden countries, is an important priority for the group. The ACTG scientific agenda for TB includes the following priorities: TB TREATMENT SHORTENING: To identify regimens to shorten drug-susceptible TB treatment to ≤ 3 months in patients with and without HIV MDR-TB TREATMENT: To identify regimens for MDR TB treatment in ≤ 6 months in patients with and without HIV PREVENTIVE THERAPY: To treat latent TB in 1 month and MDR-TB infection in 3-6 months TB-HIV CO-TREATMENT: To optimize the treatment of TB-HIV co-infection, and evaluate and minimize drug-drug interactions TRANSFORMATIVE SCIENCES: Pharmacology, biomarkers, laboratory monitoring and diagnostics, host-directed therapies This presentation will include recent accomplishments of the group, and review of ongoing studies and those in development for TB prevention and treatment shortening for drug sensitive and drug resistant TB. Developmental work with host-directed therapies, biomarker discovery and validation will be presented.

62. Innovative approach to improving access and quality of care for DR-TB: implementing the ECHO telehealth model

Overview of the ECHO model and a framework for ECHO implementation for DR-TB globally

L Chen,¹ A Raftery,¹ B Struminger² ¹UCSF Curry International Tuberculosis Center, San Francisco, CA,

²University of New Mexico Health Sciences Center, Albuquerque, NM, USA

Background: The ECHO [Extension for Community Healthcare Outcomes] telehealth model is an innovative evidence-based intervention designed to strengthen the

knowledge and practice of clinical care teams in rural and underserved communities. The ECHO model—based on a combination of multi-point videoconferencing, case-based learning, disease management and outcomes monitoring—was initially developed and shown to be effective in improving access to care and treatment outcomes for Hepatitis C in rural and underserved areas of New Mexico. The ECHO model of clinical mentoring through guided practice is being adapted in several global settings to increase access to high quality care for tuberculosis.

Objectives: To improve access to high quality TB care and treatment in both high and low burden TB settings by leveraging regional and national expertise to support a community of practice and learning. Interventions The ECHO model has been adapted to support case management of all TB cases in the low incidence setting of New Mexico. In the high burden setting of Viet Nam, it has been adapted to support case management of complex DR-TB cases. TeleECHO sessions use a cloud-based videoconferencing platform to connect multidisciplinary regional and national experts to review and provide consultation for TB cases presented over the video network by local teams. Each teleECHO clinic includes standardized case presentations, Q&A discussions and a brief clinical didactic talk.

Results: In 2015 successful TB ECHO clinics were launched in both high [Viet Nam, 2/2015] and low burden settings [New Mexico, 4/2015]. Participant feedback has been very positive. Planning is in progress for adaptation of the ECHO model to TB control programs in Namibia and Mexico, the US state of Washington, as a collaborative effort of US Regional Training and Medical Consultation Centers (Curry International TB Center, Mayo Clinic Center for TB) with Denver Metro TB Control for low-incidence states, and along the US-Mexico border for binational cases.

Conclusion: The ECHO telehealth model is being applied to high burden TB settings to maintain and improve MDR-TB control and low burden, low incidence TB settings to maintain and improve TB case management and program quality. The ECHO model is being adapted to TB control programs globally to address quality of care and to strengthen the knowledge and clinical practice of multi-disciplinary teams of TB providers.

Adaptation of the ECHO model to strengthen US-Mexico border DR-TB control

MART Castellanos,¹ M A Garcia,² B Struminger³

¹Tuberculosis, Ministry of Health Mexico, Mexico,

²Tuberculosis, Ministry of Health Mexico, Mexico DF, Mexico;

³School of Medicine, University of New Mexico, Albuquerque, NM, USA

Background: Tuberculosis is a very important public health problem in Mexico, with around 20 000 new cases per year; 33% are attributed to the six states bordering the USA. 38% of the DR TB cases in Mexico are in these border states. The Extension for Community Healthcare Outcomes [ECHO] clinical mentoring and education

model is being adapted for use along the US-MX border to promote improved patient outcomes of binational DR TB cases; the model uses video conferencing technology to facilitate discussion of binational and US-MX border patient cases among MX and US experts on DR TB, with a primary focus on Mexican TB patients living in the US or who will be referred to Mexico.

Objectives: The ECHO Model is being implemented to help ensure timely clinical review and case management of binational and US-MX border DR TB patients and to empower public health nurses and other health workers in direct contact with the patients. This clinical mentoring and education model aims to enhance TB program quality improvement through positive changes in the annual performance targets and DR TB cure indicators.

Methods: In April 2015 the New Mexico DOH and Project ECHO at the University of New Mexico launched a TB ECHO program for the State of New Mexico [NM], and in July 2015 began inviting TB program managers and expert clinicians from existing regional consultation and referral programs in the US and Mexico to participate in the monthly case management discussions about the care and treatment of binational TB cases linked to the State of NM.

Results: Beginning in July 2015 there have been monthly TB ECHO sessions which have included 4-5 binational patient case discussions each month, with participation of clinical and public health experts from Mexico and the US, as well as national and state TB program managers from both sides of the border collaborating to develop and coordinate treatment and case management recommendations.

Next Steps: The New Mexico binational case discussion experience has served as a pilot for the development of a US-MX binational DR TB ECHO program that will be supported by the US-MX Border Health Commission with plans to launch in late 2015 or early 2016.

Conclusion: Adaptation of the ECHO model for collaborative binational DR TB case management and clinical mentoring promises to strengthen binational and border state TB programs in México and USA to standardize comprehensive case review and coordination of case management to improve treatment outcomes of binational DR and complex TB cases.

Integration of ECHO for DR TB with an HIV ECHO program in Namibia

N Ruswa,¹ N Hamunime,¹ M Tadesse,¹ F Mavhunga,¹ F Tjituka¹ ¹Directorate of Special Programmes, Ministry of Health and Social Services, Windhoek, Namibia

Background: Namibia is a country in Southern Africa with a high incidence rate of TB (651/100 000) and high prevalence of HIV (13.3%). The country is sparsely populated at with 2.6 persons per square kilometre, the 2nd lowest population density in the world. There are 34 district hospitals, spread over the 825 615 km² and one central hospital in the capital. In 2014, 367 cases with drug resistant TB were registered. A clinical review

consilium was established in 2009 to assist the districts with the management of drug resistant TB cases. In addition, the country has a clinical mentorship programme for HIV care.

Objectives: To pilot a clinical case discussion system for drug resistant TB and TB-HIV using the ECHO telehealth model in Namibia, in order to improve interaction between key health care workers, experts/mentors and programme officers. Intervention All district TB offices had been equipped with laptop computers. With support from CDC and the Project ECHO, district TB and leprosy coordinators and other key members of the regional teams were granted access to the cloud-based teleconferencing system. Presentation of cases had been normally done by sending a fax and/or e-mails to a national coordinator, who would then present to the consilium. Attendance would be restricted to the persons who could be physically present. With the ECHO model, several district teams with cases to present would log on at the same time, present and listen to each other's presentations.

Results: Requiring minimal add-on resources to what was already available, the ECHO telehealth model allowed regional and district health-care workers with cases to present an opportunity to virtually attend the consilium meetings, as well as use their experience to respond to other teams' presentations. This allowed for real-time interaction, including prompt responses to queries and prompt feedback, as well as learning between teams. Teams with unstable internet connections, however, were often left out.

Conclusion: In a high TB-HIV setting with limited human resources and experts like Namibia, a telehealth conferencing system has a great potential. Because electronic gadgets (computers, cellphones, tablets) are often ubiquitous at least in the district health-care setting, yet underutilised, this presents yet another opportunity to integrate quality healthcare with available technology, maximise the benefits for the patients.

Implementation of the ECHO model for comprehensive TB case management in New Mexico, a low-incidence setting

D Fortune,¹ D Isaacks,¹ M Burgos,² A Armistad,³ B Struminger³ ¹TB Program, New Mexico Department of Health, Santa Fe, NM, ²Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, ³University of New Mexico Health Sciences Center, Albuquerque, NM, USA

Background: Project ECHO is an educational initiative started 12 years ago at the University of New Mexico Health Sciences Center with a mission to expand access to high quality medical care in rural and underserved communities across NM and globally. The ECHO model uses a combination of video conferencing technology, case-based learning, promotion of best practices and monitoring of outcomes to support professional communities of learning and practice.

Objectives: The NM TB program (TBP) wants to ensure effective nurse case management (NCM) of all persons

with active TB by empowering the public health nurses (PHN) with the knowledge and skills needed to ensure effective completion of treatment (COT) for each patient. NCM is an essential link for effective COT for all persons with active TB Disease (TBD). The TBP aims to enhance program quality improvement evidenced by changes in the annual performance targets measured by the 2020 National TB Indicators Project (NTIP).

Methods: NM averages 50 cases of active TB per year. The NM TB TeleECHO Clinic, a collaborative between the NM DOH and Project ECHO, convenes PHNs on a monthly basis across a video network to review records of all persons with active TB in NM. The focus is strengthening of NCM skills, professional learning and program quality improvement. Two trainings were held during March/April in Albuquerque to equip the NCM with information needed to initiate TB ECHO. A self-efficacy evaluation was completed to determine their baseline perceived level of competence in providing NCM. The TBP and ECHO are partnering to develop an evaluation tool. Each clinic includes a brief didactic.

Results: NM TBP launched its first TB ECHO on April 20, 2015. In the first five months there have been 130 participants from across the United States and Mexico. Twenty-seven unique persons with active TB (for a total of 85 presentations) were presented by 17 NCM. Patient ages ranged from six months to 88 years with TB from a variety of sites. A total of 478 CMEs have been awarded.

Next Steps: Launch the Navajo Nation (NN) TB ECHO Clinic and continue to provide mentoring for other TB ECHO programs regionally and nationally.

Conclusion: This collaborative effort will enhance NCM for persons diagnosed with active TB through standardized comprehensive case review and case-based learning. The TB ECHO clinics have offered accessible TB nursing educational opportunities for PHNs.

63. Zoonotic TB session II: What do humans, baboons and livestock have in common?

Human tuberculosis due to *Mycobacterium bovis* in the United States 2006–2013

C Scott,¹ J Cavanaugh,¹ R Pratt,¹ BJ Silk,¹ P Lobue,¹ P Moonan¹ ¹Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Background: *Mycobacterium bovis* is one of several closely related mycobacteria of the *M. tuberculosis* complex. Since 2005, nearly all culture-confirmed tuberculosis (TB) cases reported in the United States have been characterized by spoligotyping and MIRU-VNTR, genotyping techniques that can differentiate *M. bovis* from *M. tuberculosis*. Previous studies describing factors associated with *M. bovis* disease in humans have been limited by small cohorts, geographical scope, and availability of robust data.

Methods: We analyzed data from CDC's Tuberculosis Genotyping Information Management System to distin-

guish TB disease caused by *M. bovis* from *M. tuberculosis* among cases reported in the United States during 2006–2013. To determine demographic and clinical factors independently associated with *M. bovis* disease, as compared to persons with *M. tuberculosis*, we estimated adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) using generalized linear modeling.

Results: A total of 70 312 culture-confirmed cases of TB were reported. Of those 59 366 (84.4%) included spoligotyping and MIRU-VNTR results; 862 (1.5%) cases were identified as *M. bovis*. The annual percentage of TB cases attributable to *M. bovis* remained consistent nationally during 2006–2013 (range: 1.3–1.6%). Geographically, the incidence rate of *M. bovis* was higher than the national average (0.29 per 100 000 persons) in the US-Mexico border region (Figure). Among TB cases, the prevalence of *M. bovis* was higher among females (aPR 1.4, 95%CI 1.3–1.6), children (compared to 25–44 year olds) (0–4 years: aPR 1.9, 95%CI 1.4–2.8 and 5–14 years: aPR 4.0, 95%CI 3.1–5.3), foreign-born persons (aPR 1.4, 95%CI 1.2–1.7), Hispanics (compared to non-Hispanic Whites) (aPR 3.9, 95%CI 3.0–5.0), and residents of US-Mexico border counties (aPR 2.0, 95%CI 1.7–2.4). Cases with *M. bovis* were more likely to have exclusively extrapulmonary disease (aPR 3.7, 95%CI 3.3–4.2) or both pulmonary and extrapulmonary disease (aPR 2.4, 95%CI 2.1–2.9).

Conclusions: This is the first comprehensive analysis of *M. bovis* disease since genotype surveillance was implemented routinely in the United States. Women, children, foreign-born persons, and Hispanics are disproportionately affected by *M. bovis*, which is independently associated with extrapulmonary disease. Targeted prevention among Hispanic and foreign-born persons and residents of the US-Mexico border region is warranted.

Figure: Cumulative incidence of human *Mycobacterium bovis* tuberculosis disease, by county, United States, 2006–2013.

Figure: Cumulative incidence of human *Mycobacterium bovis* tuberculosis disease, by county, United States, 2006–2013.



*National average incidence rate for 2006–2013 was 0.289 *M. bovis* cases reported per 100,000 population (Wilson 95% confidence interval: 0.260–0.292 cases per 100,000).

Longevity of *M. bovis* in fresh and souring milk and the screening of milk from communal cattle with a high prevalence of BTB for *M. bovis*

A Michel,¹ C Geoghegan,² T Hlokwé,³ K Raseleka,³ W Getz,⁴ T Marcotty⁵ ¹Faculty of Veterinary Science, Dept. Veterinary Tropical Diseases, University of Pretoria, Onderstepoort, ²Mammal Research Institute, University of Pretoria, Pretoria, ³Zoonotic Diseases Section, ARC-Onderstepoort Veterinary Institute, Onderstepoort, South Africa; ⁴Environmental Science, Policy and Management, University of California, Berkeley, Berkeley, CA, USA; ⁵Institute of Tropical Medicine, Antwerp, Belgium

Background: Unpasteurised fresh and souring dairy products form an essential component of household diets throughout many rural communities in southern Africa. The presence of milk-borne zoonotic pathogens such as *Mycobacterium bovis*, the causative agent of bovine tuberculosis and zoonotic tuberculosis in humans, constitute a public health threat, especially in areas with poor disease surveillance in livestock and highly compromised human health due to HIV/AIDS.

Methods: In this study we used culture to determine the longevity of *M. bovis* in experimentally inoculated fresh and naturally souring milk obtained from communal cattle in the KwaZulu-Natal province of South Africa. The effect of bacterial load and storage temperature on the survival of *M. bovis* was evaluated by spiking mixtures of fresh milk and starter soured milk (aMasi) culture with three concentrations of bacteria (10^2 , 10^4 , 10^7 colony forming units/ml), followed by incubation under controlled laboratory conditions that mimicked ambient indoor (20°C) and outdoor (33°C) temperatures and periodic sampling and testing over time (0-56 days).

Results: *M. bovis* cultured from samples of the fresh and souring milk was identified by PCR analysis. At the highest spiking concentration (10^7 cfu/ml), *M. bovis* survived for at least 2 weeks at 20°C, but, at all concentrations in the 33°C treatment, *M. bovis* was absent by 3 days after inoculation. Logistic regression analysis was used to assess the effects of bacterial concentration and time since inoculation, as well as determine the potential half-life of *M. bovis* in raw souring milk. Given the most favourable tested conditions for bacterial survival (20°C), approximately 25% of mycobacteria were alive after one day of storage (95% CI: 9-53%), giving an estimated half-life of *M. bovis* in raw souring milk of approximately 12 hours (95% CI: 7-27 hours).

Conclusions: This study demonstrates that *M. bovis* may survive in fresh and souring milk for periods of time that represent a risk of exposure to people consuming these products, as well as domestic or wild animal populations that have reported opportunities to consume homemade unpasteurised dairy products. The temperature at which the milk is soured and stored substantially affects the survival time of *M. bovis*.

Zoonotic tuberculosis in Brazil: a very low prevalence or a neglected problem?

M Silva,¹ FR Araujo,² RR Da Costa,³ P Suffys,⁴ AS Rocha,⁴ MDC Guimarães⁵ ¹Embrapa Dairy Cattle, Embrapa, Juiz de Fora, MG, ²Embrapa Beef Cattle, Embrapa, Campo Grande, MS, ³João Penido Reginal Hospital, FHEMIG, Juiz de Fora, MG, ⁴IOC, Fiocruz, Rio de Janeiro, RJ, ⁵Pós Graduação em Saúde Pública, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

Background: Sputum acid-fast bacilli (AFB) microscopy and histopathology are the standard criteria for tuberculosis (TB) diagnosis in Latin America (LA), including Brazil. However, these procedures may potentially overlook zoonotic TB cases since these methods are not able to detect *Mycobacterium bovis* nor differentiate it from the rest of the *Mycobacterium tuberculosis* complex (MTC).

Results and Discussion: To our knowledge, systematic surveys on zoonotic TB in LA have only occurred in Argentina, linking health and agriculture research centers (National Agricultural Technology Institute). In that country, in the period 1982-1984, which involved 15 human laboratories, *M. bovis* accounted for 0.47% of the samples, ranging from 0.04% to 1.85%, depending on the degree of involvement with livestock in each region. The estimated proportion of zoonotic TB due to *M. bovis* in LA is 2% and 8% of pulmonary (PTB) and extrapulmonary (EPTB) TB cases, respectively. It is believed that in Mexico this proportion is greater. There is a lack of official data regarding the current prevalence of bovine TB in Brazil. According to the Ministry of Agriculture, Livestock and Food Supply there was a national average prevalence of 1.3% of the cattle from 1989 to 1998. It is also known that the incidence of zoonotic TB in Brazil was high in the last century, causing 3.5% and 13.2% of all TB and TB meningitis cases found by two small surveys in 1974 and 1955, respectively. However, more recent studies in urban centers in Brazil, also of small sizes, indicated zoonotic TB prevalence of < 1%, < 1%, zero, zero and 1.6% for, respectively, São Paulo (2001-2005), Rio de Janeiro (1987-2006), Juiz de Fora (2011), Rio de Janeiro (2011), Juiz de Fora (2014). More systematic studies on zoonotic TB, using media with pyruvate, are necessary in LA and Brazil. One alternative includes nested surveys within other studies such as the multiple drug resistance (MDR) of MTC. This could potentially save resources and construct better prevalence estimates. Brazil could also create a collaboration between The Ministry of Health and The Agricultural Research Corporation (EMBRAPA) for these surveys, as in Argentina.

Conclusion: The last published studies in Brazil found that the prevalence of zoonotic TB was very low or marginal. However, all results were based on small surveys in restricted locations or referral laboratories results, overlooking the real prevalence of zoonotic TB.

Domestic *Mycobacterium bovis* circulating in Chacma baboons and their public health implication

M Musso,¹ B Hang'ombe,¹ C Nakajima,² Y Suzuki²

¹School of Veterinary Medicine, University of Zambia, Lusaka, Zambia; ²Hokkaido University Research Center for Zoonosis Control, Hokkaido, Japan

Bovine tuberculosis (BTB), caused by *Mycobacterium bovis* has insidiously and mutely devastated livestock and wildlife of the Kafue Basin in Zambia. Until recently, the disease was diagnosed only in cattle and Kafue lechwe antelopes (*Kobus leche kafuensis*). However, a recent screening of Chacma baboons (*Papio ursinus*) revealed a spillover effect in infection. Field necropsy findings had revealed typical granulomatous lesions in the entire chest cavity affecting the lungs and all the ancillary draining lymph nodes of the affected baboon. In order to elucidate the exact strain of circulating *Mycobacterium tuberculosis* complex (MTC) bacteria, a logical and chronological step wise genotyping analysis was applied. Firstly, a MTC-discrimination multiplex PCR (MTCD-MPCR) targeting genetic regions cfp32, RD9 and RD 12 was used for species differentiation followed with the application of deletion analysis using RD4, TbD1 and 3'cfp32 probes. Then genetic fingerprinting of the identified *M. bovis* strains was done using the direct repeat (DR) based spacer oligonucleotide typing (spoligotyping) in association with mycobacterial interspersed repetitive units-variable-number tandem repeats (MIRU-VNTR). Spoligotyping and MIRU-VNTR analyses revealed that tuberculosis in baboons of Lochinvar National Park shared one distinct spoligo pattern; SB0 120, with cattle and Kafue Lechwe antelopes. This finding has significant public health implications given the close proximity with which baboons roam and forcibly enter human dwellings. This scenario reflects the baboons' nature with regards to their omnivory eating habits, spatial distribution in close relation to human settlements, habitat and resource utilization patterns, disease susceptibility, transmission modes and their social interaction patterns with access to defensible common pool resources (CPRs) available to humans. The full public health implication, impact and extent of this current finding are likely to be seen in the long-term. Multiplicative factors responsible for its occurrence in this particular specie of social animals will partly depend on the pathogenicity of this BTB strain (SB 120). Therefore future research direction in this area should determine the possible implications of this finding on human health at the wildlife-livestock-human interface.

Tuberculosis diagnostic challenges in wildlife and public health implications

M Miller,¹ SDC Parsons,¹ P Van Helden,¹ P Buss,²

F Olea-Popelka³ ¹DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, MRC Centre for TB Research, Division of Molecular Biology & Human Genetics, Faculty of Medicine & Health Sciences, Stellenbosch University, Cape Town, ²Kruger National Park, Veterinary Wildlife Services, South African National Parks, Skukuza, South Africa; ³College of Veterinary Medicine and Biomedical Science, Department of Clinical Sciences, Colorado State University, Fort Collins, CO, USA

Background: Bovine tuberculosis (bTB) affects wildlife populations worldwide. Over 21 wildlife species have been reported with bTB in South Africa alone. There is a broad diversity of species affected including carnivores, primates, and bovids. The presence of multiple susceptible hosts complicates detection and disease control.

Diagnostic challenges: There are no validated tests for bTB in most wildlife species. Some of the challenges to diagnosing bTB in wildlife are differences in epidemiology, pathogenesis, and immunologic responses between hosts; variable or absent clinical signs in infected animals until disease is advanced; frequent environmental exposure to nontuberculous mycobacteria; requirement for species-specific reagents for immunodiagnostic tests; and logistical difficulties associated with testing wildlife. To overcome these issues, the focus has been on developing blood-based tests using *Mycobacterium bovis*-specific antigens that may be used across a range of hosts. Identification of novel biomarkers, development of species cross-reactive reagents, and improved techniques for sample processing and transport are currently underway.

Public health implications: With diminishing habitats, there are increased wildlife-livestock-human interfaces and a growing threat of disease transmission. With a lack of tools for detection and control of bTB in wildlife, there is a threat of spillback to livestock, as well as transmission to both animals and humans directly through contact or ingestion of infected animals products or indirectly, through contamination of the environment. Limited bTB control in wildlife presents a public health concern for zoonotic TB.



64. TB contact investigation in high-risk populations: innovative approaches and implementation experiences

The yield of contact investigation in a rural setting in Ethiopia

DJ Dare,¹ Z Dememew,¹ Dr Habte,¹ M Ensermu,¹ G Negussie² ¹HEAL TB Project, Management Sciences for Health, Addis Ababa, ²Disease Prevention and Control, Amhara Regional Health Bureau, Bahir Dar, Ethiopia.

Background: Screening close contacts of index tuberculosis (TB) cases is one of the key strategies for case finding in high TB burden settings. According to current recommendations, contact investigation is done prospectively. Here we present results from a 'retrospective' contact investigation approach implemented in six zones in two regions of Ethiopia.

Methods: Between June-September 2014, we recruited and trained lay providers to do active case search through community based contact tracing. They first identified the list of smear positive pulmonary TB (SS+) cases treated in the catchment health centers in the previous 3 years. Then they visited the houses of each SS+ index case and enumerated their household contacts. Using a symptom-based screening checklist, they screened each household contact and referred those with symptoms to catchment health centers for diagnosis and management. In the routine system, Health Extension Workers screen household contacts of SS+ TB index cases currently on treatment. We computed the yield of this new approach and compared with the yield from the routine community TB referral.

Results: Of 77 626 HH contacts of 20 805 index SS + TB cases screened, 9142 (11.8%) had presumptive TB. Over a half (54%) of these were further evaluated at the health centers within 2 months of referral. The yield of all forms of TB among presumptive cases through the retrospective screening approach was 5%. On the other hand, the yield among 22 426 presumptive TB cases referred through the routine community TB activity by health extension workers during the same time period was 2.9%.

Conclusions: Targeting household contacts of SS+ index cases through a 'retrospective' screening approach can serve as additional high yield strategy in TB case finding. Further studies are needed to determine the optimal timing for the retrospective tracing. Mechanisms should be in place to ensure timely linkage of the presumptive TB cases to diagnostic centers.

Contact screening and expanding childhood TB diagnosis and treatment of TB in Bangladesh

S Islam,¹ M Siddiqui,¹ M Rana,¹ M Akramul Islam,¹ M Husain¹ ¹Health, BRAC, Dhaka, Bangladesh

Background and Challenges: Bangladesh is one of the high TB burden countries in the world. BRAC, a non-government organization, is jointly working with national TB control programme to combat against tuberculosis since 1994. Due to unavailability of diagnostic

facilities and scarcity of pediatricians, diagnosis and management of child tuberculosis is still a major challenge for the country especially in rural setting. It is necessary to raise awareness in the community and increase screening through contact tracing of household cases within the existing programme for identifying more child TB cases.

Interventions: Considering the different challenges, BRAC started conducting orientation to pediatrician at tertiary hospitals and district levels. A basic training is given to health care providers on sign symptoms of child TB to increase awareness in the community during mobilization. A contact tracing register was introduced in the existing programme of BRAC in late 2013 and contact tracing initiated among the family members who are in close contact with pulmonary TB cases and were sent for screening. During their households visit, BRAC's frontline health workers disseminate basic messages, identify presumptive cases and refer them to the specific centres. Poor child TB symptomatic gets financial support from BRAC for investigation and transportation purpose.

Result and lessons learnt: In 2014, a total of 929 pediatricians were reached through 64 networking meetings on child TB diagnosis and management at tertiary and district level hospitals. In addition, 1029 health care providers were trained on child tuberculosis including basic messages, identification and referral. There was an increase in child case identification from 2865 in 2013 to 3554 in 2014. In 2014, 9.7% of the total child TB cases were identified through contact tracing.

Conclusion: Evaluation of symptomatic contacts may increase identification of child cases. An orientation session could be planned for health care providers to improve the contact tracing skills. The children who are in close contact of pulmonary tuberculosis patient if even asymptomatic should be referred for screening and should do follow-up.

TB contact investigation: experiences from prisons in Uganda

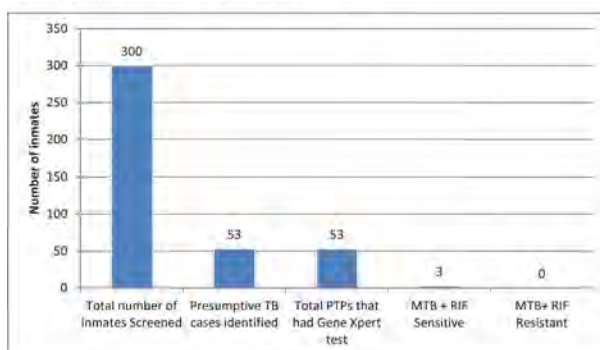
E Kizito,¹ M Kenneth,¹ M Ruhweza,¹ S Stavia,² P Donggo,³ B Woldemariam,⁴ P G Suarez⁴ ¹Project (TRACK TB), Management Sciences for Health (MSH), Kampala, ²National Tuberculosis and Leprosy Program, Ministry of health, Kampala, ³Lira regional Referral Hospital, Ministry of Health, Lira, Uganda; ⁴Track Tuberculosis Activity, Management Sciences for Health, Arlington, TX, USA

Introduction: One of the components of the WHO Stop TB strategy is to address the needs of TB contacts, and of poor and vulnerable populations. Inadequate ventilation, overcrowding and inadequate TB infection control practices in congregate settings increase the risk of transmission of all forms of tuberculosis. During 2014, Lira regional referral hospital in Northern Uganda diagnosed 12 patients with drug sensitive TB and 2 patients with multi-drug resistant TB all of whom were serving jail sentences in nearby prisons. Over the years, such patients would be transferred to the hospital for

treatment but there was no documented contact screening and investigation for all inmates.

Intervention: Lira Regional referral hospital with support from the USAID funded TRACK TB Project conducted education sessions about TB for the prisons authorities and inmates with a focus on TB transmission and infection control including the need to promptly identify and evaluate presumptive TB cases. Multi-disciplinary teams comprising nurses, clinicians and laboratory technologists visited each of the prisons to conduct the sensitization session and screening of all inmates using the intensified case finding tool (ICF). Sputum samples were collected from all inmates that were found to have TB symptoms (presumptive TB cases) and subjected to an MTB/RIF test.

Figure 1: Contact screening and investigation cascade



Results and lessons: A total of 300 inmates were screened for TB, all were males just like the index cases and the average age was 32 years of age. All these contacts were HIV negative. Fifty three symptomatic contacts were identified and had samples subjected to the MTB/RIF test; 3 contacts (1%) were diagnosed with were diagnosed with TB as shown in the cascade in the Figure. **Conclusion and next steps:** Contact investigation in Lira prison led to identification of inmates with undiagnosed TB which increased the risk of transmission within the congregate setting. We recommend TB contact screening for both household and close contacts of inmates diagnosed with TB in addition to the periodic and routine TB screening at entry into the prison setting.

TB clusters in villages: community screening and GIS mapping

S Hamusse Daba,¹ M Aseresa Melese,² DJ Dare,² B Lindtjorn³ ¹Oromia Regional Health Bureau, Addis Ababa, ²Management Sciences for Health, HEAL TB Project, Addis Ababa, Ethiopia; ³University of Bergen, Bergen, Norway

Background: Identifying TB hot spots using special analysis may contribute for targeted TB control measure and can be used as advocacy tool. We used GIS and Spatial Scan Statistics to describe the spatial distribution of TB and to identify TB hot spots in a district in Central Ethiopia.

Methods: A population-based cross sectional study conducted in the Hetosa District of Arsi Zone of central

Ethiopia from May 2013 to July. We used symptom checklists and sputum microscopy for TB diagnosis. Demographic data and geographical location of the identified smear positive TB cases and the residential addresses of all study participants in the study area were also collected using handheld Global Positioning System (GPS) receivers. We used spatial scan statistic used to identify purely spatial and space-time clusters of tuberculosis among permanent residents. The statistical significance of identified clusters was based on comparing the likelihood ratio test statistics against a null distribution obtained from Monte Carlo simulation. The number of variation was set at 999 and the significance level was set at 0.05.

Results: A total of 106 smear positive pulmonary TB cases were identified with the overall smear-positive TB incidence rate of 323.2/100 000 (range, 0-608) population per year in the study area. The most likely statically significant cluster for high rates and secondary cluster of TB were identified in three kebeles (neighborhoods), Gonde Finchema, Tado Lamem and Shaki Sherara (RR:3.10, $P=0.028$) and in three kebeles Oda Jila, Seru Ankato and Boru Lencha (RR:2.89, $P=0.052$) respectively. Furthermore, the most likely statistically significant cluster for low rate of TB was identified in one kebele Dawe Guticha Kebele (RR:1.68, $P=0.019$). Areas with high rate of TB in the purely spatial analysis were also found to have statistically significant high rate of TB in the space-time analysis. Without including purely spatial clusters, the most likely statistically significant cluster for high rates of TB was also identified in Gonde Finchema, Tado Lamem Kebeles and Shaki Sherara kebeles during the dry season between December 2013 and May 2014 (RR:6.10, $P=0.016$).

Conclusion: In this study, we have demonstrated the presence of clusters of PTB in Hetosa district of Arsi Zone of Central Ethiopia. Using spatial and spatial-temporal analysis may be useful for designing area-specific interventions for TB control.

65. The XDR experience: clinician and patient perspectives on treatment and care

Knowledge, attitudes and behaviours of XDR-TB patients and family members in the Western Cape, South Africa

M Senthilingam,^{1,2} E Pietersen,¹ J Te Riele,¹ P Sedres,¹ K Dheda,¹ R McNerney² ¹University of Cape Town, Cape Town, South Africa; ²London School of Hygiene and Tropical Medicine, London, UK

Objective: Patient-level data are required to inform strategies interrupting transmission and default in patients with extensively drug-resistant TB (XDR-TB) to improve models of care and identify potential routes of transmission. We therefore explored the experiences, lifestyle, attitudes and needs of uncured XDR-TB

patients, who failed or interrupted therapy, living without treatment in the community.

Methods: We conducted in-depth interviews with 12 community-based patients from South Africa. Family members were interviewed when patients were unavailable. Interviews were analysed using inductive thematic analysis.

Results: The thematic experiences identified from the interviews were: i) living with but not being cured of XDR-TB, ii) altered lifestyle in the community, iii) experiences with community healthcare and iv) local community members, and v) wants and needs. Patients identified mistrust in healthcare, futility of treatment regimens, a need for a purpose in life, and subsistence as major concerns. Restriction of living in the community for patients whose treatment had failed resulted in self-imposed isolation. Defaulters focused more on the never-ending drug regimen and bad experiences with healthcare contributing to non-adherence. Family members emphasized an under-recognized experience of unforeseen burden, obligation, worry, and discomfort. Lack of knowledge and lack of concern about transmission was evident. **Conclusion:** Current models of care are not adequately meeting the needs of uncured XDR-TB patients and relatives. These data inform the need for community-based palliative care, vocational facilities to improve economic opportunities, home-based infection control, and improved psychosocial support to increase patient adherence, reduce transmission, provide income, and relieve burden on family members.

Social constraints of DR-TB care: the construction and management of stigma

A Daftary ¹University of Toronto, Toronto, ON, Canada

The social inequality and marginalisation experienced by patients living with multi drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is seldom characterised. This presentation draws upon contemporary understandings of stigma theory, and qualitative evidence from studies involving patients and health care workers in KwaZulu Natal, South Africa, to develop insight into the construction and management of stigma in drug-resistant TB. Felt and enacted TB in MDR- and XDR-TB, as compared to drug-susceptible TB, may reflect the distinct ways in which each form of TB is experienced and managed by patients, and by health care providers. The coincident risk of HIV infection may add an additional layer of social complexity into the lived experience of drug-resistant TB, patients' consequent health-seeking behaviours and treatment decisions may reflect their need to mitigate multiple constraints and resist dual stigmatisation. A better understanding of how stigma is produced, managed and/or resisted in drug-resistant TB can inform the development of health care policies and practices that prevent stigma reification, with specific implications in TB service delivery, adherence support, prevention of acquired drug-resistance, and the care of HIV coinfecting patients

The patient journey: treatment for XDR-TB in South Africa

M Loveday,¹ L Vanleeuw,¹ V Mehlokhulu¹ ¹Health Systems Research Unit, South African Medical Research Council, Cape Town, South Africa.

To better understand patients with DR-TB and inform interventions on treatment adherence, morbidity and mortality, we collected socio demographic information as well as data on patients' treatment experiences from 79 DR-TB patients. We found that many DR-TB patients have low levels of education and depend on disability and child support grants for survival. Experiences of health services varied, but travel to the specialised TB hospital for monthly management and repeat medications was time consuming, costly and at times unsuccessful. Treatment adherence together with treatment outcomes can be improved by making access to treatment easier and improving health service functioning.

A view from the other side: perspectives on clinical management of XDR-TB

I Master ¹MDR TB Unit, King Dinuzulu Hospital Complex, Durban, South Africa

A practical look from the coal face from the clinician's perspective of the XDR program in South Africa. The situation is looked at in 3 periods. The period prior to 2006, between 2006 and 2013 and from 2013 onwards. A look at the difficulties, problems facing clinicians and the patient and what changed over the years. A short look as well at what is facing clinicians in the current period and going forward.

ABSTRACT PRESENTATIONS FRIDAY 4 DECEMBER 2015

e-POSTER SESSIONS

01. Zoonotic tuberculosis: trends, detections and interpretation

EP-100-04 Development of a single-tube triplex real-time PCR assay for differential diagnosis of *Mycobacterium tuberculosis* complex

WL Huang,¹ R Jou^{1,2} ¹Centers for Disease Control, Taipei, ²National Yang-Ming University, Taipei, Taiwan. Fax: (+886) 2 2653 1387. e-mail: rwj@cdc.gov.tw

Background: To set up a laboratory-based surveillance system for *Mycobacterium bovis* infection in high-risk areas and to monitor adverse reactions of BCG vaccination, we need to have a simply and rapid test for simultaneous detection of *M. bovis*, *M. bovis*-BCG and other *Mycobacterium tuberculosis* complex (MTBC).

Methods: A single-tube triplex real-time PCR using three fluorescence probes was developed. For validation study, we tested 72 reference *Mycobacterium* species including 12 *M. tuberculosis*, 1 *M. microti*, 1 *M. africanum*, 3 *M. bovis*, 17 *M. bovis*-BCG and 38 nontuberculous mycobacteria (NTM), and 625 clinical MTBC isolates. In addition, for clinical evaluation, 226 smear-positive sputum specimens were tested. Results were compared to that of spoligotyping, a line-probe assay and/or bacterial culture.

Results: The detection limit of the triplex real-time PCR is 10 fg DNA. Of the 72 reference isolates tested, no discordant result was observed. Specificity of the triplex real-time PCR is 100%. Of the 625 clinical isolates tested, 14 *M. bovis* were identified using the triple real-time PCR and confirmed by both commercial tests. Furthermore, of the 226 sputum specimens, 64 (28.3%) were culture-negative, 69 (30.5%) were non-MTBC and 75 (33.2%) were MTBC culture-positive, 10 (4.4%) were contaminated, and 8 (3.5%) had no culture results. Of the 75 MTBC positive isolates, the sensitivities of the triple real-time PCR and the line-probe assay were 97.3% (73/75) and 93.3% (70/75), respectively. Besides, of the 226 sputum specimens, we further differentially identified 2 *M. bovis* cases later confirmed by bacterial cultures.

Conclusion: The performance of the triple real-time PCR for detecting MTBC was comparable to that of the line-probe assay. In addition, the triple real-time PCR can be applied for *M. bovis* surveillance.

EP-101-04 Risk factors associated with bovine tuberculosis in Ecuadorian workers from farms and slaughterhouses

F Proano-Perez,¹ R Benitez-Capistros,² W Benitez-Ortiz,² L Ron-Garrido,² F Portaels,³ A Linden,⁴ L Rigouts³

¹Universidad De Las Fuerzas Armadas Espe, Sangolqui, ²International Centre for Zoonoses, Universidad Central Del Ecuador, Quito, Ecuador; ³Biomedical Sciences, Institute of Tropical Medicine, Antwerp, ⁴University of Liege, Liege, Belgium. Fax: (+593) 223 4952. e-mail: freddyproanoperez@yahoo.com

Background: Bovine tuberculosis (BTB) is a chronic zoonotic disease caused by *Mycobacterium bovis*, which has a worldwide distribution in domestic and wildlife animals. In Ecuador, there is no national BTB control program.

Design/Methods: The aim of this study was to evaluate the state of the disease in cattle and humans, and evaluate the risk factors associated in the transmission of BTB. Twenty dairy herds comprising 2022 cattle were selected from medium and large size herds located in Mejia canton. In humans, the study was carried out in 157 people, conformed by farm workers and slaughterhouse workers, with the purpose to evaluate the prevalence of *Mycobacterium* spp. in risk populations by tuberculin skin test (TST) and analyse risk factors.

Results: The true annual incidence was 1.70%, and the true prevalence was 7.41% and 7.13%, in 2 years. The number of skin test-positive cases also increased significantly with age ($P = 0.03$), contacts with other species of animals ($P < 0.01$), and introduction of new cattle ($P = 0.04$). Herd prevalence was 55% in the first year and 65% in the follow up study. *Mycobacterium* spp. was estimated in 29% [C.I. = 22 - 36% at 95%] of the farm and slaughterhouse workers. The results establish a significant association among the positivity of TST to masculine gender ($P = 0.026$), consumption of milk coming from farms ($P = 0.030$), consuming raw milk ($P = 0.000$), and consumption of elaborated cheeses made by hand ($P = 0.003$). Consumption of raw milk gave an odds ratio of 4.65 [C.I. = 2.01-10.75 at 95%].

Conclusion: This study shows the necessity for a national BTB control program in Ecuador which should be supported by sanitary policies to allow the identification of the endemic areas nationwide, establishing animal movement restrictions, culling, sanitary slaughtering, compensation strategy for culling and laboratory tests to identify the *Mycobacterium* species and strains involved. In addition, due to the lack of knowledge in cattle farmers about this zoonoses, education of farm and abattoir workers about the disease could help prevent new cases in animals and humans, and help improve the use of preventive measures.

EP-102-04 Zoonotic tuberculosis: the case of mahouts and captive Asian elephants in southern India

V Kummannoor P Pillai,¹ D Abraham² ¹Government Medical College Hospital, Kottayam, ²Kerala State Animal Husbandry Department, Kozhikode, India. e-mail: kpvda@hotmail.co.in

Background and challenges to implementation: Cases of tuberculosis in captive elephants are mostly caused by *Mycobacterium tuberculosis*. In the hands-on and open systems of captive elephant management in southern India, infected captive elephants present the risk of zoonotic tuberculosis to their mahouts (traditional elephant keepers). There are nearly a thousand captive Asian elephants and not less than 3,000 mahouts in southern India. Post-mortem examinations of captive elephants have shown caseous nodules in lung parenchyma from which *M. tuberculosis* was isolated by culture on LJ media. Systematic and regular tuberculosis screening of mahouts and captive elephants still remains a challenge.

Intervention or response: Over a three year period we piloted systematic tuberculosis screening of both mahouts and captive elephants at several different locations in southern India. One time screening of nearly 800 elephants and their mahouts was achieved. Screening of mahouts was done by clinical examination and tuberculin skin testing, followed by chest X-ray and sputum collection as required. Screening of elephants was done with the USDA licensed rapid serum test DPP Vet Assay® (Chembio Diagnostics Inc. Medford NY), followed by trunk wash culture for isolation and identification of mycobacteria. Past mahouts of eight elephants from which *M. tuberculosis* was isolated at post-mortem examination were screened for tuberculosis infection.

Results and lessons learnt: One case of cutaneous tuberculosis in the palm was identified in a mahout who attended an elephant with active tuberculosis. Prevalence of latent tuberculosis infection among mahouts is 53% and the seroprevalence of tuberculosis infection among captive elephants in southern India is nearly 15%. Mahouts and captive elephants in southern India are highly migrant and locating the subjects for contact tracing and follow-up testing is challenging. Mahouts, mainly because of their nomadic lifestyles, are least aware of their basic health care needs as well the need for regular tuberculosis screening. Awareness of the owners of captive elephants for tuberculosis screening of elephants is also minimal.

Conclusions and key recommendations: For early diagnosis and treatment, regular and systematic tuberculosis screening of mahouts and captive elephants are essential. Provisions need to be made for paid leave for mahouts identified with active tuberculosis to complete full course treatment.

EP-103-04 Detection of potential reservoirs of *M. tuberculosis* and *M. bovis*

K P Hanumanthappa¹ ¹All India Institute of Medical Sciences, New Delhi, India. Fax: (+91) 112 658 8663. e-mail: hk_prasad@hotmail.com

Background: Several pathogenic mycobacteria such as *M. tuberculosis*, *M. bovis*, and *M. avium* subspecies *paratuberculosis* are capable of causing clinical disease in humans as well as animals. For e.g., *M. tuberculosis* and *M. bovis* are responsible for human and bovine tuberculosis; whereas *M. avium* subspecies *paratuberculosis* is the causative agent of Johne's disease among bovines and has been implicated in Crohn's disease among humans. The presence of pathogenic mycobacteria in diverse species weaves a complex web perpetuating its survival in the environment. However, the consequence of the prevalence of pathogenic mycobacteria in diverse species has not been systematically assessed; owing to the technical difficulties in terms of: primary isolation, demanding culture conditions, time taken, cost and laborious nature of the classical methods of identification. Identification of mycobacteria has been restricted to a limited number of referral laboratories. Further, it has not been considered essential to distinguish *M. bovis* and *M. tuberculosis* in clinical samples as would be the case in other microbial diseases, since patients respond to a common panel of anti-tubercular therapy.

Methods: In this regard we have developed Nested-PCR and visual format assays using molecular beacons for direct identification of *M. tuberculosis* and *M. bovis* in clinical samples. Identical techniques would go a long way in assessing the presence of the various mycobacterial pathogens in the clinical samples & its prevalence in the environment.

Results: Our own in house studies have demonstrated the presence of *M. bovis* apart from *M. tuberculosis* in clinical samples. Similarly besides *M. bovis*, *M. tuberculosis* has been detected and isolated from bovine samples, (Reverse Zoonoses), demonstrating that the intimate association of patients and cattle facilitates the transmission of these pathogens from humans-cattle-humans.

Conclusion: Therefore, there is a dire need to develop technology that reliably facilitates identification of mycobacterial pathogens in circulation. This would help in the generation of data for the systematic identification of the prevailing & potential reservoirs of infection. The impact such facts would be significant in developing versatile strategies for the prevention of the spread of mycobacterial pathogens among humans and other susceptible hosts.

EP-104-04 Isolation of *Mycobacterium tuberculosis* in livestock workers and implications for zoonanthroponotic transmission in Ibadan, south-western Nigeria

S Cadmus,¹ V Akinseye,¹ A Adegbulu,¹ N Ovwighose,¹ M Ayoola,¹ J Ogugua,¹ H Adesokan,¹ E Cadmus¹

¹University of Ibadan, Ibadan, Nigeria. e-mail: sibcadmus@yahoo.com

Background: Tuberculosis (TB) remains a disease of global health importance particularly in countries of sub-saharan Africa where knowledge of the disease is poor. Again in Africa, little is also known about the epidemiology of TB among livestock workers who play key roles in the transmission of the disease along the human-animal-ecosystem interface. We determined the prevalence of pulmonary mycobacterial infection, risk factors associated with its occurrence among livestock workers in Ibadan, south-western Nigeria.

Methods: We conducted a cross-sectional study among livestock workers between August, 2014 and March 2015. Sputum samples were cultured and subjected to a two-step multiplex PCR technique based on genus typing and genomic regions of difference respectively. An interviewer-administered questionnaire was also used to assess their TB related knowledge, attitude and practices.

Results: Overall, 184 livestock workers (traders =114; butchers = 70) were screened. Majority (81.5%) were males, aged between 21- 49 years, while over a third (38.6%) had no formal education and 46.7% did not have more than 10 years work experience. Though majority (80%) were knowledgeable about TB, most (95%) had poor TB related attitude and practices. In all, 6.1% (7/114) of the livestock traders and 7.1% (5/70) of the butchers had positive cultures. Molecular characterization techniques identified six of the seven isolates from the traders as non-tuberculous mycobacteria (NTM) whereas from the butchers, four *Mycobacterium tuberculosis* and one NTM were identified. Importantly, age and educational status were significantly associated with TB infection among the workers ($P < 0.05$).

Conclusion: We isolated and confirmed *M. tuberculosis* (and not *M. bovis*) as mycobacterial species responsible for pulmonary TB infections in livestock workers (though *M. bovis* has earlier been reported among this group in the area). Given poor attitude and practices of these workers towards TB, coupled with their direct contact with cattle in farms and markets, health threats at this interface may promote zoonanthroponotic transmission of *M. tuberculosis* and its emerging multi-drug resistant strains to cattle in the study area. We therefore reiterate the importance of molecular typing methods in the identification of mycobacteria in infected humans and cattle and also advocate multidisciplinary approaches of One Health to mitigate public health problems associated with TB in Africa.

EP-105-04 Is there a difference in time to sputum culture conversion between *Mycobacterium bovis* and *Mycobacterium tuberculosis* disease?

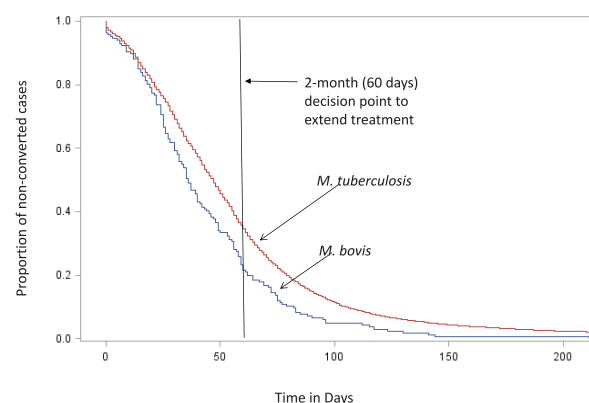
C Scott,¹ J Ershova,¹ J Cavanaugh,¹ G M Mazurek,¹

B J Silk,¹ P Lobue,¹ P Moonan¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. Fax: (+1) 404 718 8308. e-mail: ibk9@cdc.gov

Background: *Mycobacterium bovis* is intrinsically resistant to pyrazinamide (PZA) due to a single nucleotide polymorphism of the *pncA* gene. PZA offers sterilizing activity on semidormant bacilli and, when used in combination with rifampin and isoniazid, shortens the duration of tuberculosis treatment from 9 months to 6 months. Guidelines recommend extending treatment of tuberculosis due to PZA resistant organisms (including *M. bovis*) from 6 to 9 months; however, the evidence base used to develop treatment guidelines have not distinguished *M. bovis* from *M. tuberculosis* disease. We compare the time to sputum culture conversion between *M. bovis* and *M. tuberculosis* cases.

Design/Methods: This retrospective cohort analysis included all culture-positive tuberculosis cases with spoligotyping and 24-locus MIRU-VNTR results among patients who received standard 4-drug treatment at the time of diagnosis in the USA during 2006–2011. We excluded from analysis cases with initial or acquired resistance to rifampin or isoniazid and cases who were dead at diagnosis or died during the course of treatment. The time to sputum culture conversion was estimated with Kaplan-Meier curves using treatment start date and date of first consistently culture-negative sputum. We used Cox proportional hazard modeling to calculate adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI) and identify factors associated with time to culture conversion.

Figure: Time (in days) from start of treatment to conversion to negative sputum culture for *Mycobacterium bovis* compared to *M. tuberculosis* disease



Results: A total of 26 419 cases, 195 (0.7%) *M. bovis* and 26 224 (99.3%) *M. tuberculosis* cases were included in the study. At two months of treatment (the point at which the decision to extend treatment is made), 78% of *M. bovis* and 65% of *M. tuberculosis* cases converted sputum culture to negative (Figure). *M. bovis* cases converted sputum-cultures to negative 40% faster than

M. tuberculosis cases (aHR 1.4, 95%CI 1.2–1.6). Directly observed therapy (aHR 1.1, 95%CI 1.0–1.1) and provider type (aHR 1.1, 95%CI 1.06–1.13) did not substantially impact conversion rates but were statistically significant.

Conclusion: In this population-based, cohort study, *M. bovis* cases converted sputum-cultures to negative sooner than *M. tuberculosis* cases. The loss of PZA among *M. bovis* cases does not appear to lengthen time to culture conversion among those who received standard 4-drug treatment at diagnosis. Randomized controlled trials may be needed to confirm that *M. bovis* disease can be treated in 6 months.

EP-106-04 New diagnostic tests for bovine tuberculosis

S-H Wang,¹ J M Balada-Llasat,¹ W G Hunt,² G Gebreyes,¹ J Torrelles,¹ P Jeff¹ ¹Ohio State University, Columbus, OH, ²Nationwide Children's Hospital, Columbus, OH, USA. Fax: (+1) 614 293 4556. e-mail: shu-hua.wang@osumc.edu

Background: Bovine Tuberculosis (TB) is one of the World Health Organization's seven neglected endemic zoonotic diseases. Currently, there is no a rapid-point-of-care, easy-to-use diagnostic test for bovine TB. We proposed to improve and implement a lipoarabinomannan antigen-antibody (LAM-Ag-Ab) test and develop a pyrazinamide (PZA) drug susceptibility culture test, where PZA resistance is a surrogate marker for *Mycobacterium bovis* infection.

Design/Methods: In collaboration with Michigan Department of Agriculture and Rural Development, we collected urine from cattle suspected of bovine-TB disease in Michigan (US), and conducted the LAM-Ag-Ab test in urine and the PZA culture.

Results: Our results showed that 29 of 35 cows suspected of bovine TB tested positive by the urine LAM-Ag-Ab test. These results were obtained in only 25 minutes, without the requirement of specialized personnel or equipment. Using the US Department of Agriculture bovine TB detection procedures, 12 of 21 animals (57%) were positive by interferon gamma release assay (IFN- γ) blood test, 18 of 21 animals (86%) were positive by gross pathology and histopathology, and 19 of 21 animals (90%) were positive for *M. bovis* culture. When compared to IFN- γ , the LAM-Ag-Ab test showed higher sensitivity (33.3% more accurate). In some cases the LAM-Ag-Ab vs. visual pathology inspection or culture results were discordant. That is, the LAM-Ag-Ab was positive in 14.3 % (3 of 21 animals) more cases than pathology but this test gave LAM negative (infection indicator) in comparison to culture in 9.5% of the specimens (2 of 21 animals). The evaluation of the PZA culture is ongoing, however, using *M. bovis* spiked urine in the lab setting, this test was optimized. Specifically, we validated detection and differentiation of *M. tuberculosis* complex infections and determination of PZA drug-resistance in 14 days.

Conclusion: Urine LAM-Ag-Ab and PZA culture tests offer the potential to diagnose *M. bovis* infection in

cattle in a more rapid and less expensive fashion than current methods. We anticipate that processing the urine using "quick and easy" biochemical procedures will further increase the sensitivity of the LAM-Ag-Ab test.

EP-107-04 Identification of environmental non-tuberculous mycobacteria of public health importance in cattle in Zimbabwe

N Chin'ombe,¹ L Padya,² M Magwenzi,¹ J Mbanga,² P Nziramasanga¹ ¹University of Zimbabwe, Harare, ²National University of Science and Technology, Bulawayo, Zimbabwe. e-mail: nyasha.chinombe@gmail.com

Background: The genus *Mycobacterium* is made up of highly heterogeneous bacteria that are found ubiquitously in the environment and in animals such as cattle. To date, more than 100 *Mycobacterium* species have been identified. Some of the *Mycobacterium* species are now known to be opportunistic pathogens in humans. Rapid laboratory identification of these bacteria at species level is therefore critical if infections are to be controlled. Since cattle live in close proximity with people, we set out to identify nontuberculous *Mycobacterium* species of public health importance in cattle in Zimbabwe.

Design/Methods: Cattle cowdung samples were collected throughout Zimbabwe and mycobacteria were isolated using culture method. DNA was isolated from the cultures and 16S ribosomal RNA gene of *Mycobacterium* was amplified by polymerase reaction. The amplicons were sequenced. Bioinformatics analyses of the sequences were used to identify the mycobacteria at species level.

Results: A total of 134 cowdung samples were collected throughout Zimbabwe. Out of these, 49 samples were positive for suspected mycobacteria by acid fast test. PCR products were sequenced in 26 samples that amplified well. Analysis of the sequences showed that 7 (27%) belonged to *Mycobacterium neoaurum*, 6 (23%) to *Mycobacterium fortuitum*, 3 (12%) to *Mycobacterium goodii*, 2 (1%) to *Mycobacterium arupense*, 2 (1%) to *Mycobacterium septicum/peregrinum* and 1 isolate (0.04%) to *Mycobacterium elephantis*. There were 5 (19%) isolates that were non-mycobacteria.

Conclusion: Several species of genus *Mycobacterium* that may cause human diseases were isolated and identified by 16S rDNA sequencing in Zimbabwe. The study therefore provides a molecular basis for species identification of NTM species in animals and humans.

EP-108-04 Human tuberculosis due to *Mycobacterium bovis* in England, Wales and Northern Ireland: a 12-year national cohort analysis of the epidemiology

J Davidson,¹ M Lalor,¹ L Thomas,¹ I Abubakar,^{1,2} D Zenner¹ ¹Public Health England, London, ²University College London, London, UK. e-mail: jennifer.davidson@phe.gov.uk

Background: Public and political interest in the control of bovine tuberculosis (TB) in animals is high in the UK, with high profile interventions including badger and infected cattle culls aiming to prevent transmission to humans. We described the epidemiology of human *M. bovis* in the UK, identified factors associated with human *M. bovis* disease compared to *M. tuberculosis*, and quantified the occurrence of animal contact and unpasteurised milk consumption in *M. bovis* cases in England, Wales and Northern Ireland (EW&NI) to inform public health policy.

Design/Methods: We conducted a retrospective cohort study including all culture confirmed TB cases speciated as *M. bovis* between 2002 and 2013 in EW & NI. Additionally we carried out a multivariable case-case analysis comparing *M. bovis* cases to *M. tuberculosis* cases to identify factors that distinguish *M. bovis* cases.

Results: Between 2002 and 2013, there was 318 *M. bovis* TB cases, of which 90.6% (288/318) were clinically notified. 50.6% (161/318) of cases were aged over 65 years. Of notified cases, 65.6% (189/288) were UK born, with 60.8% (155) aged over 65 years. The majority (66.2%; 45/68) of non-UK born cases were aged between 15 and 44 years. On average, 27 *M. bovis* cases were identified annually compared to 4940 *M. tuberculosis* cases. Being 65 years or older, UK born or long-term UK resident, of white ethnicity and not having a social risk factor were independently associated with *M. bovis* in multivariable analysis when compared to *M. tuberculosis* cases. From additional exposure information collected for *M. bovis* cases, the most frequent (41.7%; 86/206) exposure was consumption of unpasteurised milk, with the majority (79.6; 43/54) having consumed more than 10 years before diagnosis. 20.4% (42/206) of cases had work related animal exposures, 14 of which had contact with *M. bovis* infected animals.

Conclusion: There is a low number of *M. bovis* cases in EW&NI, accounting for a low proportion of TB cases. Compared to *M. tuberculosis* cases, *M. bovis* cases were more likely to occur amongst older white UK born individuals, likely to be attributed to reactivation of infection acquired before widespread milk pasteurisation. A low number of new infections occur mainly amongst individuals with *M. bovis* related exposures and those likely to have acquired the infection abroad. The findings suggest there is a low risk of acquisition of *M. bovis* in humans in EW&NI, with effective control measures to prevent the zoonotic spread in place.

02. TB in children: perspectives from around the world

EP-109-04 Accuracy of diagnostic tests for childhood pulmonary tuberculosis: estimation via Bayesian latent class analysis

S Schumacher,¹ M Van Smeden,² N Dendukuri,¹ M Nicol,³ M Pai,¹ H Zar⁴ ¹McGill University, Montreal, QC, Canada; ²Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; ³University of Cape Town and National Health Laboratory Service, Cape Town, ⁴Dept of Paediatrics & Child Health, Red Cross Children's Hospital and MRC Unit on Child & Adolescent Health, University of Cape Town, Cape Town, South Africa. e-mail: samuel.schumacher@mail.mcgill.ca

Background: The absence of a gold standard diagnostic test for childhood PTB complicates the assessment of novel tests and also makes diagnosing individual patients and estimating population prevalence difficult. Latent Class Analysis is a statistical modeling technique that allows simultaneous estimation of test accuracy and disease prevalence in the absence of a gold standard.

Design/Methods: We analyzed data from a prospective cohort study of 910 hospitalized children with suspected PTB in South Africa in whom MGIT, smear microscopy and Xpert were done on respiratory specimens and TST and Chest X-ray had been performed. We fitted a hierarchical Bayesian latent class model based on how observed test results and patient characteristics relate to the unobserved true disease status (TB or not TB). We incorporated both predictors of the pre-test probability and covariates modifying test accuracy in our model. Conditional dependence between microbiological tests was modeled via a random effect, representing unobserved bacillary burden.

Results: Median age was 25 months (IQR 13-59), 22% were HIV infected, 28% were malnourished (MN, based on weight for age Z-score <-2) and 57% were started on tuberculosis treatment. We estimated sensitivity of MGIT, Xpert and smear respectively as 52% (95%CrI 40-68), 44% (95%CrI 34-57) and 18% (95%CrI 13-25) with specificities above 98% for all three tests. X-ray was estimated to have sensitivity of 61% (95%CrI 52-70) and specificity of 80% (95%CrI 75-85). TST sensitivity decreased with increasing immunosuppression from 80% (HIV-MN-) to 69% (HIV-MN+) to 47% (HIV+MN-) to 34% (HIV+MN+). TB prevalence was estimated to be 32% (95%CrI 24-41) overall, 48% (95%CrI 38-59) among the treated and 10% (95%CrI 4-18) among the untreated. In comparison, using classification based on a clinical case definition, 18% of children had definite TB (microbiologically confirmed), 34% had no TB (not clinically diagnosed and improved without treatment on follow up) and 48% had possible TB (all others).

Conclusion: Bayesian Latent Class Analysis makes optimal use of the imperfect information from available test results and is a valuable modeling framework for childhood PTB and other diseases when no gold standard exists. Increased use of Latent Class Analysis should

facilitate development and evaluation of improved novel tests but also refine our understanding and optimal use of technologies that are currently available.

Table

Test	Sensitivity % (95% CrI)	Specificity % (95% CrI)
Culture	52 (40-68)	100 (99-100)
Xpert	44 (34-57)	99 (98-100)
Smear	18 (13-25)	100 (99-100)
CXR	61 (52-70)	80 (75-85)
TST (HIV-Maln-)	80 (71-87)	70 (64-77)
TST (HIV-Maln+)	69 (54-81)	
TST (HIV+Maln-)	47 (28-68)	
TST (HIV+Maln+)	34 (17-55)	

CrI = credible interval (Bayesian analog of frequentist confidence interval); CXR = chest X-ray; TST = tuberculin skin test; HIV = human immunodeficiency virus; Maln = Malnutrition based on weight for age Z-score <-2.

EP-110-04 Characteristics and outcomes of drug-resistant tuberculosis children: a multicenter retrospective study of Médecins Sans Frontières programs

M Bastard,¹ A Hayrapetyan,² N Sapaev,³ T Dlamini,⁴ S Khurkhumal,⁵ C Hewison,⁶ F Varaine,⁶ M Bonnet^{1,7}

¹Epicentre, Paris, France; ²National Tuberculosis Control Office, Yerevan, Armenia; ³Deputy Chief Doctor of the Republican TB Dispensary, Nukus, Uzbekistan; ⁴Ministry of Health-TB National Control Program National Manager, Mbanane, Swaziland; ⁵Director of the National TB Program, Sukhumi, Abkhazia, Georgia; ⁶Médecins Sans Frontières, Paris; ⁷Unité Mixte Internationale UMI233-U1175, Institute of Research for Development, Montpellier, France. e-mail: mathieu.bastard@geneva.msf.org

Background: Paediatric drug-resistant tuberculosis (DR-TB) remains highly neglected and very little data is available on the characteristics and outcomes of children with DR-TB. We present results from a retrospective study of seven Médecins sans Frontières DR-TB programs.

Methods: Demographic, clinical and bacteriological characteristics of children (<15 years) at treatment initiation were described. We also presented preliminary DR-TB treatment outcomes for patients starting treatment at least two years before censoring date of the database.

Results: Between 2006 and 2013, 259 children (53.8% female) started on treatment. Median age was 8 [IQR 4-12], 72.5% were new cases, 19.1% were contacts of a multidrug-resistant tuberculosis (MDR-TB) cases and 13% (27/208) were HIV-positive. The main symptoms at admission were fever (36%) and weight loss (21%). Majority had pulmonary TB (66.7%) and 13.4% had cavities on chest X-ray. Of 259 children who started a DR-TB treatment, only 52 (20.1%) were bacteriologically confirmed (43 were confirmed by culture and 9 by smear). Drug susceptibility testing among culture positive showed that 25.9% had poly-drug resistant TB and 74.1% had MDR-TB. Among MDR-TB, majority had no resistance to second line drugs (61.3%), 35.8% had resistance to injectables, and 3.2% to fluoroquinolones. Main side-effects experienced during treatment were

gastrointestinal and hepatic. Of 42 children with a final outcome: 16 cured (38.1%), 21 completed treatment (50%), 3 died (7.1%), 1 failed treatment and 1 defaulted from treatment (2.4%).

Conclusions: Our study, showing that 80% of the children start a DR-TB treatment without confirmed resistance, reinforces the urgent need of TB diagnostic and resistance test adapted to children in order to avoid unnecessarily exposing children to long and potentially toxic treatment. Preliminary outcome results are encouraging.

EP-111-04 Role of chest X-ray in the diagnosis of intra-thoracic childhood tuberculosis

S H Syed Usman,¹ R Nathavitharana,² B Velayutham,¹ V Chandrasekaran,¹ G Sharma,¹ D Baskaran,¹

S Swaminathan¹ ¹National Institute for Research in Tuberculosis, Chennai, India; ²Beth Israel Deaconess Medical Center, Boston, MA, USA. e-mail: drsyed@rediffmail.com

Background and aims: Children with TB are frequently misdiagnosed (both under and over-diagnosed). In the absence of bacteriologic confirmation, chest radiograph plays an important role in the diagnosis of pediatric tuberculosis (TB). We evaluated the role of chest X-ray in the initial diagnostic work up.

Patients and methods: Children <15 years with clinical signs and symptoms suggestive of TB not responding to antibiotics were enrolled. Children underwent chest-Xray, sputum or gastric lavage for AFB smear and M.tuberculosis culture. The X-rays were reviewed by two independent radiologists in blinded manner. Further a panel, consisting of a paediatric pulmonologist, pulmonologist and general physician, reviewed any abnormal X-rays and classified as-Abnormal suggestive of TB, Abnormal non-TB and normal.

Results: 813 children were enrolled and given an initial treatment decision. 9/813 (1.1%) patients had positive smears, and 26/813 (3.2%) cultures were positive and of these, 4, 11 and 11 had abnormal X-ray suggestive of TB, abnormal X-ray and normal X-rays respectively. Of 813 X-rays assessed, 125 (15%) were read as abnormal and 523(64%) as normal by both readers. There was discordance in 165 (20%) X-rays and kappa was 0.47 indicating moderate level of inter-reader agreement. Of 160 patients with abnormal X-rays determined by panel, 57 (36%) were started on anti-tuberculosis therapy (ATT), of these 16(28%) were based on bacteriologic confirmation and 41 (72%) were based on radiologic and clinical features.

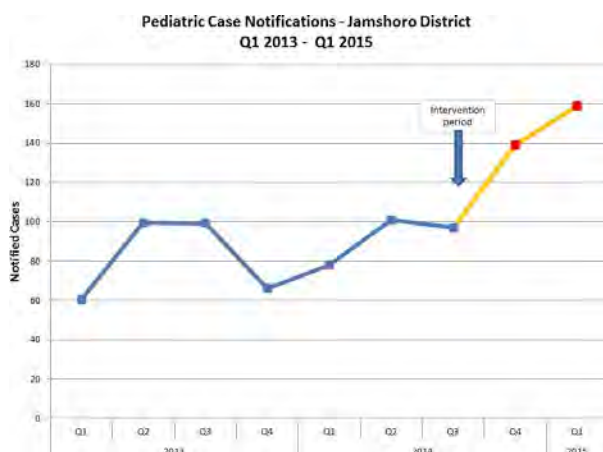
Conclusion: The role of X-ray for the diagnosis of TB in a paediatric clinic setting is unclear given the range of abnormalities and lack of specificity. Further research is warranted to determine the use of other imaging modalities for childhood TB diagnosis and a comprehensive diagnostic strategy.

EP-112-04 Increasing childhood TB notifications through systematic screening in public-sector hospitals in rural Pakistan

A Malik,^{1,2} F Amanullah,¹ S Saleem,¹ M Jaswal,¹ H Hussain^{1,2} ¹The Indus Hospital, Karachi, ²Interactive Research and Development, Karachi, Pakistan. e-mail: amyn.malik@irdresearch.org

Background: An estimated 0.5 million children develop TB each year and account for 6-10% of all TB cases of all ages. This is likely an underestimate of the true child TB burden, owing to poor access to diagnostics and underreporting. Active screening is known to increase adult TB case notification urban settings.

Design/Methods: Lay screeners were recruited and trained on using interactive algorithms (Decision Support System) on handheld android devices to screen children at the pediatric outpatient departments of three large secondary and tertiary care public hospitals in Jamshoro district of Sindh, from Quarter 4 of 2014. Children with one or more symptoms of TB (cough $\geq$ 2 weeks or contact history of TB in the last 2 years or a combination of two of the following: fever $\geq$ 2 weeks, night sweats or weight loss) were referred to a medical officer who clinically evaluated and ordered diagnostic tests including chest X-ray, AFB smear, and Xpert MTB/RIF assay. All tests were offered free of cost to the children. Diagnosed patients were started on TB treatment and caregivers were asked to bring other children in the household for screening. Medical officers at participating hospitals were trained in pediatric TB, and management of complex cases was supervised by a pediatric TB specialist at The Indus Hospital using free applications like Skype and WhatsApp.



Results: Screeners assessed 33 505 children between October 2014 and March 2015, of which 859 were classified as children with presumptive TB. Of these, 221 children were diagnosed with TB disease and were started on treatment. This resulted in an over two fold increase in pediatric TB case detection and notification across 12 BMUs in the intervention district. In the control district of Hyderabad there was no change in pediatric TB case notification. Interestingly of the 221 children started on treatment, 57% were in the 0-4 year

age group. This is contrary to the pattern seen at the Indus Hospital TB program where the majority of children with TB belong to the >5 year age group.

Conclusion: Children with TB disease often remain undiagnosed as symptoms are nonspecific. Higher case detection in the 0-4 year age group in our rural setting likely occurred because of the integration of TB screening with the EPI program, resulting in earlier TB detection in this vulnerable group. Active screening at pediatric outpatient departments of rural hospitals can increase child TB detection and notification many fold.

EP-113-04 Effect of empirical tuberculosis treatment on mortality of children with clinical suspicion of intrathoracic tuberculosis

M Bonnet,^{1,2} M Nansumba,^{2,3} M Bastard,⁴ P Orikiriza,² P De Beaudrap,^{1,2} Y Boumli,^{2,3} J Kiwanuka,^{3,5} E Kumbakumba^{3,5} ¹Institut de Recherche pour le Développement (IRD), Montpellier, France; ²Epicentre, Mbarara, ³Mbarara University of Science and Technology, Mbarara, Uganda; ⁴Epicentre, Paris, France; ⁵Mbarara Regional Reference Hospital, Mbarara, Uganda. e-mail: maryline.bonnet@geneva.msf.org

Background: Use of empirical tuberculosis (TB) treatment is common in high burden countries due to lack of effective TB diagnostic tests. We assessed the effect of empirical TB treatment on mortality of children with clinical suspicion of intrathoracic TB in Uganda.

Methods: Children <14 years old with at least one of the following signs (unexplained weight loss, persistent respiratory symptoms, fever, fatigue or reduced playfulness) underwent clinical investigation, chest X-ray, tuberculin skin test (TST) and sputum mycobacterial tests (microscopy, XpertMTB/RIF, culture) and were followed for 3 months. Decision to initiate treatment was based on mycobacterial, clinical and radiological findings. The effect of empirical treatment on mortality was adjusted on age, sex, malnutrition (weight for height z-score), HIV infection, TB contact history, TST results (5mm cut-off).

Results: 392 children were included: median (interquartile range, IQR) age of 4 years [1.4, 7.5], 45% female, 31.2% HIV infected and 20.5% with moderate to severe malnutrition. 144 (36.7%) children were started on treatment (18 with confirmed TB and 126 empirically). At 3 months of follow-up, 25/392 (6.4%) children died: 15/144 (10.4%) on TB treatment vs. 10/248 (4.0%) not on treatment ($P = 0.005$). Median (IQR) time to death was 20 days (8, 75): 13 for children on TB treatment vs. 21 for non-treated ones. There was significantly more deaths in the following groups: <2 years old (12%, 15/125) vs. older ones (3.7%, 10/267), moderately to severely malnourished (15.2%, 12/79) vs. others (3.6%, 11/306), empirical treatment (11.9%, 15/126) vs. confirmed TB (0%, 0/18), negative (6.7%, 19/284) vs. positive TST result (1.0%, 1/99) and no TB contact history (7.6%, 24/315) vs. exposure (1.3%, 1/76). After multivariate analysis, empirical TB treatment (aOR 4.1, 95%CI 1.6-10.5) and negative TST result (aOR 12.5, 95%CI 4.7-26.3) remained associated with death.

Conclusion: The results suggest that children on empirical TB treatment are more likely to die than confirmed TB cases or non-treated cases. This could be explained by the difficulty to diagnose TB in children, the increased likelihood of starting empirical treatment in children with severe clinical condition or comorbidities and the possibility of misdiagnosis of other severe infections. They highlight the urgent needs for more effective TB diagnosis tests for children presenting with severe clinical conditions.

EP-114-04 Impact of Xpert® sputum diagnostics in children with TB disease on treatment decision in a high-burden setting

J Bacha,¹ J Benjamin,¹ L Campbell,¹ P Clowes,² C Mangu,² A Dinardo,³ K Ngo,³ A Mandalakas³ ¹Baylor College of Medicine Children's Foundation - Tanzania, Mbeya, ²National Institute of Medical Research - Mbeya Medical Research Centre (NIMR-MMRC), Mbeya, Tanzania; ³Baylor College of Medicine, Houston, TX, USA. e-mail: bacha@bcm.edu

Background: 2014 WHO policy update recommends GeneXpert (GXP) as the initial diagnostic test in children suspected of having TB, leading to countries working on improving access to GXP. However, GXP may have limited impact in children due to pauci-bacillary, culture negative nature of childhood TB and use of clinical diagnosis in children. The added diagnostic value of GXP in children in resource limited settings remains unclear and needs investigation.

Design/Methods: Retrospective chart review between March 2013 and December 2014 of patients seen at the Baylor Tanzania Centre of Excellence (COE) in Mbeya, Tanzania. Data on children referred for presumptive TB and diagnosed with TB were captured using a standardized data collection tool and unique data base.

Results: Of 504 children (57% HIV-infected) referred for presumptive TB, 35% (176/504) were diagnosed with TB. 70% (355/504) completed GXP testing as part of their evaluation. GXP was completed by 69% (226/328) of children where TB was excluded and 73% (129/176) of children diagnosed with TB. Among children not diagnosed with TB, GXP was negative in >99% (327/328) and not resulted in 1 child. Of those diagnosed with TB disease, GXP was positive in 9% (12/129), negative in 90% (116/129) and not resulted in 1% (1/129). Median time to antituberculosis treatment (ATT) among children with TB disease was 3 days (0-142), and did not vary widely between those with GXP not done (2 days, 0-25d), GXP positive (3 days, 0-28d), or GXP negative (4 days, 0-142d). Older children were more likely to have a positive GXP while younger children were more likely to not complete GXP (ANOVA, $P=0.001$; Table). Hospitalized children were less likely to have done GXP than outpatient referrals ($P=0.003$). There was no association between HIV status or presence of severe acute malnutrition and GXP result/use ($P=0.431$ and $P=0.306$).

Conclusion: In our setting, clinicians were less likely to use GXP in hospitalized or younger children and use of GXP testing did not reduce time to ATT. Likely reasons

include high rates of empirical treatment in children, as well high severity of illness leading to lower treatment initiation thresholds. In such settings, GXP availability may not have a large impact on clinicians' decision making. More sensitive pediatric POC testing with lower limits of detection may eventually influence clinician behaviour, leading to less empiric treatment and improved resource allocation.

Table Characteristics of children diagnosed with TB disease based on GXP testing/results

Characteristics	Patients diagnosed with TB disease			χ^2 (df)	P value
	GXP positive ($n=12$)	GXP negative ($n=116$)	GXP not done ($n=47$)		
Median age (years, range)	12.0 years (2.3–19.0)	6.2 years (0.6–18.3)	3.1 years (0.3–18.3)	9.37* (2)	0.001
HIV-positive (%)	6 (50%)	69 (60%)	25		
HIV-exposed (%)	0 (0%)	9 (8%)	2 (4%)	†	0.431
Inpatient status (%)	5 (42%)	41 (35%)	31		
	11.68 (2)	0.003			
SAM (%)	6 (50%)	31 (27%)	16		
	2.37 (2)	0.306			
Mean time to ATT (days, range)	4.5 (0–28)	13.5 (0–142)	3.2 (0–25)	5.09* (2)	0.007

* (df) = ANOVA F-value);

† Fisher's exact test was used for analyses involving cell sizes of 5 or fewer individuals.

TB=tuberculosis; GXP = GeneXpert; HIV=human immunodeficiency virus; SAM= severe acute malnutrition; df = degrees of freedom; ATT = anti-tuberculosis treatment.

EP-115-04 Long-term safety, tolerability, and pharmacokinetics of delamanid in children aged 12–17 years

J Hafkin,¹ M Gler,² M Frias,³ A De Leon,⁴ N Hittel,⁵ L Geiter,¹ C Wells,¹ S Mallikaarjun¹ ¹Otsuka Pharmaceutical Development and Commercialization, Rockville, MD, USA; ²Otsuka Manila Research Center, Makati City, ³De La Salle Health Sciences Institute, Cavite, ⁴Lung Center of the Philippines, Quezon City, Philippines; ⁵Otsuka Novel Products Germany, Munich, Germany. e-mail: jeffrey.hafkin@otsuka-us.com

Background: Limited data exists with which to guide the treatment of multidrug-resistant tuberculosis (MDR-TB) in children. Delamanid, a novel anti-TB agent with bactericidal activity, has demonstrated efficacy in previous clinical trials of MDR-TB in adults. The aim of this current trial is to assess the long-term safety, tolerability, and pharmacokinetics of delamanid in children (ages 12–17 years) with MDR-TB.

Design/Methods: A Phase 2, open-label, uncontrolled, trial of delamanid in children with MDR-TB aged 12–17

was performed at De La Salle Health Sciences Institute and Lung Center of the Philippines. Delamanid 100mg BID was administered with an optimized background regimen (OBR) for six months followed by OBR alone in accordance with WHO guidelines. Clinical and safety assessments were performed approximately every 2-4 weeks for up to one year; sparse PK sampling for concentrations of delamanid and DM-6705 (a key delamanid metabolite) was performed on days 1, 14, 56, 98, 154, 182, 189, 196, 203, 210, and 238.

Results: Nine patients were screened and seven enrolled in the trial. Six (86%) had confirmed MDR-TB, and one (14%) had probable MDR-TB. All seven (100%) had pulmonary disease, and six (86%) had previously received treatment for TB. The median age was 15 years (13-17); four were male, three female; the median weight and BMI were 38.5 (26-45) kg and 15.9 kg/m² (15-20), respectively. No patients discontinued trial participation or follow-up prior to the end of the trial; however, one patient had delamanid withdrawn permanently due to nonadherence and subsequent pregnancy. No serious adverse events were reported; the most common adverse event reported was headache, occurring in five patients (71.4%). No patient experienced an absolute QTcF >500ms. Over the course of delamanid treatment, the median C_{max} ranged from 354 to 657ng/mL. Compared to adults, median delamanid concentrations were higher in children—though within the range seen in adult clinical trials. Median DM-6705 levels, however, remained lower in children than in adults.

Conclusion: Long-term exposure to delamanid 100 mg BID was safe and well-tolerated by this cohort of children (ages 12-17 years) with MDR-TB. Delamanid plasma concentrations in this age group were within the range of those seen in adult clinical trials, suggesting that the current standard adult dosing is adequate for this age group. Additional data collection activities are underway to assess the same parameters in children <12 years with MDR-TB.

EP-116-04 Poor bacteriological yield of alternative sampling strategies for paediatric tuberculosis at a primary care clinic in Johannesburg, South Africa

C Hanrahan,¹ L Mutunga,² J Bassett,² H France,² S Omar,³ N Ismail,³ H Dansey,² A Van Rie^{4,5} ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ²Witkoppen Health and Welfare Centre, Johannesburg, ³National Institute for Communicable Diseases, Johannesburg, South Africa; ⁴University of Antwerp, Antwerp, Belgium; ⁵University of North Carolina School of Public Health, Chapel Hill, NC, USA. e-mail: chanraha@jhsph.edu

Background: Diagnosis of paediatric tuberculosis (TB) is challenging due to paucibacillary disease and difficulty in collecting sputum. Hospital studies have demonstrated the utility of alternative sampling strategies such as nasopharyngeal aspirate (NPA) and new diagnostics such as Xpert MTB/RIF (Xpert). We aimed to determine the

optimal sampling strategy and diagnostics at primary care, where children present with less severe disease.

Design/Methods: We enrolled a prospective cohort of children (age 6 weeks - 10 years) with signs and symptoms of TB at Witkoppen Health and Welfare Centre, a primary care clinic in Johannesburg, South Africa. Tuberculin skin testing (TST) and chest X-ray (CXR) were performed in all. In those unable to expectorate, one induced sputum (IS), one gastric aspirate (GA) and two NPAs were collected. Stool was collected from all children. Samples were processed at the National TB Reference Laboratory for smear microscopy, liquid culture and Xpert. Determine TB LAM Ag (urine LAM) was done on-site for all HIV-infected children. All children were followed up clinically for 2 months. TB disease status was classified using consensus clinical case definitions.

Results: From July 2013-December 2014 we enrolled 119 children. Median age was 21 months (IQR: 12-42), and 18% were HIV-infected. About half (*n*=69, 58%) were contacts of known TB cases. TST was positive in 24%, and 55% had a CXR suggestive of TB. Spontaneous sputum was successfully collected in 12%. Among the 105 unable to expectorate, one IS was successfully collected in 98%, NPA in 96%, and GA in 58%. Stool was collected in 96% of all children, and urine in 62% of HIV-infected children. A physician initiated TB treatment in 49 (41%) children; only 2 (4%) had confirmed TB, 46 (94%) probable or possible TB and 1 (2%) unlikely TB. Among the 70 children not treated, 36 (51%) had probable or possible TB, and 34 (49%) unlikely or not TB. Of all 469 samples collected, smear microscopy was positive in 0%, Xpert in <1% (*n*=4) and culture in <1% (*n*=2). NPA had the highest yield (3/101 patients, 3%). Among HIV-infected children with probable or possible TB, 2/11 (18%) were positive by urine LAM, while 1/2 (50%) were positive in those with unlikely or not TB.

Conclusion: At primary care, alternative sampling strategies proved feasible but resulted in a low diagnostic yield with available tools. Extensive efforts to bacteriologically diagnose children did not contribute to clinical management, as almost all children started treatment based on clinical findings.

EP-117-04 Experiences of care givers for children with tuberculosis in and around Gaborone, Botswana

C Stillson,¹ H Okatch,^{1,2} R Frasso,^{1,3} L Mazhani,⁴ T David,⁴ T Arscott-Mills,^{1,4,5,6} L Ntshimane,⁵ A Steenhoff^{1,4,5,6} ¹Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; ²University of Botswana, Gaborone, Botswana; ³Center for Public Health Initiatives, University of Pennsylvania, Philadelphia, PA, USA; ⁴Department of Paediatric & Adolescent Medicine, Faculty of Health Sciences, University of Botswana School of Medicine, Gaborone, ⁵Botswana-U Penn Partnership, Gaborone, Botswana; ⁶Children's Hospital of Philadelphia, Philadelphia, PA, USA. e-mail: christian.stillson@gmail.com

Background: The length and complexity of treatment for tuberculosis (TB) poses challenges for children who are

too young to manage their own care. This leaves the responsibility for treatment delivery on their caregivers. The knowledge, attitudes and beliefs of these caregivers towards TB likely have a direct effect on disease outcome. Previous studies have noted low health literacy in caregivers for children with TB. We sought to investigate the lived experience of caregivers for children on treatment for TB, and to explore caregivers' experiences with health care staff, perceived challenges, unmet needs and barriers to successful treatment in Gaborone, Botswana and its surrounding districts.

Methods: Semi-structured interviews were conducted with 28 caregivers of children currently on anti TB treatment. Interviews were guided by a piloted interview instrument and conducted in Setswana or English at the interviewees' discretion. Audiotapes of interviews were transcribed and translated into English where necessary. Transcripts were then uploaded into the qualitative analysis software NVivo 10 (QSR International) to facilitate a systematic thematic analysis. A coding schema was developed from the transcripts by two investigators versed in local culture and context. All transcripts were then double coded and analyzed for inter-coder reliability.

Results: Respondents reported both positive and negative experiences as caregivers. Many reported barriers to timely diagnosis and effective TB treatment for their children. These included misdiagnoses before beginning TB treatment, low levels of TB health education at the time of diagnosis, inconsistent access to medication at their point of care, and difficulty administering medication to the child. Respondents also reported significant relief in seeing improvements in their child's condition as TB treatment progressed.

Conclusions: Caregivers identified multiple barriers in timely diagnosis and treatment of pediatric TB and in their knowledge of TB. The barriers identified by caregivers in administering tablets highlight the need for child-friendly drug formulations. Efforts to improve TB outcomes in this and similar settings should be focused on improving diagnosis, consistent provision of quality education, and ensuring the availability of child-friendly formulations of TB drugs.

03. Drug-resistant TB: outcomes - I

EP-118-04 Effectiveness of individualized regimen for treatment of isoniazid-mono-resistant tuberculosis: a multicenter study of Médecins Sans Frontières programmes

M Bastard,¹ E Sanchez,¹ P Du Cros,² A Telnov,³ C Hewison,⁴ H Khamraev Atadjan,⁵ M Bonnet,^{1,6} F Varaine⁴ ¹Epicentre, Paris, France; ²Médecins Sans Frontières, London, UK; ³Médecins Sans Frontières (MSF), Geneva, Switzerland; ⁴MSF, Paris, France; ⁵Teaching Assistant of the Department of Public Health Administration, Nukus Branch of Tashkent Pediatric Medical Institute, Nukus, Uzbekistan; ⁶Unité Mixte Internationale UMI233-U1175, Institute of Research for Development, Montpellier, France. e-mail: mathieu.bastard@geneva.msf.org

Background: Although data exist for multi-drug resistant TB (MDR-TB) patients, very little is available on other resistant forms of TB, such as poly-drug resistant TB, and particularly those resistant only to isoniazid or to isoniazid and streptomycin (H(S) resistant).

Methods: We retrospectively analysed data from seven DR-TB programs. Confirmed H(S) resistant patients starting treatment before July 2011 were included in the study. Patients received an adapted treatment regimen with first or second line drugs according to their clinical status and previous DRTB exposure. Characteristics at treatment initiation, extension to MDR-TB during treatment and treatment outcome were described. Cox-proportional hazards model was fitted to explore risk factors of unsuccessful treatment outcome.

Results: A total of 310 H(S) resistant patients started on treatment: 65.8% female, median age of 36 [IQR 26-48], 43.1% were new cases, 74.7% had cavities on chest X-ray and 25.9% had a BMI < 18.5 kg/m² and 9.5% were HIV-positive. Smear was positive in 68.4% and streptomycin (S)-resistance was found in 76.2% of patients. At initiation, 30.6% of patients received first line drugs only and 69.4% received second line drugs (injectables and fluoroquinolones). Extension to MDR-TB during treatment was found in 37/310 (11.9%) patients and did not differ by regimen received. Among them, 10/37 (27.0%) extended also resistance to injectables and 5/37 (13.5%) to fluoroquinolones. Treatment outcomes were: 30.3% cured, 41.6% completed treatment, 2.6% died, 13.9% failed treatment and 11.6% defaulted from treatment. Successful outcome did not differ according to S-resistance ($P = 0.314$) and prescription of second line drugs compared to first line drugs ($P = 0.15$). Among treatment failures, 86.1% became MDR-TB, 23.3% became resistance to injectables and 11.6% became resistant to fluoroquinolones. In multivariate analysis, being ≥ 35 years (aHR=2.21, 95%CI 1.26-3.87) and a BMI<18.5 kg/m² (aHR=2.84, 95%CI 1.70-4.75) were independently associated with an unsuccessful treatment outcome.

Conclusions: Despite treatment adaptation, the proportion of patients who failed treatment is particularly high compared to what is generally observed among full

susceptible TB. Development of resistance to rifampicin, injectables and fluoroquinolones are of particular concern and underlines the need for close monitoring and for revising the treatment recommendations for H(S) resistant patients.

EP-119-04 Interim treatment outcomes in drug-resistant TB patients who were offered second-line drug susceptibility testing at point of entry in Delhi, India

A Khanna,¹ S Chandra,² A Bhatnagar,³ H Mahmud,⁴ N Singla,⁵ B Neeti¹ ¹Directorate of Health Services, State TB Office, New Delhi, ²World Health Organization, Country Office for India, New Delhi, ³Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, ⁴New Delhi TB Centre, New Delhi, ⁵National Institute of TB and Respiratory Diseases, New Delhi, India. e-mail: chandras@rntcp.org

Background and challenges to implementation: Early detection of second line drug-resistant TB (DR-TB) with subsequent individualized treatment regimen is the mainstay for successful treatment outcomes in DR-TB patients. Delhi State with its load of over 6000 DR-TB patients on treatment since 2009, took the initiative of second line drug sensitivity test (SL DST) for all the multidrug resistant/Rifampicin resistant patients diagnosed at point of entry. Accordingly, framework for laboratory and treatment center scale up was planned for a State wide roll out of base line SL DST to all the diagnosed DR-TB patients from April 2014. Our aim is to assess the interim treatment outcomes of those patients who were enrolled for early SL DST since April 2014-June 2014 in Delhi.

Intervention or response: Facilities for second line drug sensitivity test (SL DST) were scaled up in the city across the three culture DST labs. Sample of all patients who were diagnosed as DR-TB starting April 2014 was tested for SL DST at the three certified labs. This is in contrast to the earlier guideline of testing only follow up positives of a DR TB treatment regimen for SL DST. Based on CDST results obtained for Ofloxacin and Kanamycin drugs, the treatment regimen was individualized in accordance with the program guidelines.

Results and lessons learnt: With the introduction of SL DST for all the diagnosed MDR-TB cases, the first cohort of patients registered in April-June 2014, had their interim culture conversions reported after 9 months of standardized treatment with DR-TB and XDR-TB regimens. In the study period, 22% baseline Ofloxacin resistant TB cases were diagnosed among the samples processed for culture. Of the 406 DR TB patients enrolled for treatment, there were 264 culture conversions (65%) and 24 (7%) deaths (as compared to 55% culture conversions and 12% deaths with the earlier protocol having SLDST for follow up positives of DR TB treatment). Similarly, out of 26 XDR-TB initiated on treatment in the study period, 8 (31%) have culture converted during the study period. Significant improvement ($P < 0.01$) in culture conversions and decline in death rates was observed for DR-TB and XDR-TB

started on treatment in April-June 2014 (when compared with same cohort of patients previous year).

Conclusions and key recommendations: Early second line DST with added benefit of an individualized DST guided DR-TB regimen, engenders successful treatment outcomes among DR-TB and XDR-TB patients. This emphasizes the need to fast track the scale up of SL DST facilities and implement guidelines for DST guided individualized regimen within the standard program framework across high burden settings.

EP-120-04 An analysis of factors associated with successful treatment outcomes among drug-resistant tuberculosis patients in Kenya

D Mibei,¹ J Kiarie,¹ M Kamene,¹ A Wairia² ¹Kenya Ministry of Health, Nairobi, ²TB ARC, Center for Health Solutions, Nairobi, Kenya. e-mail: dorothonmibei@gmail.com

Background: Successful treatment outcomes among drug resistant (DR-TB) patients are of public health importance to prevent further spread of drug resistant strains to the general population. In addition, this will prevent the development of more resistance which would further pose more challenges in its management. Treatment of DR-TB is long and involves the use of more toxic drugs. There are factors that have been documented to affect treatment outcomes; nutritional status, resistance pattern and model of care. This study analyzed treatment outcomes of DR-TB patients in Kenya and the factors associated with successful treatment outcomes.

Design/Methods: A retrospective analysis of secondary data from the National Tuberculosis, Leprosy and Lung disease program was done. DR-TB data from the national database (TIBU) for the year 2012 was downloaded and exported to Excel. Data cleaning was done and the data was then exported to SPSS version 21 for analysis. Univariate, Bivariate and Multivariate analysis was done.

Results: A total of 205 DR-TB patients; 185 MDR-TB, 9 monoresistant and 11 PDR, were included in the analysis. Of these, 169 (82.4%) had a successful treatment outcome, 18 (9%) died and 18 (9%) were lost to follow up. Among MDR-TB patients, 154 (83.2%) had a successful treatment outcome. Factors analyzed to determine association with treatment outcomes included; age, gender, facility type, resistance pattern, nutritional status and support, model of care and HIV status. Only gender ($P = 0.04$) and HIV status ($P = 0.02$) were found to be predictors of successful treatment outcomes. Females were more likely to have successful treatment outcomes than males (OR = 3.86, 95%CI: 1.47, 10.12) and HIV negative status increased the likelihood of a successful treatment outcome (OR = 3.53, 95%CI: 1.4, 8.9). More males (120-58.5%) were reported than females. Treatment success rates were higher among females with 76 (89.4%) being treated successfully. All the DR-TB patients were tested for HIV and 152 (74.1%) of them were HIV negative with 131 (86.2%) registering successful treatment outcomes. Among the HIV positive

patients, 38 (71.7%) were successfully treated of whom 35 (71.7%) were on ART.

Conclusion: Successful treatment outcomes were higher than the WHO target. There is need however to assess and address the issues among HIV positive patients and males so as to improve treatment outcomes in these groups.

EP-121-04 9-month short-course MDR-TB treatment in HIV- and non-HIV-co-infected patients in Uzbekistan and Swaziland: interim outcomes of two prospective studie

E Casas,¹ T Gashu,² J Greig,³ K Keus,² T Ndlamini,⁴ H Khamraev Atadjan,⁵ C Berry,⁶ P Du Cros³ ¹Médecins Sans Frontières (MSF), Operational Center Amsterdam, Amsterdam, Netherlands; ²MSF, Operational Center Amsterdam, Matsapha, Swaziland; ³MSF, Operational Center Amsterdam, London, UK; ⁴Ministry of Health, Mbabane, Swaziland; ⁵Public Health Administration, Tashkent, Uzbekistan; ⁶MSF, Operational Center Amsterdam, Nukus, Uzbekistan. e-mail: esther.casas@amsterdam.msf.org

Background: The WHO-recommended treatment regimen for multidrug resistant tuberculosis (MDR-TB) is lengthy, toxic, and has only a 54% success rate. A success rate of 84% has been reported for a 9-11 month regimen; evidence for this regimen is lacking in high MDR-TB and HIV co-infection settings. MSF, with the respective ministries of health, is using the short-course regimen in Uzbekistan and Swaziland. We present interim outcomes of two prospective, observational studies of the safety and effectiveness of short-course MDR-TB treatment.

Design/Methods: We analysed outcomes from September 2013-December 2014. All consenting MDR-TB patients diagnosed using molecular or culture/drug susceptibility testing were included. Outcomes are defined according to pre-2013 WHO definitions. Toxicity was documented with Division of AIDS (DAIDS) grading. Ethics approval: MSF Ethics Review Board (ERB) and the ERBs of Swaziland and Uzbekistan.

Results: Characteristics of the 105 Uzbekistan patients: median age 30.1 years (IQR 24.0-43.2), 51 (48.6%) male, none HIV-positive, and 74 (70.5%) new cases. Outcomes at analysis: 66 (62.9%) on treatment, 20 (19.0%) cure, 4 (3.8%) treatment complete, 2 (1.9%) died, 3 (2.9%) treatment failure, and 10 (9.5%) lost to follow-up. Culture conversion after 4 months of treatment was 89.3% (95%CI 61.6-84.8). Characteristics of the 57 Swaziland patients: median age 35.0 years (IQR 28.3-43.1), 23 (40.4%) male, 42 (73.7%) HIV-positive (15 [35.7%] male, median age 35 years [IQR 30-38]), and 42 (73.7%) new cases. Outcomes at analysis: 39 (68.4%) on treatment, 10 (17.5%) cured, 6 (10.5%) died, 2 (3.5%) treatment failure, and none lost to follow-up. Outcomes among HIV patients: 29 (69%) on treatment, 6 (14%) cured, 6 (14%) died, and 1 (2.4%) treatment failure. Culture conversion after 4 months of treatment was 90%. Severe adverse events grade 3 and 4 occurred in 5 (9.4%) and 13 (24.5%) patients in Swaziland and in 8 (7.6%) and 2 (1.9%) patients in

Uzbekistan, respectively, 3 (5.7%) experienced severe ototoxicity. ECG at 4 weeks: median QTc increase of 16.5 ms (Swaziland) and 21 ms (Uzbekistan); acquired prolonged QT syndrome in one patient resulted in treatment failure (Uzbekistan).

Conclusion: The short-course regimen had satisfactory culture conversion and interim outcomes in high HIV co-infection and drug-resistant populations. Safety, including the first ECG data reported for this regimen was also satisfactory.

EP-122-04 Why did some patients fail second-line therapy for drug-resistant pulmonary tuberculosis? A case series in Karachi, Pakistan

N Salahuddin,¹ S Butt,¹ A Mashhadi,¹ S Adnan,¹ M Y Memon,¹ M Basir,¹ H Hussain¹ ¹Indus Hospital, Karachi, Pakistan. e-mail: naseemsal@hotmail.com

Objective: To define causes of failure of treatment of Drug Resistant Pulmonary Tuberculosis (DR-PTB) in a tertiary care hospital in a high burden tuberculosis country.

Intervention: A retrospective case series study was conducted at our hospital. All cases diagnosed and treated as DR-PTB over 57 months between June 2010 and March 2015 were included. Failure of treatment was defined as: persistent positive cultures beyond 10 months of treatment; culture conversion from negative to positive; progressive clinical or radiological deterioration. Demographics, clinical, laboratory, and outcome data were retrieved from medical records. Progress was determined clinically and by monthly sputum cultures. A radiologist interpreted pre treatment chest radiograph severity.

Results: 722 patients were diagnosed with DR-PTB and treated under Programmatic Management of Drug Resistant TB (PMDT). 7 had XDR, 24 MDR and 5 PDR. All patients received quality assured second line drugs (SLDs) through direct supervision. Group 5 drugs were added to original SLDs on a failing regimen in 27 (75%); 36 (5%) failed treatment. 50% presented within 1-10 months of their illness, while others presented from 11-48 months before diagnosis and treatment. 44% waited 1-3 months before SLDs became available. Mean age was 33 years (5-65), and 41.7% were female. At enrolment 4 (11%) were treatment naïve, 32 (90%) had received prior treatment as drug sensitive TB (21 Cat1, 11 Cat 2). 4 patients had coexisting diabetes, 8% had Hepatitis B, 11% Hepatitis C and none had HIV and 3 were smokers. Pre treatment mean hemoglobin was 10.9 gm and average BMI was 17.3. Severe disease was evident in 12 patients (36%), defined as loss of 25-50% lung volume, and moderate disease in 15 (46%) defined as 5-10% loss of lung volume. None discontinued treatment because of adverse events. Discontinuation of treatment was by consensus among clinicians. Surgery was not an option for lack of proper facility. 19% have died, 41% are alive, and 19% could not be traced by phone calls.

Conclusion: 5% of all DR-PTB cases failed treatment. National failure level was 5% in 2011. Presumptive causes are: low BMI, anemia, pre treatment delay and baseline severe parenchymal disease. Since 2012 time to treatment at our PMDT site is considerably shortened due to early availability of SLDs. Also, since 2013 introduction of GeneXpert has considerably reduced time to diagnosis and treatment. This will greatly improve outcome of MDR treatment.

EP-123-04 Inappropriate treatment of multidrug-resistant tuberculosis patients: effects on culture conversion and final outcomes

P Chitneni,¹ M Buckley,¹ J Rohr,¹ D Theron,² E Kendall,³ R M Warren,⁴ K Jacobson^{1,4} ¹Boston University / Boston Medical Center, Boston, MA, USA; ²Brewelskloof Hospital, Worcester, South Africa; ³Johns Hopkins Hospital, Baltimore, MD, USA; ⁴Stellenbosch University, Tygerberg, South Africa. e-mail: PoojaChitneni@gmail.com

Background: In many high burden countries, recognition of multidrug resistant tuberculosis (MDR-TB) occurs weeks after initial tuberculosis (TB) diagnosis because patients do not receive drug susceptibility testing (DST) until they fail drug susceptible (DS) TB therapy and because culture-based DSTs take weeks to produce results. While awaiting DST results, many MDR-TB patients are begun on DSTB therapy. We aimed to assess whether time on DSTB treatment was associated with delayed sputum culture conversion and worse final outcomes in patients with MDR-TB.

Design/Methods: We analyzed a retrospective cohort of 223 patients who began MDR-TB treatment between 2007 and 2010 in a rural TB hospital in the Western Cape Province, South Africa. We used Cox proportional hazards modeling from time of starting appropriate MDR treatment to culture conversion, stratifying patients by whether they received DSTB treatment for less than vs. greater than one month after having an MDR-TB positive sputum culture collected. DSTB treatment was defined as being on isoniazid, rifampicin, ethambutol, and pyrazinamide. We performed logistic regression analysis to evaluate the association between time on DSTB therapy and final treatment outcomes; good outcomes included cure, treatment completion and transfer out in good condition, and poor outcomes included treatment failure, death, default, and transfer in poor condition.

Results: While on MDR-TB therapy, 202 patients (90.6%) converted their cultures to negative. Mean time to culture conversion was 1.57 months. In univariate analysis, being on inappropriate DSTB treatment for greater than one month was associated with longer culture conversion times (adjusted HR=0.76 [0.57-1.01] $P = 0.056$). There was no significant difference in likelihood of poor treatment outcomes at 24 months between patients on inappropriate first line treatment for more than one month compared to those on inappropriate treatment for less than 1 month (unadjusted OR=1.39 [0.82-2.36] $P = 0.230$).

Conclusion: Our data suggest that for MDR-TB patients there is a trend toward delayed culture conversion in patients who received more than one month of inappropriate DSTB therapy. Future treatment algorithms will need to consider whether starting patients on empiric therapies with delays until DST is available may worsen short and long term outcomes, and future studies need to examine whether there is a time threshold before these inappropriate empiric therapies have an impact.

EP-124-04 High survival and treatment success with concurrent MDR-TB and HIV treatment in KwaZulu-Natal, South Africa

J Brust,¹ S Shah,^{2,3} S Allana,² T Mthiyane,⁴ K Mlisana,^{4,5} P Moodley,^{4,5} I Master,⁶ N Gandhi² ¹Montefiore Medical Center & Albert Einstein College of Medicine, Bronx, NY, ²Rollins School of Public Health, Emory University, Atlanta, GA, ³U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁴University of KwaZulu-Natal, Durban, ⁵National Health Laboratory Services, Durban, ⁶King Dinuzulu (George V) Hospital, Durban, South Africa. Fax: (+1) 718 561 5165. e-mail: jcb26@columbia.edu

Background: More than 80% of patients with MDR TB in South Africa are co-infected with HIV. Treatment outcomes for patients with MDR TB-HIV co-infection have historically been poor, but most studies either predated the availability of antiretroviral therapy (ART) or were performed retrospectively. We prospectively compared treatment outcomes in MDR TB-HIV co-infected patients on ART with MDR-TB patients without HIV infection.

Methods: In this observational cohort study, culture-confirmed MDR TB with and without HIV co-infection were treated with a standardized South African MDR TB regimen, including kanamycin, moxifloxacin, pyrazinamide, ethambutol, ethionamide and terizidone. Subjects were followed until one year after the completion of their MDR TB treatment. All HIV-infected patients received ART, using the standard regimens available in South Africa. Patients were seen monthly to monitor response to therapy and obtain sputum cultures. CD4 counts and HIV viral loads were performed every 3 months. Treatment outcomes were determined using standard consensus definitions for MDR-TB.

Results: Among the 206 enrolled subjects, 151 were HIV-infected, 131 (64%) were female, and the median age was 33 years (IQR 26-41). Median time to sputum culture conversion was 59 (IQR 51-113) days and was similar among those with and without HIV co-infection. At MDR-TB treatment initiation, median CD4 count was 225 (IQR 132-408) cells/mm³ and 68% had an undetectable viral load. At the time of censoring, subjects had been followed for a median of 725 days (IQR 497-904) and 22 (11%) had died. 110 (53%) had been declared cured, 20 (10%) had defaulted, 2 (1%) had failed therapy, and 53 (26%) were still receiving therapy. Among those who died, 18 were HIV-infected (12% of HIV+ve) and 4 were HIV-negative (7% of HIV-ve; $P = 0.34$). Median time to death was 263 days (IQR 74-616). The median CD4 count at 24-months was 372 cells/mm³.

(IQR 239-536), with a median increase of 78 (IQR -29-177) cells/mm³ from baseline. 81% had an undetectable VL after 1 year of concurrent MDR-TB HIV therapy.

Conclusion: Subjects with MDR-TB HIV co-infection receiving concurrent ART experienced favorable survival and treatment outcomes similar to a comparable cohort of HIV-uninfected MDR-TB patients. Although taking both MDR TB therapy and ART is challenging for patients due to pill burden and adverse events, the recommendation to provide concurrent therapy is supported by prospectively collected data.

EP-125-04 Outcomes for adolescents undergoing multidrug-resistant tuberculosis treatment in Lima, Peru

J Furin,¹ M Milstein,² D Tierney,³ C Mitnick,² P Isaakidis⁴
¹Case Western Reserve University, Cleveland, OH, ²Harvard Medical School, Boston, MA, ³Brigham and Women's Hospital, Boston, MA, USA; ⁴Médecins Sans Frontières, Mumbai, India. e-mail: meredith_milstein@hms.harvard.edu

Background: Multidrug-resistant tuberculosis (MDR-TB) is understudied among adolescents, a unique subpopulation undergoing emotional maturity, physical development, and transitioning into roles with greater responsibility and time constraints. This adolescent period may have social implications, leading to different health outcomes than adults. We aim to identify whether MDR-TB treatment outcomes in adolescence differ from adults and the predictors for these outcomes.

Design/Methods: We conducted a retrospective cohort study to assess whether adolescence was associated with MDR-TB treatment outcome. Predictors included demographics, disease severity indicators and comorbidities. Outcomes were separately assessed for adolescents (10-19) and adults (>20). χ^2 tests, Fisher's exact tests, or *t*-tests were used to identify significant differences between adolescents and adults. Cox proportional hazards models were used to assess the effects of baseline covariates on time-to-death.

Results: We found identified 90 adolescents and 577 adults in the cohort. Successful outcomes were observed in 76% adolescents and 64% adults ($P = 0.0362$). Further, 11% adolescents and 22% adults died ($P = 0.0159$). Significant differences in baseline characteristics between adolescents and adults included previous receipt of 2 or less regimens (59% vs. 25%, respectively; $P < 0.0001$), bilateral, cavitary findings on chest X-ray (44% vs. 57%, respectively; $P = 0.0252$), low hematocrit (57% vs. 86%, respectively; $P < 0.0001$), and average number of resistant agents (4.99 [SD: 1.58], 5.50 [SD: 1.71], respectively; $P = 0.0051$). In assessing whether characteristics differed within adolescents, as stratified by positive and negative outcomes, significant differences included being enrolled in Northern Lima (52% vs. 27%, respectively; $P = 0.0476$) and having extra-pulmonary TB (0% vs. 14%; $P = 0.0131$). Univariate cox proportional hazards analysis in adolescents found that having at least one comorbidity (cardiovascular disease, diabetes, hepatitis, seizures, renal failure, psychiatric

disorder, smoking, alcohol or substance abuse) was a significant predictor of death $P = 0.0178$).

Conclusion: Adolescents showed more successful outcomes, less death, and less presentation of severity indicators and comorbidities than adults. To better understand specific risk factors that impact treatment outcomes for MDR-TB in adolescents, further analysis should be completed. Next steps will include: 1) multivariable cox proportional hazards analysis to identify all predictors of negative outcomes.

04. LTBI: a potpourri

EP-126-04 Prevalence of LTBI infection among household contacts of multidrug-resistant and new TB patients in Ho Chi Minh City, Viet Nam

G Fox,¹ N Nguyen,² T A Nguyen,¹ T L Nguyen,¹ N A Le,¹ B Tran Ngoc,³ R Menzies,⁴ G Marks¹ ¹Woolcock Institute of Medical Research, Sydney, NSW, ²National Lung Hospital, Sydney, NSW, Australia; ³Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam; ⁴McGill University, Montreal, QC, Canada. Fax: (+61) 291 140 010. e-mail: foxsimile@gmail.com

Background: Household contacts of patients with multidrug resistant (MDR)-TB are a high-priority group for screening, according to recent World Health Organization (WHO) guidelines. However, the difference in transmission associated with exposure to MDR-TB, compared to drug susceptible TB, is poorly understood. This study aimed to compare the prevalence of latent tuberculosis infection (LTBI) among household contacts of patients with smear positive MDR-TB and new TB in Viet Nam, and assess demographic characteristics associated with these outcomes.

Design/Methods: 136 household contacts of smear positive MDR-TB patients and 182 household contacts of newly diagnosed TB were screened in nine District TB units in Ho Chi Minh City, Viet Nam. Tuberculin skin testing (TST) was performed on all contacts with a 10mm cut-off was used to define LTBI. Chest X-ray, symptom screening and GeneXpert were used to exclude active disease. Multivariable logistic regression was used to calculate the associations between demographic characteristics and LTBI.

Results: The LTBI prevalence was 39% (30.8-47.2 %) among contacts of MDR-TB patients and 25.8% (19.4-32.2%) among contacts of new patients. Contacts of MDR-TB patients had a higher prevalence of infection in comparison to the contacts of new AFB (+) patients (adjusted OR = 1.8; 95%CI: 1.1 – 3.1). TST positivity was more common among contacts who were those identifying themselves as a minority ethnic group (Chinese or Khmer) (adjusted OR: 2.6; 95%CI: 1.1-6.2). Infection increased with age. No other social or demographic risk factors for infection were identified.

Conclusion: Household contacts of MDR-TB have a high risk of becoming infected, compared to contacts of patients with new TB. Our findings support WHO

recommendations that household contacts of MDR-TB patients should be a high-priority group for routine contact investigation.

EP-127-04 Evaluation of TB contact tracing in Brazil: operational research

N H Orfão,¹ A Wysocki,² M A Ponce,² T Arakawa,¹ A Beraldo,¹ L M Lopes,¹ M E Brunello,¹ A Kritski,³ T C Scatena Villa¹ ¹Ribeirão Preto School of Nursing, Ribeirão Preto, SP, ²Ceres University, São José do Rio Preto, SP, ³Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil. e-mail: lilisew@yahoo.com.br

Background: Tuberculosis (TB) control actions has been decentralized to Primary Health Care (PHC) in Brazil since 2004 and TB contact tracing is considered a cornerstone of the national TB program (NTP). PHC arrangements related to the process of care influences the performance of TB control strategy, requiring researches to evaluate the incorporation of TB contact tracing in PHC settings. Aim: to analyze PHC services performance to PTB contact tracing in a decentralized priority setting for TB control in Brazil.

Methods: Operational research, conducted in São José do Rio Preto (SJRP) – SP - Brazil. The study population included 336 pulmonary TB (PTB) contacts (study population) of 213 PTB patients followed by PHC in all five health districts of SJRP among 2012-2013. Contacts of PTB patients that lived in SJRP but was followed in other city had been excluded from the study. Data about PTB contact tracing were collected from System Notification and Monitoring of Cases of Tuberculosis (TB-WEB), System of TB Chemoprophylaxis and documental analysis of Medical records. PTB contacts were categorized in 2 groups: under and above 10 years old, according to NTP recommendations. Descriptive statistics and Chi square test for categorical variables were carried out as statistical analysis.

Results: 69 (20.5%) PTB contacts had no evaluation but were incorrectly registered as “no indication for isoniazid preventive therapy (IPT)”. Regarding the 211 (78.7%) PTB contacts under 10 years old: 87 (41.2%) met the indication criteria for IPT, 39 (39.1%) did not do IPT and of these, 10 (25.6%) was incorrectly registered as “no indication for IPT”. Of the 56 (82.4%) PTB contacts above 10 years old: 19 (33.9%) met the indication criteria for IPT and of these, 9 (47.4%) did not do IPT. PTB contacts under 10 years old were more evaluated by X-ray (Only X-ray $P = 0.0324$; X-ray+Tuberculin Test $P < 0.001$). There was no information in medical records about: PTB convocation to Health assessment (54.2%), respiratory symptoms, vaccination with BCG and morbidities (100%) and active finding when TB contact did not go to PHC (58.3%).

Conclusion: PHC is performing incomplete TB contacts evaluation, incorrect registers of IPT indications and absence of notes in medical records regarding the identification, search and evaluation of contacts. There is need to systematize an active case finding and surveillance for PTB contacts in PHC.

EP-128-04 Predictive value of the QuantiFERON test in the Danish population

T Hermansen,^{1,2} T Lillebaek,¹ K Langholz,² P Andersen,¹ P Ravn² ¹Statens Serum Institut, Copenhagen, ²Nordsjaelland Hospital, Hillerød, Denmark. e-mail: thomasstighermansen@hotmail.com

Background: Interferon- γ release assays (IGRA) are used for the diagnosis of latent infection with *M. tuberculosis* (LTBI). The QuantiFERON-TB Gold In-Tube Test (QFT) has been used in Denmark since 2005. The aim of this study was to determine the predictive value of the QFT among individuals who had a QFT performed between 2005 and 2011 and subsequently developed (incident TB).

Methods: Results of QFT and information on TB diagnosis were obtained. Incident TB was defined as development of TB more than 3 months after a QFT result. We determined the risk of incident TB depending on the initial QFT result, and calculated the positive and negative predictive values, and assessed individual risk factors such as age.

Results: 15 745 persons had an available QFT result representing 46 258 person-years of follow-up, with a median follow-up time of 2.86 years (IQR 1.70). Of all tests performed, 85.2% (13,422) were negative, 9.6% (1519) positive and 5.1% (804) indeterminate. Nineteen patients with a positive test and 17 patients with a negative test developed incident TB. The incidence rate for QFT-positive individuals was 4.14/1000/year and for QFT-negative individuals 0.44/1000/year. The positive predictive value (PPV) of the test was 1.25% (19/1519) and the negative predictive value (NPV) was 99.87% (13,405/13,422). The test was affected by patient age; among patients <35 years the PPV was 2.22% and NPV 99.95%, and among patients ≥ 35 years the PPV was 0.90% and NPV 99.84%. Only 5.3% (1/19) of the incident TB cases, who had an initial positive QFT, received prophylactic isoniazid treatment.

Conclusion: In a Danish cohort of persons screened with the QFT, we found a positive QFT to be a predictor for progression to TB, with an approximately ten times higher incidence rate compared to QFT-negative individuals. The predictive value of the QFT was influenced by age, with both a higher PPV and NPV among children and adults <35 years.

EP-129-04 Performance of QuantiFERON-TB Gold In-Tube vs. the tuberculin skin test in screening for latent tuberculous infection in health care workers in Georgia

V Mirtskhulava,^{1,2} R Kempker,³ M Kipiani,¹ N Tabagari,² J Whitaker⁴ ¹National Center for Tuberculosis and Lung Diseases, Tbilisi, ²David Tvildiani Medical University, Tbilisi, Georgia; ³Emory University, Atlanta, GA, ⁴Mayo Clinic, Rochester, MN, USA. e-mail: verikomir@gmail.com

Background: Limited data exists on the performance of QuantiFERON-TB Gold In-Tube (QFT-GIT) vs. Tuberculin Skin Test (TST) for serial screening of latent tuberculosis infection (LTBI) among Healthcare workers

(HCWs) in low and middle income TB endemic countries.

Design/Methods: We conducted a retrospective analysis of QFT-GIT and TST results of 163 HCWs. Our participants were HCWs who had TST and QFT-GIT performed at baseline and had repeated testing between March 2009 and September 2010 as part of a prior study.¹ Proportions of concordant results of the two diagnostic tests were compared between HCWs with a bacillus Calmette-Guerin (BCG) scar vs. no BCG scar and between HCWs with self-reported daily occupational TB exposure vs. those who did not see TB patients on a daily basis. The proportions were compared by two-proportion z-test. Logistic regression was used to assess risk factors for discordant results at baseline and repeated testing.

Results: Among 163 HCWs, 79% (129) of HCWs were found to have a BCG Scar by visual inspection. Forty-five percent (73) reported daily occupational TB exposure. Mean time between baseline and follow-up LTBI tests was 69 weeks (standard deviation 25 weeks). Proportion of concordant results of QFT-GIT and TST was higher among those HCWs with no BCG scar compared to the group with a BCG scar both at baseline (79% vs. 67%, $P < 0.18$) and repeated testing (79% vs. 70%, $P < 0.27$). Furthermore, proportion of concordant results of the two diagnostic tests for LTBI was higher among HCWs with daily occupational TB exposure compared to those HCWs who did not see TB patients on a daily basis at baseline (78% vs. 63%, $P < 0.04$) and repeated testing (75% vs. 69%, $P < 0.36$). In multivariate analysis, we found that the HCWs with discordant LTBI test results TST-positive / QFT-GIT negative group, were less likely to report daily occupational TB exposure (adjusted odds ratio (aOR): 0.4, $P < 0.02$) compared to the HCWs with concordant LTBI test results at baseline LTBI screening. The association was not significant at repeated testing (aOR: 0.7, $P < 0.31$).

Conclusions: Concordance between the two tests for LTBI was higher among HCWs with high occupational TB exposure at baseline screening and the difference between the two tests performance vanished at repeated testing. 1. Whitaker J A, Mirtskhulava V, Kipiani M, et al. Prevalence and incidence of latent tuberculosis infection in Georgian healthcare workers. PLOS ONE 2013; 8: e58202.

EP-130-04 Occupational screening for latent tuberculous infection in German health care workers

A Nienhaus,¹ A Schablon² ¹Institute for Statutory Accident Insurance and Prevention in the Health and Welfare Services, Hamburg, ²University Clinics Hamburg Eppendorf, Hamburg, Germany. e-mail: albert.nienhaus@bgw-online.de

Background: Healthcare workers (HCWs) in countries with low incidence of tuberculosis are still considered a high-risk group for latent TB infection (LTBI) and are sometimes routinely screened for LTBI. In this study the German Occupational TB Network data is analysed in

order to estimate the prevalence and incidence of LTBI in German HCWs.

Design/Methods: 4123 HCWs were screened with the QuantiFERON Gold in tube (QFT) at least once, a second QFT was performed on 1117 HCWs either in the course of contact tracing or serial examination following German OSH regulations. TB history and occupational exposure was assessed with a standardized questionnaire. Active TB was excluded by X-ray when the QFT was positive.

Results: 9.2% of the HCWs were QFT positive. No active TB was diagnosed. Positive in at least two consecutive QFT were 5.6%. Instable QFT results were observed in 3.6%. Reversions occurred about 10 times more often than conversions. Risk factors for a stable positive QFT result (positive in at least two QFTs) were age >55 years (OR 3.8), foreign country of birth (OR 2.4), personal history of TB (OR 6.5) and workplace, e.g., internal medicine (OR 1.4), infection ward (OR 1.8) or geriatric care (OR 1.8). Using a borderline zone from 0.2 to <0.7 IU/ml reduced the number of instable QFT results by 41.3%.

Conclusion: In countries with a low incidence of TB and high hygiene standards the LTBI infection risk for HCWs seems to be low. Introducing a borderline zone from 0.2 to <0.7 IU/ml may help to avoid unnecessary X-rays and preventive chemotherapy. No case of active TB was observed during the study period of eight years. Therefore, it seems reasonable to restrict TB screening to HCWs who had known contact with infectious patients or materials.

EP-131-04 Cost-effectiveness of the testing and treatment of latent tuberculous infection: a systematic literature review

C Angeletti,¹ M Sane Schepisi,¹ D Goletti,¹ R Mancini,¹ R Mancini,¹ G Sotgiu,² A Matteelli,³ H Getahun,³ E Girardi¹ ¹National Institute for Infectious Diseases IRCCS L. Spallanzani, Rome, ²University of Sassari, Sassari, Italy; ³World Health Organization, Geneva, Switzerland. e-mail: monica.saneschepisi@inmi.it

Background: We conducted a systematic literature review to summarise current evidence on the cost-benefit and cost-effectiveness of latent TB infection (LTBI) testing and treatment.

Methods: We searched studies on costs and outcomes of any screening strategies and any drug regimen for LTBI compared to no intervention in any setting and population group using the following databases: MEDLINE, EMBASE, CINAHL, The Cochrane Central Register of Controlled Trials, NHS Economic Evaluations Database and Health Economics Evaluations Database. The search was updated on 15 March 2015 with no time limit. For the purpose of the analysis countries were categorized using income and estimated TB incidence as follows: A. upper-middle income countries with TB incidence less than 100/100 000; B. low income and/or high TB incidence countries.

Results: Our literature search yielded 5997 unduplicated records and after considering their references and the

bibliography of relevant reviews on the topic, we finally included 45 original articles published between 1981 and 2014. Nine studies analyzing testing and treatment of LTBI in persons migrating to category A countries, show that this intervention may determine savings for the health care system or have a favorable incremental cost-effectiveness ratio, when screened persons originate from countries with a TB incidence above 120-150/100 000. Similarly savings or a favorable incremental cost-effectiveness ratio are reported in 7 studies (all conducted in category A countries) on contacts of patients with active TB, and in 7 studies on persons living with HIV/AIDS both in category A and category B countries. Limited evidence is available for other population groups.

Conclusion: The available evidence suggest that screening and treatment for latent TB infection may be a cost-effective intervention for persons migrating from high TB incidence countries, contacts of active TB cases and persons living with HIV. However, extrapolation of cost-effectiveness measures from one setting to another is difficult due to marked variability in economic inputs, in epidemiologic and natural history parameters, as well as in assumptions on preventive treatment effectiveness.

EP-133-04 Institutional and structural barriers to TB screening in South Africa: qualitative insights from health care providers and patients from the TEKO trial

C Tudor,¹ D Kerrigan,² E Variava,³ J Golub,^{2,5} K Motlhaoleng,⁴ L Lebina,⁴ N Martinson⁴ ¹International Council of Nurses, Geneva, Switzerland; ²Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA; ³Department of Health Tshepo Hospital, Klerksdorp; ⁴Perinatal HIV Research Unit (PHRU), Soweto, South Africa; ⁵Johns Hopkins University School of Medicine, Baltimore, MD, USA. e-mail: tudor@icn.ch

Background: Tuberculosis (TB) remains the leading cause of mortality among people living with HIV (PLHIV) globally. The TEKO study in South Africa is comparing the impact of latent tuberculosis screening for newly diagnosed HIV patients via QuantiFERON®-TB Gold In-Tube test (QGIT) at time of blood drawn for CD4 count compared to a tuberculin skin test (TST). Prior to trial implementation a baseline qualitative study was conducted to assess patient and provider experiences, attitudes and operational issues related to TB-HIV services in all clinics in the study.

Design/Methods: Fifty-six in-depth interviews were conducted: 28 with PLHIV and 28 with care providers from 14 public clinics in North West Province, South Africa. Key domains explored included TB screening, diagnosis, isoniazid preventive therapy (IPT), and treatment processes. All participants were asked their thoughts about the use of a blood test to screen for latent TB. All interviews were audio recorded and transcribed. Narrative analysis was used to document key elements of the TB screening and management process from each interview. Narratives were synthesized across participants looking for patterns of consensus and diversity.

Results: A common complaint was that long queues in the clinics presented a challenge to access HIV-TB services and that going to the clinic was “an all-day event.” However, the majority of patients rated the quality of care and services highly. There were also concerns expressed about the variability in TB screening and diagnosis procedures. In addition to the lack of staff, there was confusion reported by providers regarding the current state of TB-related guidelines for PLHIV. For example, only a few clinics had started using the TST per national guidelines. Additionally, many patients had never heard of or received IPT. When patients and providers were asked about a blood test to screen for TB nearly all were supportive of the idea and felt it would help overcome logistical barriers to current screening practices. Structural factors such as HIV-TB-related stigma, poverty and food insecurity were raised as barriers to retention in care and adherence to TB-HIV medications.

Conclusion: Findings underscore the need for institutional capacity building in clinics, including training of providers on the implementation of national guidelines on TST and IPT for PLHIV; as well as community awareness programs to push demand for these services.

EP-134-04 Impact of rifapentine price reduction on utilization for TB treatment in the USA

A Deluca,¹ M Macaraig,² K McGinnis,^{2,3} D Wegener,⁴ J Kanouse,⁴ M Frick,⁵ L McKenna⁵ ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²New York City Department of Mental Health and Hygiene, Long Island City, NY, ³U.S. Centers for Disease Control and Prevention, Atlanta, GA, ⁴National TB Controllers Association, Smyrna, GA, ⁵Treatment Action Group, New York, NY, USA. e-mail: andelUCA@jhsph.edu

Background: USA (US) tuberculosis (TB) programs reported that the high cost of rifapentine (RPT) was a deterrent to adoption of a new 12 dose once-weekly regimen of isoniazid and RPT (3HP) for the treatment of TB infection. In 2013, in response to a community-driven advocacy campaign, RPT's manufacturer, Sanofi Aventis, reduced the price per 32-tablet blister pack by 56%, from US\$52 to US\$32 for those eligible for federally discounted pricing. A survey of US TB programs was conducted to assess whether the price reduction had an impact on RPT use.

Design/Methods: In December 2014, a web-based survey was sent to the 62 TB programs receiving federal funding. One knowledgeable respondent per TB program completed the survey. Descriptive analysis was performed on survey responses.

Results: Of the 62 US TB programs, 61 (98%) responded to the survey. A total of 46/61 (77%) respondents were aware of the RPT price drop, and 45/60 (75%) knew their TB programs have access to RPT at the reduced price. Among TB programs that were both aware of the price reduction and able to access it, 24/36 (67%) reported increased use of RPT after the price decrease. Among all TB programs, the majority (62%) were not using RPT “as often as they would like”. Over 50% of TB

programs reported barriers to use, including cost to the program (72%), directly observed therapy requirement for 3HP (72%), quantity of pills for 3HP (56%), and concerns about safety (52%). Over 60% of TB programs want more information about use of RPT in HIV-infected individuals, those with elevated liver function tests, and pregnant women.

Conclusion: Use of RPT increased following the 2013 price reduction. Pricing advocacy can remove an important barrier to programmatic uptake of TB innovations. There is a need for further education to increase awareness of the reduced cost of RPT and to address concerns about use of RPT in special populations. Dissemination of research findings, communication about discounted drug availability, and considerations of patient acceptability (e.g., daily pill quantity) must occur in parallel with efforts to achieve affordable drug pricing. As improved drug regimens become available domestically and internationally, these lessons could help communities planning for the launch of new treatment options. Advocates, TB-affected communities, and public health professionals can work proactively with pharmaceutical companies to achieve affordable pricing that facilitates drug access.

EP-135-04 Integrating existing programs to address barriers to treatment of latent tuberculous infection

J Burzynski,¹ K McGinnis,^{1,2} C Chuck,¹ M Macaraig¹

¹Department of Health and Mental Hygiene, New York, NY,

²U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: mmacaraig@health.nyc.gov

Background: Adherence to treatment for tuberculosis (TB) infection with 9 months of isoniazid is low. In New York City (NYC) a 3-month, once-weekly regimen of isoniazid and rifapentine (3HP) under directly observed therapy (DOT) increased treatment completion, but in-person clinic DOT was a barrier. A second initiative using video conferencing for remote DOT observations (VDOT) was effective with active TB patients. This describes how NYC addressed clinic DOT barriers for patients on 3HP by offering observations by VDOT.

Intervention: NYC integrated 3HP with VDOT (V3HP) by updating staff responsibilities and policies, including adapting current 3HP and VDOT protocols, patient follow-up procedures, medication issuance, and documentation procedures for electronic medical records. Patients eligible for V3HP must meet current 3HP and VDOT criteria and be willing to use a personal video-enabled device during business hours. To prevent interruption of program services, resources were obtained in advance, such as a license for the video software, hardware equipment, language services, and a reference guide to help patients use the software. Buy-in and training was accomplished by presentations to supervisors and physicians, in-servicing nurses, and training three centralized staff members to conduct V3HP observations and record outcomes. Excel databases were created to monitor staff workload and

technology issues. DOT observations and adverse reactions were documented in an existing electronic medical record system. The pilot will enroll patients from February 2015 to August 2015. Treatment completion will be compared with historical data.

Results: In the pilot's first nine weeks 18 patients accepted V3HP. No observations were done on five patients: three preferred clinic DOT, one had technical issues and returned to clinic DOT, and one stopped treatment due to side effects from the first clinic-based dose. Among the 12 remaining patients, 41 VDOT observations have been conducted (range: 1–8 doses); median time was 5.5 minutes (range: 3–32). All patients have been adherent to VDOT. No major side effects have been reported. Language services are provided for one patient. Technological issues stemming from connection problems have been the most prevalent issue to date.

Conclusions: Combining existing programs can provide treatment delivery options that overcome barriers. Further analysis will determine if these efforts improve treatment completion for TB infection.

05. Rats, videos and secretions: the landscape of TB detection

EP-136-04 Differences in secretion of MPT64 antigen between *Mycobacterium africanum* West African type 2 and *Mycobacterium tuberculosis sensu stricto*

A Ofori-Anyinam,^{1,2} F Kanuteh,² I Adetifa,³ S Agbla,² B De Jong,¹ M Antonio,² F Gehre^{1,2} ¹Institute of Tropical Medicine, Antwerp, Belgium; ²Medical Research Council Unit, The Gambia, Fajara, Gambia; ³KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya. e-mail: nofori@mrc.gm

Background: High *Mycobacterium tuberculosis* strain diversity in West Africa, with all lineages within the *M. tuberculosis complex* (MTBC) present, makes this region ideal for assessing the performance of diagnostics and vaccines. The 24kD secreted protein, MPT64, associated with virulence and produced solely by members of the *M. tuberculosis complex* is a target of widely used rapid speciation tests, yet the impact of strain diversity on the performance of these tests in West Africa has not been clearly shown. Previous reports indicated the inability of these tests to detect strains which had lost mpt64 or acquired mutations. In the Gambia, up to half of Tuberculosis (TB) infections are caused by *Mycobacterium africanum* West African type 2 (MAF2), a strain genetically distinct from other *M. tuberculosis* strains. Preliminary sputum RNA expression data showed a down regulation of mpt64 in MAF2 compared to *M. tuberculosis*. We hypothesised that differences might exist in the rate of secretion of the MPT64 antigen between *M. tuberculosis* and MAF2 which might influence detection by MPT64 rapid tests.

Design/Methods: Sputum from patients with suspected TB within the Greater Banjul area, where 80% of all individuals with TB in the Gambia are found, were

decontaminated, confirmed by smear microscopy for Acid-Fast Bacilli (AFB) and cultured in the Bactec Mycobacteria Growth Indicator Tube (MGIT) 960 machine. 173 AFB positive and blood agar negative cultures were tested with the Becton Dickinson (BD TBcID) and Standard Diagnostics (SD Bioline) rapid speciation kits on the day of MGIT positivity. Cultures which tested negative were re-incubated at 37°C and subjected to follow up rapid tests at 3, 10, 15 and 90 days. All cultures were spoligotyped to determine strain lineages. Survival analysis and regression modelling of the data was performed using STATA version 12.1.

Results: We observed time and lineage specific differences in the detection of *M. tuberculosis* and MAF2 by the rapid tests. MTB strains converted to positivity approximately three times faster than MAF2 within the 10 day window proposed for conducting the test described in the BD TBcID manual (Hazard Ratio=2.85, 95%CI=1.88-4.32, $P = <0.001$). Although the SD Bioline kit did not specify a time frame for testing, similar observations were made.

Conclusion: Our findings underscore the need to incorporate molecular tests in routine identification and confirmation of all members of the MTBC. Ultimately, future development of diagnostics and vaccines should be guided by implications of strain diversity on product success.

EP-137-04 Rapid diagnosis and epidemiology of *Mycobacterium tuberculosis* complex strains in The Gambia by metagenomic DNA sequencing directly from sputum

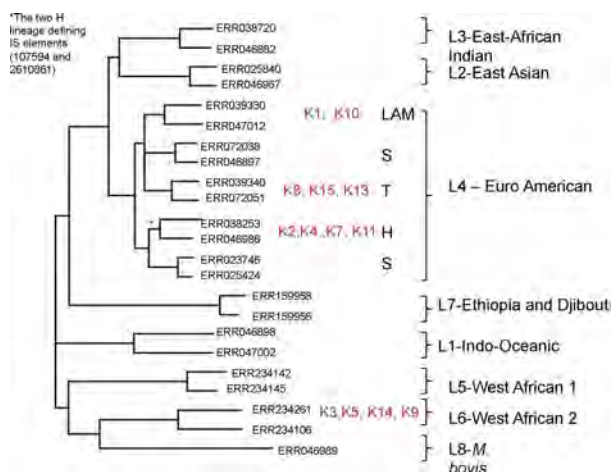
E Doughty,^{1,2} M Sergeant,² I Adetifa,³ M Antonio,¹ M Pallen² ¹Medical Research Council Unit, The Gambia, Fajara, Gambia; ²University of Warwick, Coventry, ³London School of Hygiene & Tropical Medicine, London, UK. e-mail: emma.doughty@warwick.ac.uk

Background: Absence of timely and accessible diagnosis is widely considered a barrier to patient treatment and control of the tuberculosis (TB) epidemic. Currently used methods are slow, infeasible in many locations and provide limited information including drug sensitivity. Our initial data show that metagenomics is a promising method for diagnosis to circumvent these issues.

Design/Methods: For preliminary studies, DNA was extracted from 16 AFB smear positive sputum after attempts to deplete human DNA and sequenced using the Illumina MiSeq. The MTBC- and human-derived DNA contents were determined by mapping against the respective reference genomes. TB Phylogenetic lineages were assigned from SNPs and the positions of IS6110 elements identified in tuberculous reads, then verified by spoligotyping of cultured isolates. The microbiome was analysed using microbial identification software. Optimisation of laboratory methods is on going before evaluation of this method for direct diagnosis, epidemiology and in vivo research of organisms in sputum.

Results: Using this method, the medians for human DNA content in each sample and coverage of the *M.*

tuberculosis genome were 73% (range: 4.03-99.3%) and 0.0185X coverage (range: 0.002-0.693X), respectively. This provided enough coverage for phylogenetic placement of 13 of the 16 samples at lineage level shown in the maximum likelihood tree (figure), as confirmed by spoligotyping. Microbiome analysis showed no additional obligate pathogens and analysis of microbiome ecology was deemed inappropriate for the small sample size. Future studies will evaluate the clinical and epidemiological impact of metagenomic diagnosis by comparison to traditionally used methods and analyse the sputum-association microbiome with better resolution than currently used 16S rRNA genotyping methods. **Conclusion:** The preliminary data show promise for diagnosis of tuberculosis and other respiratory pathogens by direct sputum metagenomics. The purposes of numerous culture-dependent methods are integrated into a single rapid approach for any respiratory pathogen; including detection of mixed strains and co-infections, high-resolution epidemiological characterisation and identification of drug-resistance mutations, with increased pathogen genomic coverage. Further technology developments may make this feasible at point-of-care, from other clinical sample types and scalable to local demand.



EP-138-04 Diagnosis of pulmonary and extra-pulmonary tuberculosis in Paraguay using the electronic nose (Paranose study)

C Magis-Escurra,¹ R Coronel Teixeira,² M Rodriguez,² J Gerritsen,³ G Chaparro Abente,² D Perez,² J Yntema⁴ ¹Radboud University Medical Centre, Nijmegen, Netherlands; ²Instituto Nacional de Enfermedades Respiratorias y Ambientales, Asuncion, Paraguay; ³ENose Company, Zutphen, ⁴Radboud University Medical Centre, Nijmegen, Netherlands. e-mail: cecile.magis-escurra@radboudumc.nl

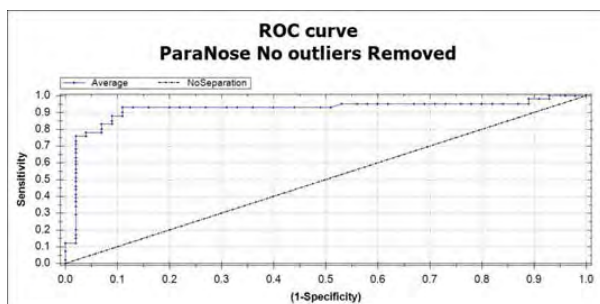
Background: Diagnostic techniques for TB still remain largely unattainable in developing countries due to the requirement of extensive laboratory facilities and the need for an increasing number of trained staff. A pilot study in Bangladesh, with a prototype of an electronic nose device, found a sensitivity of 95.9% and specificity

of 98.5% to detect pulmonary TB. The company developed is a simplified, easy-to-use, point-of-care device that can be produced at low cost. We tested the diagnostic accuracy of this electronic nose device in a TB reference centre in Asunción.

Design/Methods: Observational study in adult patients with pulmonary TB, pleural TB, and matched healthy controls, after signing informed consent, from May until December 2014. TB diagnosis was established by gold standard (culture of *Mycobacterium tuberculosis* complex) or other supporting evidence. Clinical data included age, gender, symptoms, body weight, comorbidity, onset of disease, co-medication and factors influencing breath. Chest X-ray, blood chemistry and HIV testing were done in TB patients, and sputum samples were taken for microscopy and culture for *M. tuberculosis* if expectorating. Measurements of the air composition was done breathing normally during 5 minutes.

Results: 86 participants were evaluated with the device. Thirty eight patients had pulmonary TB, 3 pleural TB, and 45 were healthy controls. The results of breath samples showed 41 positive and 45 negative signals, a result above or below the threshold value calculated by the model. We subsequently compared the outcomes with our database and concluded that 40 were proven TB negatives and 38 participants had proven TB. That resulted in 5 possible false positives and 3 possible false negatives. Sensitivity in this first analysis is 93% and specificity 89% which is shown in the ROC curve. Factors influencing the diagnostic accuracy are not yet completely evaluated.

Conclusion: It is a simple, non invasive test, and showed a high accuracy to detect TB in Paraguay. The demonstrated sensitivity is much higher than any other currently available test to diagnose active TB. These results implicate that the device may be of great value in variable future settings. Of course, more research needs to be done in patients with paucibacillar TB, in different regions in the world, and to study the influence of consumption of food or either toxic substances shortly before the test is performed.



EP-139-04 GxAlert monitors and reduces high testing error rates in Nigeria's GeneXpert® machine

K Jimoh Agbaiyero,^{1,2} L Ekbladh,^{1,2} M Benezet,² J Takle,³ C Macek³ ¹Abt Associates, Abuja, Nigeria; ²Abt Associates, Bethesda, MD, ³SystemOne, Boston, MA, USA. e-mail: kehindeagbaiyero@yahoo.com

Background: Nigeria is a WHO high burden country for drug-resistant tuberculosis (DR-TB). However, national diagnostic and surveillance capacities are compromised due to high error rates on GeneXpert MTB/RIF machines testing for DR-TB. The Nigerian Tuberculosis and Leprosy Control Program (NTBLCP) pursued development of a cost-effective technology, GxAlert, to improve DR-TB reporting speed and accuracy and to monitor individual GeneXpert machine error rates to strengthen both healthcare system responses to DR-TB and management of geneXpert investments.

Design/Methods: Abt Associates and SystemOne developed GxAlert for the NTBLCP. GxAlert is an innovative, cost-effective solution that networks geneXpert machines, sending average error rates by individually identified machine in real time to an online database. This cuts reporting time from months to seconds and enables more timely interventions such as recalibration of machines and staff supervision. GxAlert tracks service warranty thresholds and module replacement for each device. GxAlert is configured on geneXpert systems by installing a modem from a local telecom to access the internet and send encrypted data to the online GxAlert database. Piloted in 8 laboratories, GxAlert has since expanded to 46 GeneXpert sites in Nigeria.

Results: The GeneXpert testing error rate in 35 facilities decreased to 5% and below in March 2015 from 9% and above in April, 2014. Data on machines were producing higher than normal error rates were uploaded automatically from GeneXpert systems to a secure online dashboard display to improve national level program management, while SMS alerts were sent to Facility Managers, Local Government supervisors and State program managers for immediate action. Faster, better quality data on MDR-TB portion of total TB indicators are now reported with very minimal error rates.

Conclusion: The use of GxAlert to network GeneXpert test results and operational status is a cost-effective model for national sustainability of rapid molecular diagnostic systems. GxAlert enables quick remote technical support, troubleshooting, and maintenance of the geneXpert machines as well as ongoing disease surveillance by collecting and displaying compiled test results and incidence rates by facility area. Based on Nigeria, a pilot of the GxAlert approach in other high-burden DR-TB countries is recommended.

EP-140-04 Loss-of-function mutations in *pepQ* confer cross-resistance to bedaquiline and clofazimine in *Mycobacterium tuberculosis*

D Almeida,¹ T Ioerger,² S-Y Li,¹ S Tyagi,¹ K Andries,³ K Mdluli,⁴ J Grosset,¹ J Sacchettini,⁵ E Nuernberger^{1,6}

¹Johns Hopkins University Center for TB Research, Baltimore, MD, ²Texas A&M University, College Station, TX, USA;

³Tibotec BVBA, Beersse, Belgium; ⁴Global Alliance for TB Drug Development, New York, NY, ⁵Texas A&M University, College Station, TX, ⁶Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: deepak.almeida@gmail.com

Background: Bedaquiline (BDQ), a new mycobacterial ATP synthase inhibitor active against *M. tuberculosis* has recently been approved by the FDA for treatment of multidrug-resistant tuberculosis. A new non-target-based mechanism of cross-resistance to BDQ and clofazimine (CFZ, C) mediated by mutation of Rv0678 was recently described and shown to be responsible for failure to convert sputum cultures. For new TB drugs, it is essential to define and catalog the mutations conferring resistance in order to carry out proper follow-up of patients who fail and relapse after receiving the drug, to design appropriate diagnostic tests (including rapid molecular tests), and to conduct population level surveillance for changes in susceptibility. Here we present our findings on mice efficacy studies where mutants with reduced susceptibility to BDQ were selected and found to be also cross-resistant to CFZ.

Methods: Efficacy studies in mice evaluating BDQ with or without CFZ selected mutants that grew on BDQ- and CFZ-containing plates. Minimum inhibitory concentrations (MICs) were determined using doubling concentrations in 7H11 agar. Mutation analysis was carried out by whole genome sequencing and confirmed by PCR. To confirm cross-resistance in vivo, BALB/c mice were infected with either the H37Rv parent strain or one resistant mutant (J5) and then randomized to receive no treatment, isoniazid (10 mg/kg) alone, BDQ (12.5, 25, or 50 mg/kg) alone, CFZ (20 mg/kg) alone, or BDQ 25 mg/kg plus CFZ for 4 weeks before determining lung CFU counts. Complementation of the J5 mutant with the wild type gene was performed and the complemented strain was tested for BDQ and CFZ susceptibility in vitro and in vivo alongside the parent and J5 strains.

Results: A total of 5 mice, 2 from BDQ alone and 3 from BDQ-CFZ treated group harboured mutants with higher MICs. Their MIC for BDQ and CFZ were 0.12-0.25 and 0.5-1 µg/ml, in contrast to that of H37Rv wild type which were 0.03 and 0.25 µg/ml, respectively. Whole genome sequencing studies revealed that 4 out of 5 respective isolates had mutations in the *pepQ* (Rv2535c) gene. In-vivo efficacy studies in mice with one of the resistant mutant (J5) showed reduced killing by BDQ and CFZ as compared with wild type H37Rv. Complementation with wild type *pepQ* restored the susceptibility to BDQ and CFZ in vitro and in vivo.

Conclusion: Mutations in *pepQ* gene reduce susceptibility to BDQ and CFZ.

EP-141-04 Characterization of *Mycobacterium tuberculosis* complex isolates with discordant rifampicin susceptibility test results

C N Beylis,^{1,2} Y Ghebrekristos,^{1,2} J Wojno,^{1,2} M Nicol,^{1,2} J Simpson,³ P Da Silva⁴ ¹National Health Laboratory Service, Cape Town, ²University of Cape Town, Cape Town, ³National Health Laboratory Services, Cape Town, ⁴University of Witwatersrand, Johannesburg, South Africa. e-mail: yonas.ghebrekristos@nhls.ac.za

Background: The Xpert MTB/RIF is the initial screening test for all TB suspects in the South African National TB Control programme, with rifampicin (RIF) resistance confirmed by subsequent lineprobe assay (LPA) (GenoType MTBDRplus) and/or phenotypic (culture based) drug susceptibility testing. In the majority of cases, there is concordance between the 2 genotypic tests, as well as between the overall genotypic and phenotypic results. Disputed *rpoB* mutations have been described where genotypic tests detect an *rpoB* alteration but phenotypic tests miss the RIF resistance (low level RIF resistance). We aim to further characterize the discordant rifampicin results by *rpoB* sequencing and rifampicin MIC testing.

Design/Methods: Consecutive isolates with discordant Xpert: LPA results as well as isolates with possible disputed *rpoB* alterations detected by the LPA were selected. Sanger sequencing of the *rpoB* gene from codons 462–591 was performed. MIC determination was performed using the Mycobacterial Growth Indicator Tube (MGIT) 960 system and Epicenter Software with RIF concentrations 0.0625, 0.125, 0.25, 0.5, 1, 5 µg/ml. Analysis of results was performed on MS Excel.

Results: Ninety one isolates had Xpert RIF resistant, LPA RIF susceptible results, of which 80 had *rpoB* sequencing performed. Xpert was false resistant in 55 (68.7%) and LPA was false susceptible in 25 (31.3%). A total of 205 isolates with possible disputed *rpoB* alterations was detected by the LPA, of which sequencing results were available for 140. Four mutations made up 70.6% of the total detected, of which L511P, D516Y, H526N and L533P were detected in 44 (31.4%), 22 (15.7%), 17 (12.1%) and 16 (11.4%) respectively. All of these isolates had a RIF MIC lower than 1 µg/ml

Conclusion: The majority of the discordant Xpert and LPA results was false Xpert resistance, likely due to technical errors and / or delays during processing of specimens. False LPA susceptible results also occurred, likely due to errors in processing and / or interpretation. The most common disputed *rpoB* alterations detected in Cape Town echo those detected worldwide. The LPA is useful to screen for disputed *rpoB* alterations. *rpoB* sequencing and MIC testing are useful tools to troubleshoot discordant results, as well as to inform the TB clinician about which disputed *rpoB* alterations confer low level rifampicin resistance.

EP-142-04 Rat detection technology improves TB case finding in Tanzanian prisons

G Mgone,^{1,2} C Cox,² T Edwards,² C Mulder,² E Valverde,³ G Mwesiga,² J Maeda,² J Malewa⁴ ¹Sokoine University of Agriculture, Pest Management Centre, Morogoro, ²Anti-Persoonsmijnen Ontmijnende Product Ontwikkeling - APOPO, Sokoine University of Agriculture, Morogoro, Tanzania; ³Anti-Persoonsmijnen Ontmijnende Product Ontwikkeling - APOPO, Veterinary School, University Eduardo Mondlane, Maputo, Mozambique; ⁴Ministry of Home Affairs, Tanzania Prisons Service, Dar Es Salaam, Tanzania. Fax: (+255) 232 601 485. e-mail: gfmgone@hotmail.com

Background: The prevalence of tuberculosis (TB) in prisons in sub-Saharan Africa is higher than in the general population and prisons are considered an important source of TB transmission. TB control in prisons through proper screening and diagnosis is challenging in most low-income countries with a high burden of TB. The use of APOPO TB detection rats has recently demonstrated an increase in case detection of over 40% in DOTS centres in Tanzania and Mozambique. We report findings of an intervention implementing TB detection rats for improving TB case finding in selected prisons in Tanzania.

Design/Methods: Sputum samples ($n = 8979$) were collected from 4561 individuals of a prison population consisting of inmates, prison staff and their families seeking TB diagnosis at Ukonga prison dispensary (January 2013 to April 2015) and Keko prison dispensary (February 2015 – April 2015) in Dar es Salaam, Tanzania. Samples were routinely examined by conventional Ziehl Neelsen (ZN) direct smear microscopy at the two dispensaries and were subsequently securely transported to APOPO TB detection laboratory at Sokoine University of Agriculture, in Morogoro, Tanzania. Samples were heat inactivated before being tested by the detection rats. Samples indicated as TB positive by detection rats were concentrated and confirmed by light emitting diode fluorescence microscopy (LED-FM) or ZN microscopy.

Results: Detection rats tested 4,561 individuals from the prison population. A total of 505 individuals (11.1%) were diagnosed as smear-positive TB by the prison dispensaries, whereas rats detected an additional 170 TB patients. Thus, detection rats increased the case detection in the prison population by 34%, and increased the prevalence of smear-positive TB to 14.8% ($n = 675$ patients).

Conclusion: Using detection rats in combination with smear-microscopy has been dramatically improving TB case finding in prisons in Tanzania. This finding is consistent with those found in general populations tested by rats in Tanzania and Mozambique. The high sample throughput due to high speed of rats which screens up to 140 sputum in 20 minutes, reasonable accuracy, in combination with their low operational costs make the detection rat technology very suitable for mass screening of high-risk populations in different geographic regions with high TB burden. Plans are underway to deploy

detection rats in active TB case finding in selected prisons in Tanzania and Mozambique.

EP-143-04 Do instructional videos on sputum submission result in increased tuberculosis case detection?

G Mhalu,¹ J Hella,¹ F Mhimbira,¹ B Doulla,² B Mutayoba,² T Seimon,³ M Weiss,⁴ L Fenner⁴ ¹Ifakara Health Institute, Pwani, ²Ministry of Health, Dar Es Salaam, Tanzania; ³Interactive Research and Development, Karachi, Pakistan; ⁴Swiss Tropical and Public Health Institute, Basel, Switzerland. e-mail: gmhalu@ihi.or.tz

Background: Sputum smear microscopy remains the cornerstone of diagnostic algorithms in national tuberculosis (TB) control programs in low-income settings. Instructions on how to produce a good sputum sample are often included in manuals, but to formulate this comprehensibly proves exceedingly difficult. Objective: We examined the effect of an instructional video about the production of diagnostic sputum on case detection of TB.

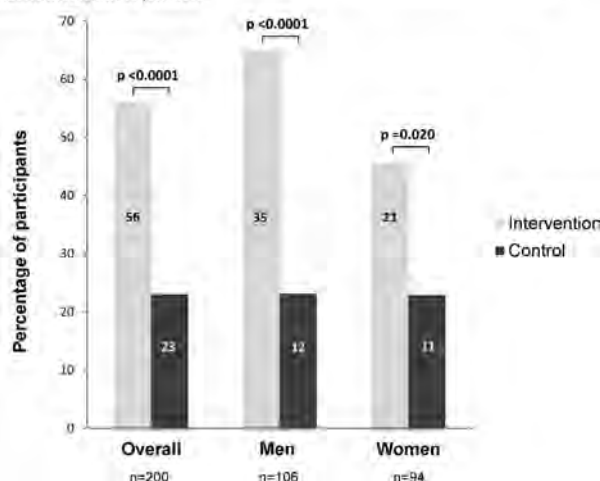
Methods: We prepared a culturally adapted instructional video for sputum submission. We analyzed 200 presumptive TB cases coughing for more than two weeks who attended the outpatient department of the governmental hospital in Mwananyamala (Dar es Salaam, Tanzania). They were randomly assigned to either receive instructions on sputum submission using the video before submission (intervention group, $n=100$) or using routine verbal instructions (control group, $n = 100$). Sputum samples were examined for volume, quality, and presence of acid-fast bacilli by experienced laboratory technicians blinded to study groups.

Results: Median age was 39.1 years (interquartile range 37.0-50.0); 94 (47%) were females, 106 (53%) were males, and 49 (24.5%) were HIV-infected. We found that the instructional video on intervention was associated with detection of a higher proportion of microscopically confirmed cases (56%, 95% confidence interval [95%CI] 45.7-65.9%, sputum smear positive patients in the intervention group vs. 23%, 95%CI 15.2-32.5%, in the control group, $P < 0.0001$); an increase in volume of specimen defined as a volume ≥ 3 ml (78%, 95%CI 68.6-85.7%, vs. 45%, 95%CI 35.0-55.3%, $P < 0.0001$); and specimens less likely to be salivary (14%, 95%CI 7.9-22.4%, vs. 39%, 95%CI 29.4-49.3%, $P = 0.0001$, Figure). Older age, but not the HIV status or sex, modified the effectiveness of the intervention by improving it positively. When asked how well the video instructions were understood ($n = 100$), the majority of patients in the intervention group reported to have understood the video instructions well (97%). Most of the patients thought the video would be useful (92%).

Conclusion: Sputum submission instructional videos increased the yield of TB cases through better quality of sputum samples. If confirmed in larger studies, instructional videos may have a substantial effect on the case yield using sputum microscopy and also molecular tests. This low-cost strategy should be

considered as part of the efforts to control TB in resource-limited settings.

Figure. Sputum smear-positive microscopy results in the intervention (exposure to the sputum submission instruction video) and control group (standard of care), overall and stratified by sex. Numbers on the bars indicate absolute number of patients.



ORAL ABSTRACT SESSIONS

01. Symptoms, sputum, sequences: TB diagnosis and resistance

OA-300-04 Clinical and sputum characteristics as predictors of *Mycobacterium tuberculosis* positive sputum in community-wide active case finding for tuberculosis

J Ho,^{1,2,3} P Nguyen,³ T A Nguyen,³ K H Tran,⁴ S V Nguyen,⁴ N V Nhung,⁵ G Fox,^{2,3} G Marks^{1,2,3}

¹University of New South Wales, Sydney, NSW, ²Woolcock Institute of Medical Research, Sydney, NSW, Australia;

³Woolcock Institute of Medical Research, Hanoi, ⁴Ca Mau Centre for Social Disease Prevention, Ca Mau, ⁵National Tuberculosis Program, Hanoi, Viet Nam. e-mail: jho@gmp.usyd.edu.au

Background: We are currently conducting a randomized controlled trial of community-wide active case finding in which we conduct a house-to-house survey and collect a single, spontaneously expectorated sputum specimen from all persons who can produce this. The specimen is tested using Xpert MTB/RIF. Confirmation is by chest X-ray and TB culture. This approach has the advantage of ensuring a high participation rate in difficult-to-access communities but scalability may be limited by the cost of Xpert testing. In this study we seek to establish whether the absence of reported symptoms or the macroscopic appearance of the sputum could be used to exclude TB and hence allow some sputum specimens to be discarded without testing.

Methods: This study was performed in Ca Mau Province, Vietnam. All participants were screened for the presence of TB symptoms. Those able to produce sputum ≥ 1 ml were tested using Xpert, regardless of reported symp-

toms. Sputum quality was assessed using a color chart, representing salivary, mucoid, muco-purulent, purulent and blood stained sputum. Sputum volume was estimated visually. Likelihood ratios (LR) were calculated as the prevalence of a given result in Xpert positive participants divided by prevalence of that same result in Xpert negative participants.

Results: Among 33 337 sputum specimens submitted for testing, 21 624 (65%) were ≥ 1 ml and were tested by Xpert MTB/RIF. 93% of those tested were ≤ 2 ml. 159 participants had positive Xpert MTB test results (0.75% of those with valid Xpert tests). The prevalence of current cough, daily cough ≥ 2 weeks, current sputum production, daily sputum ≥ 2 weeks and hemoptysis were 33%, 15%, 28%, 13% and 1%, respectively. Nearly all sputum specimens were mucoid (93%) or muco-purulent (6%) in appearance. The LR for mucoid sputum was 0.90 and for muco-purulent sputum it was 2.37. Only 50 (0.24%) sputum specimens were classified as salivary and one (2%) of these was Xpert MTB positive. The highest LR for any symptom being present was 3.67 (hemoptysis) and the lowest LR for any symptom being absent was 0.70 (current sputum and current cough). The false negative rate for each of these symptoms was $>0.4\%$.

Conclusion: In the setting of community wide active case finding for TB, neither the absence of symptoms nor macroscopic sputum quality has strong negative predictive value for the Xpert MTB result. Hence these attributes will not be useful in excluding some specimens from testing. Support: NHMRC Australia.

OA-301-04 A multicenter study on the new version of the GenoType MTBDRsl assay for detection of resistance to fluoroquinolones and second-line injectable drugs

E Tagliani,¹ P Miotto,¹ A Cabibbe,¹ M Mansjo,² S Hoffner,² D Hillemann,³ A Zalutskaya,^{8,9} D M Cirillo,^{1,2} A Skrahina⁴ ¹Emerging Bacterial Pathogens Unit, San Raffaele Scientific Institute, Milan, Italy; ²Unit for Highly Pathogenic Bacteria, Public Health Agency of Sweden, Solna, Sweden; ³Diagnostic Mycobacteriology, Research Center Borstel, Borstel, Germany; ⁴Republican Research and Practical Centre for Pulmonology and TB, Minsk, Belarus. e-mail: tagliani.elisa@hsr.it

Availability of rapid molecular tests for the detection of extensively drug-resistance (XDR) TB is critical in areas with high rates of MDR and XDR-TB and in settings with limited conventional drug susceptibility test (DST) capacity. We conducted a multicenter study to evaluate the performance of the new GenoType MTBDRsl V2.0 (Hain Lifescience) assay for detection of mutations leading to fluoroquinolones (FQs) and second-line injectable drugs (SLIDs) resistance. The assay targets mutations in *gyrA*, *gyrB* genes for FQ-R, and in *rrs* and *eis* genes for SLID-R. Performance was evaluated on 228 *M. tuberculosis* complex isolates (73 FQ-R, 147 SLID-R) and 231 smear positive specimens (57 FQ-R, 63 SLID-R) comparing results to phenotypic DST and sequencing. For indirect testing, the concordance of MTBDRsl V2.0 with

phenotypic DST for FQ-R was 94.7% (95%CI 91.0-97.0%), the test sensitivity and specificity were 83.6% (95%CI 73.4- 90.3%) and 100% (95%CI 97.6-100%) respectively. For SLIDs, the concordance of the assay with phenotypic DST was 87.7%, the sensitivity and specificity were 86.4% (95%CI 79.9-91.0%) and 90.1% (95%CI 81.7-94.9%) respectively. The test correctly identified 86.4% of SLID-R isolates, including 27/127 (21.3%) strains carrying mutations in *eis* promoter only. The concordance between MTBDRsl V2.0 and gene sequencing was >97% for all the genomic regions analyzed. For direct testing, the overall diagnostic accuracy for FQ-R was 97.0% (95%CI 93.9-98.5%) and the sensitivity and specificity were 93.0% (95%CI 83.3-97.2%) and 98.3% (95%CI 95.1-99.4%) respectively. The test correctly identified 53 (92.9%) FQ-R specimens. The diagnostic accuracy for SLID-R detection in specimens was 90.9% (95%CI 86.5-94.0%) with sensitivity and specificity of 88.9% (95%CI 78.8-94.5%) and 91.7% (95%CI 86.5-95.0%) respectively. The test correctly identified 56 (88.9%) SLID-R cases. Compared to V1.0, the sensitivity for FQ-R remained unvaried, whereas MTBDRsl V2.0 showed an improvement for the detection of XDR-TB with specificity and sensitivity of 81.8% and 80.4% for direct and indirect testing respectively. The inclusion of probes to detect mutations in *eis* lead to higher sensitivity for detection of KAN-R for both direct and indirect testing (96% and 95.4% respectively) as compared to V1.0 (66.9%). MTBDRsl V2.0 thus represents a reliable test for the rapid detection of resistance to second-line drugs and a useful screening tool to guide appropriate MDR-TB treatment.

OA-302-04 A six-marker serum biosignature shows promise in the diagnosis of TB disease in African primary health care clinic attendees presumed to have TB

N Chegou,¹ J Sutherland,² A Crampin,³ M Van Der Vyver,⁴ R Howe,⁵ H Mayanja-Kizza,⁶ G Walzl¹
¹Biomedical Sciences, DST/NRF Centre of Excellence for Biomedical Tuberculosis Research & SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Tygerberg Campus, Cape Town, South Africa; ²Medical Research Council Unit, Fajara, Gambia; ³Karonga Prevention Study, Chilumba, Malawi; ⁴Faculty of Health Sciences, University of Namibia, Windhoek, Namibia; ⁵Armauer Hansen Research Institute, Addis Ababa, Ethiopia; ⁶Makerere University, Kampala, Uganda. Fax: (+27) 219 389 863. e-mail: novel@sun.ac.za

Background: There is an urgent need for simple, rapid, inexpensive and yet accurate tools for the diagnosis of TB disease at points-of-care in resource-limited settings. In the present study, we investigated the accuracy of host inflammatory biomarkers detected in serum samples obtained from individuals suspected of having pulmonary TB disease at primary health care clinics situated in six African countries (Ethiopia, Uganda, The Gambia, Malawi, Namibia and South Africa), for the diagnosis of TB disease.

Design/Methods: We collected serum samples from individuals presenting with symptoms requiring investigation for pulmonary TB at the respective clinics, prior to microbiological diagnosis of TB disease. We then evaluated the levels of >40 host inflammatory biomarkers in the stored serum samples using the Luminex platform. On the basis of laboratory, clinical and radiological findings, participants were classified into the following groups using a pre-established diagnostic algorithm: definite TB, probable TB, possible TB, questionable disease status or no-TB.

Results: In a pilot study conducted on 148 individuals recruited from the Ethiopian and South African study sites, a 5-marker serum biosignature diagnosed TB disease with a sensitivity of 86% and specificity of 90%. We then evaluated the accuracy of this biosignature in a validation cohort including 717 individuals who were recruited from field sites situated in Uganda, The Gambia, Malawi, Namibia and South Africa. Of the 702 individuals who were finally analyzed in the validation study, 175 were definite TB cases, 11 were probable and 29 were possible TB cases whereas 487 of the study participants did not have TB. In six individuals the diagnosis of TB remained uncertain. A 6-marker biosignature comprising of CRP, prealbumin, IFN- γ , Complement factor H, apolipoprotein-A1 and IP-10 ascertained TB disease with a sensitivity of 89% and specificity of 76.0%, with positive and negative predictive values of 61.1% and 94.0% respectively, in the test sample set, regardless of HIV infection status or study site.

Conclusion: We have identified a host serum biosignature with promise in the diagnosis of TB disease regardless of HIV infection status or ethnicity in Africa. These results hold promise for the development of a field-friendly point-of-care screening test for TB.

OA-303-04 Xpert® MTB/RIF molecular probe binding characteristics associated with discordant confirmatory rifampicin resistance testing

R Berhanu,¹ P Da Silva,² K Schnippel,³ R Kularatne,² L Scott,⁴ W Stevens,^{2,4} C Firnhaber,^{3,5} C Lippincott¹
¹Right To Care, Helen Joseph Hospital, Johannesburg; ²National Health Laboratory Services, Department of Clinical Microbiology and Infectious Diseases, University of the Witwatersrand, Johannesburg; ³Right to Care Research Department, Centurion South Africa, Centurion; ⁴Department of Molecular Medicine and Haematology, School of Pathology, University of the Witwatersrand, Johannesburg; ⁵Clinical HIV Research Unit, Department of Internal Medicine, Faculty of Health Science, University of Witwatersrand, Johannesburg, South Africa. e-mail: rebecca.berhanu@righttocare.org

Background: Xpert MTB/RIF (Xpert) is the first-line diagnostic test for *Mycobacterium tuberculosis* (MTB) infection and rifampicin resistance in South Africa. Xpert rifampicin resistance is treated presumptively as multi-drug resistant tuberculosis (MDR) while awaiting confirmatory line probe assay (LPA) and phenotypic

drug-sensitivity testing (DST). No guidance exists regarding management of patients with discordant results. We aim to describe factors associated with discordant confirmatory rifampicin resistance.

Table Patients with rifampicin resistance diagnosed by Xpert MTB/RIF and subsequent discordant rifampicin resistance compared to patients with confirmed rifampicin resistance.

	RIF resistant- TB patients initiating treatment <i>n</i> = 270 <i>n</i> (%)	Con- firmed RIF resis- tance* <i>n</i> = 225 <i>n</i> (%)	Discor- dant RIF resis- tance † <i>n</i> = 44 <i>n</i> (%)	<i>P</i> value ‡
Male	129 (47.8)	105 (46.5)	24 (54.6)	0.3
HIV infection	218 (81.6)	185 (82.6)	33 (76.7)	0.4
Median CD4 (IQR)	82 (25–173)	86 (25–169)	67 (16–195)	0.7
Xpert probe results available	178 (65.9)	142 (62.8)	36 (81.8)	0.02§
Xpert quantitative value				
Very low	28 (15.7)	17 (12.0)	11 (30.6)	0.006§
Low, medium, high	150 (84.3)	125 (88.0)	25 (69.4)	
Detection method				
Probe drop-out	139 (78.1)	131 (92.2)	8 (22.2)	<0.001§
Probe delay Δ CT $\geq$ 4	39 (21.9)	11 (7.8)	28 (77.8)	
Median C _T (IQR)	18.75 (14.7–22.4)	18.35 (14.4–21.8)	22.15 (17.7–28.95)	<0.001§
Xpert probe				
Probe B	35 (19.7)	17 (12.0)	18 (50)	<0.001§
Probe E	66 (37.1)	58 (40.8)	8 (22.2)	
Probe A, C, or D	77 (43.3)	67 (47.2)	10 (27.8)	
Δ CT#				
Δ CT 4–4.9	20 (52.6)	1 (10.0)	19 (67.9)	0.002§
Δ CT $\geq$ 5	18 (47.4)	9 (90.0)	9 (32.1)	
Median Δ CT (IQR)	4.8 (4.4–7.6)	8.0 (6.0–9.1)	4.45 (4.25–5.35)	<0.001§

* Any test confirming RIF resistance, i.e., second Xpert, line probe assay, phenotypic DST.

† Discordance defined as two or more RIF sensitivity tests with discordant results (Xpert to Xpert discordance, Xpert to LPA discordance or Xpert to phenotypic DST discordance).

‡ Difference of proportions calculated using χ^2 , difference of continuous variables calculated using Wilcoxon rank-sum (Mann-Whitney test), *P* value presented.

§ *P*-value <0.05 (two-sided, >95% confidence).

Delayed binding of a Xpert MTB/RIF probe with Δ CT > 4 (cut-off for resistance in the Generation 4 cartridge).

RIF = rifampicin; TB = tuberculosis; HIV = human immunodeficiency virus; IQR = interquartile range; CT = cycle threshold; Δ CT = difference between the maximum and minimum probe CT value; DST = drug susceptibility testing.

Design/Methods: We retrospectively reviewed a cohort of patients with Xpert rifampicin resistance who were referred to an outpatient, decentralized drug-resistant TB treatment facility in Johannesburg, South Africa between June 2012 and January 2015. LPA, DST or repeat Xpert

were considered confirmatory tests of rifampicin resistance. Patients without a confirmatory test were excluded. The burden of MTB is reflected by Xpert version G4's cycle threshold (CT). The hybridization pattern of the five molecular beacon probes (A-E) was classified as dropout (no hybridization) or delayed (Δ CT $\geq$ 4).

Results: Among the 270 patients included in the analysis, 129 (47.5%) were male, and 218 (81.6%) were HIV-infected with a median CD4 count of 82 cells/mm³. Rifampicin resistance was confirmed in 226 (83.7%) while discordance, defined as one or more confirmatory tests indicating rifampicin sensitive TB, occurred in 44 (16.3%). Xpert probe dropout (139, 78.1%) occurred more commonly than probe delay (39, 21.9%). Discordance was associated with Xpert probe delay (*P* < 0.001) and very low MTB burden (CT > 28) (*P* = 0.006). Discordance was 12.74 times as likely to occur (95%CI 6.18 - 25.19) in patients with probe delay compared to probe dropout. The median CT value in patients with discordance was higher (22.15, IQR 17.7–28.95) than in those with confirmed rifampicin resistance (18.35, IQR 14.4–21.8) (*P* < 0.001). Of the 39 patients with probe delay, Δ CT 4–4.9 had a greater association with discordance than Δ CT $\geq$ 5 (*P* = 0.02). Probe B (50%) and Probe E (22.2%) accounted for the majority of discordant results.

Conclusion: Clinicians and national TB programs using Xpert need to be aware of the association of delayed Xpert probe binding with discordant rifampicin resistance. Further research is needed to determine if delayed probe binding with discordance is a marker for false positive Xpert rifampicin resistance, infection with mixed strains of MTB or another cause.

OA-304-04 Evaluation of Genotype MTBDRsl v2 line probe assay for the detection of second-line *Mycobacterium tuberculosis* resistance in culture isolates

N Ismail,¹ Y Gardee,^{1,2} A W Dreyer^{1,2} ¹National Institute for Communicable Diseases, Johannesburg, ²University of Witwatersrand, Johannesburg, South Africa. Fax: (+27) 118 855 339. e-mail: yasming@nicd.ac.za

Background: South Africa is listed by WHO as 4th in Africa amongst the 22 high burden TB nations globally. Studies have indicated that rapidity in diagnosis of Drug Resistant (DR)-TB would lead to early appropriate and effective treatment. Phenotypic drug susceptibility testing (DST) is labour intensive with a long turn-around-time (TAT) to results. Molecular assays offer the advantage of speed. WHO Expert Group 2013 conclusions on Genotype MTBDRsl v1 were that the assay cannot replace phenotypic DST but it may be used as a supplementary test for DST for fluoroquinolones (FLQ) and second-line injectable anti-TB drugs (SLID) as a “rule-in” test for XDR-TB. Genotype MTBDRsl v2 LPA has been redesigned for the detection of FLQ (gyr A & gyrB) and SLID (rrs & eis) resistance mutations.

Design/Methods: Objective: Evaluate the diagnostic performance of MTBDRsl v2 for the detection of secondline drug resistance in *M. tuberculosis* Isolates.

Methods: A total of 134 *M. tuberculosis* Isolates were analysed by MTBDRsl v2 using manufacturer's instructions. The collection comprised of 78 well-characterized *M. tuberculosis* Quality Control (QC) strains used in the WHO Supra National Laboratory Network (SRLN) and 58 Rifampicin-resistant laboratory isolates. Sensitivity and specificity of MTBDRsl v2 was determined with BACTEC MGIT 960 DST as a reference method, WHO 2013 recommended critical concentrations were used for DST.

Results: LPA and DST had (134/134) (100%) results available. The sensitivity and specificity for MTBDRsl v2 was calculated by means of a 2X2 table. FLQ sensitivity was 98.96% and specificity 97.37%, SLID sensitivity was 100% and specificity 100%. Individual SLID results were respectively, Amikacin sensitivity 100% and specificity 100%, Kanamycin sensitivity 100% and specificity 100% and Capreomycin sensitivity was 96.33% and specificity 100%. 36 isolates had gyr A mutations, 6 isolates gyr A MUT3C/D94G mutations. No gyr B mutations were found. 10 isolates were FLQ hetero-resistant. 21 isolates had rrs MUT1/ A1401G mutation with 3 isolates showing low-level Kanamycin resistance, eis WT2 absent.

Conclusion: MTBDRsl v2 performed well with high sensitivity and specificity for FLQ and SLID. We recommend that if mutations are present true resistance is shown. The rest would require confirmation. Including this test in the National TB Program would aid in faster diagnosis and appropriate treatment for DR-TB.

OA-305-04 Pyrazinamide drug susceptibility testing predicts smear and culture conversion in MDR-TB

G E Velásquez,^{1,2} R I Calderon,³ M Becerra,^{3,4,5}

C C Contreras,³ R Yataco,³ J Galea,³ L Lecca,³

M B Murray^{3,4,5,6} ¹Brigham and Women's Hospital, Division of Infectious Diseases, Boston, MA, ²Massachusetts General Hospital, Division of Infectious Diseases, Boston, MA, ³Partners In Health / Socios En Salud, Lima, ⁴Harvard Medical School, Boston, MA, ⁵Brigham and Women's Hospital, Division of Global Health Equity, Boston, MA, ⁶Harvard T.H. Chan School of Public Health, Boston, MA, USA. e-mail: gvelasqu@post.harvard.edu

Background: The relevance of phenotypic pyrazinamide drug susceptibility testing on MDR-TB treatment outcomes is not well understood. Here we evaluate the association between pyrazinamide resistance and sputum smear and culture conversion among multidrug-resistant tuberculosis patients.

Design/Methods: We enrolled patients with active tuberculosis in two health regions of Lima, Peru from September 2009 through August 2012. We obtained sputum smears and cultures at baseline and at two months of therapy, and tested for pyrazinamide resistance using the modified Wayne method (pyrazinamidase assay). We restricted our analysis to patients with

multidrug-resistant tuberculosis who were treated with first-line drugs during the first two months of treatment. We constructed a multivariate logistic regression model to test the association between baseline pyrazinamide resistance and two-month smear and culture positivity, adjusting for age, sex, and baseline ethambutol resistance.

Results: Three hundred and eleven multidrug-resistant tuberculosis patients were eligible for the study, of whom 157 (50.5%) were resistant to pyrazinamide at baseline. Pyrazinamide resistance was associated with higher odds of two-month smear positivity (OR = 2.31; 95%CI, 1.40-3.81) and two-month culture positivity (OR = 4.27; 95%CI, 2.36-7.72) after we adjusted for age, sex, and baseline ethambutol resistance.

Conclusion: We demonstrate that pyrazinamide resistance as measured by the modified Wayne method (pyrazinamidase assay) is predictive of lower two-month sputum smear and culture conversion among multidrug-resistant tuberculosis patients. Our findings reinforce the clinical value of including routine pyrazinamide drug susceptibility testing in baseline investigations for patients with active tuberculosis.

OA-306-04 An amplicon-based next generation sequencing platform for the Illumina MiSeq for 10 genes involved in first- and second-line drug resistance

D Operario,^{1,2} S Heysell,^{1,2} A Koepfel,^{1,2} E Houpt,^{1,2}

S Turner,^{1,2} S Pholwat,^{1,2} S Banu,³ G Kibiki⁴ ¹University of Virginia, Charlottesville, VA, ²University of Virginia, Charlottesville, VA, USA; ³International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh;

⁴Kilimanjaro Clinical Research Institute, Moshi, Tanzania.

e-mail: scott.heysell@gmail.com

Background: Commercially available line probe assays for detection of mutations in *M. tuberculosis* drug resistance genes are of insufficient sensitivity. Emerging reports describe specific amino acid changes within resistance determining regions (RDRs) correlating with low/high level phenotypic resistance. Conventional sequencing (Sanger) provides more precise amino acid data, but is expensive, labor intensive, and may not provide a precise indication of a mixed genotype. Thus, we developed a simplified, high throughput protocol for sequencing on the Illumina MiSeq for rapid characterization of RDRs impacting key first and second-line anti-TB drugs.

Methods: An amplicon-based sequencing assay was designed for 12 RDRs in 10 genes: inhA, katG, rpoB, embB, pncA, gyrA, gyrB, rpsL, rrs, eis. 17 amplicons were employed to cover a read length of 150 to 300 base pairs, over a total of 2,924 bases of the *M. tuberculosis* genome. After quality filtering, sequencing trimming, and alignment to a custom reference sequence (H37Rv), potential mutation loci were called using a haplotype-based variant detection algorithm (freebayes). We then tested this platform on DNA extracts from phenotypically diverse *M. tuberculosis* isolates across our collab-

orative study sites (Bangladesh, Siberia, Tanzania, Thailand) and compared these results to Sanger sequencing. **Results:** 229 *M. tuberculosis* isolates, the majority MDR by phenotypic drug-susceptibility testing, were sequenced on the Illumina MiSeq. Turnaround time was approximately 60 hours. A minimum coverage of 100x was achieved in 91%, yielding over 5 million high-quality ($\geq Q30$) reads for multiple samples within a single run. In a subset of isolates ($n=109$) with complete Sanger sequencing, accuracy for the MiSeq was $>95\%$ for the majority of gene RDRs (*inhA*, *katG*, *rpoB*, *rpsL*, *gyrA*, *gyrB*, *rrs*, *eis*) but less so for *pncA* (89.8%) and *embB* (83.3%). The depth of sequencing result on the Illumina MiSeq revealed mixed genotype not detected by Sanger.

Conclusions: Next generation sequencing platforms, such as this developed for the first time on the Illumina MiSeq, have the potential to more specifically ascribe variants in drug-resistance present at unprecedented levels of detection, but must ultimately be coupled with studies of quantitative phenotypic resistance and sound clinical epidemiology. Currently, this high throughput protocol may be envisioned for reference laboratories to track drug-resistance trends at the population level.

OA-307-04 The role of sputum TB quantitative viability microscopy to predict patient infectiousness

S Datta,^{1,2,3} J Sherman,^{1,2} T Valencia,^{1,2} M Tovar,^{1,2} E Ramos,^{1,2} R Gilman,⁴ C Evans^{1,2,3} ¹IFHAD: Innovation for Health and Development, Lima, ²Innovacion Por la Salud Y el Desarrollo (IPSYD), Lima, Peru; ³Wellcome Trust Centre for Global Health Research, London, UK; ⁴Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: sumo.datta31@gmail.com

Background: Close contacts of people with smear-positive pulmonary TB are recommended to undergo contact investigation. However, acid-fast sputum microscopy cannot accurately assess infectiousness, and does not differentiate live from dead TB. TB quantitative viability microscopy (TQVM) with fluorescein diacetate predicts the amount of culturable *Mycobacterium* TB in sputum and rapidly assesses early response to TB treatment but implications for infectiousness are unknown.

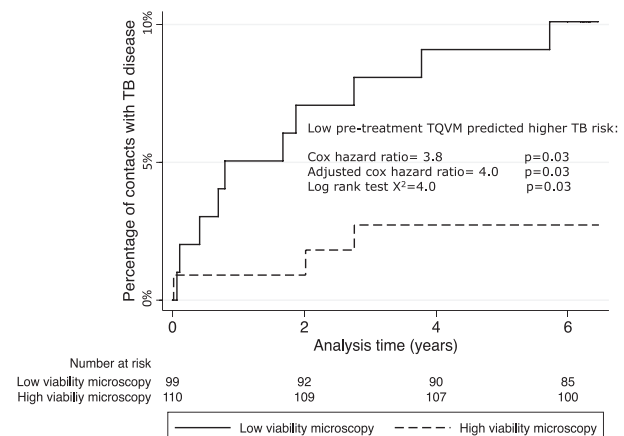
Objective: To evaluate sputum TQVM for predicting treatment outcome and infectiousness.

Methods: 35 newly diagnosed, sputum smear-positive patients in Lima, Peru, and 209 of their household contacts were recruited. All patients gave pre-treatment sputum samples that underwent laboratory decontamination with sodium hydroxide and were tested with TQVM, quantitative culture and auramine-microscopy to quantify acid-fast bacilli (AFB). Patients and contacts were interviewed for demographic and clinical data at recruitment, and followed-up for 6 years.

Findings: TQVM concentrations were median 5.1% (interquartile range IQR 2.4-11%) of AFB concentrations. Quantitative culture results were median 1.8% (IQR 0.42-2.2%) of AFB concentrations. Patients with

constitutional symptoms had higher TQVM, quantitative culture, and AFB concentrations (all $P \leq 0.006$). Adverse treatment outcomes occurred in 9.4% (3/32) patients, all of whom had multi-drug resistant tuberculosis (MDR-TB) but outcome was not predicted by pre-treatment results for TQVM, quantitative culture or AFB. 6.4% (13/209) of household contacts developed TB disease during follow-up for median 6.3 years (IQR 6.5-6.5). Contacts of patients with lower than median TQVM results in sputum were more likely to develop TB disease (univariable cox regression hazard ratio HR=3.8 $P=0.03$). This association persisted after adjustment for disease severity, chemoprophylaxis, drug-resistance and social determinants (adjusted HR=4.0, $P=0.03$, Figure).

Conclusions: A minority of TB in pre-treatment sputum were viable, whether assessed with TQVM or culture. Although, TQVM was highest in patients with more severe constitutional symptoms, this was not associated with treatment outcome. Paradoxically, patients with more TQVM-positive cells in their sputum were less infectious to their household contacts. TQVM-negative cells may be slowly metabolising TB that is better adapted to survive airborne transmission and cause infection.



02. Around the world vulnerability takes many forms

OA-308-04 Effectiveness of tuberculosis integration in reproductive health on case notification in 13 provinces of Afghanistan

A Momand,¹ M Rashidi,¹ G Qader,¹ M Seddiq,² K Ayoubi,² S M Sayedi,¹ M Shefa,¹ P G Suarez³

¹Management Sciences for Health, Kabul, ²Ministry of Public Health, Kabul, Afghanistan; ³Management Sciences for Health, Boston, MD; USA. e-mail: amomand@msh.org

Background and challenges to implementation: In Afghanistan, tuberculosis (TB) disease affects mostly women especially during their reproductive years that affect their children and families that leave women

marginalized and vulnerable for TB. Chronological data from 2009-2014 shows that around 62% of TB cases notified were among women. To overcome the challenges, USAID supported TB CAP and TB CARE projects assisted NTP to integrate TB control activities in reproductive health services. The aim of this assessment was to determine the role of female health care workers in case notification in Afghanistan

Intervention or response: TB CAP and TB CARE 1 assisted NTP to develop and revised Standard Operational Procedures (SOPs) on case detection and diagnosis, Treatment, TB IC, drug management manual and TB guideline, develop and disseminate 62 000 information, education and communication (IEC) material, trained 4600 front line female health workers from 2010 –2014 in 380 health facilities in 13 provinces to increase the case detection among women. In January 2015, Challenge TB and NTP team reviewed and analyzed the data from 2009-2014, using standardized NTP recording and reporting questioner, documented all form TB cases and new sputum smear positive (NSS+) cases.

Results and lessons learnt: The study revealed that number of all form TB cases among women primarily in reproductive age increased by 45.4% and number of new sputum smear positive cases increased by 50% respectively from 2009 till 2014.

Conclusions and key recommendations: The study determine that the integration of TB in reproductive health services contributed in increased case finding by providing institutional capacity and technical leadership to implement TB control activities in their working areas therefore we recommend this integrated approach to all similar settings

OA-309-04 Engagement of workplaces in TB care: support and achievements in Bangladesh

K Khatun,¹ M Siddiqui,¹ M Akramul Islam,¹ M Chowdhury,¹ S Alam,¹ S Islam,¹ M M Rahman,² M Quader³ ¹BRAC, Dhaka, ²National Tuberculosis Programme, Dhaka, ³Bangladesh Garment Manufacturers and Exporters Association, Dhaka, Bangladesh. Fax: (+88) 029 888 026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: The garment industry of Bangladesh is a main earning source from abroad for the last 25 years which provides employment of about three million people. As employees spend most of their working hours here, the workplace is the ideal place to tackle TB. TB interrupts workflow, lowers productivity and raises the direct and indirect costs such as the replacement and retraining of workers. To address this problem, a partnership programme was initiated in 2010 between BRAC and BGMEA (Bangladesh Garment Manufacturers and Exporters Association) with the support of NTP. BGMEA possesses more than 4000 factories with 2.4 million workers.

Intervention or response: A total of 11 DOTS centers are established in health centres of BGMEA to diagnose and treat TB cases among workers under DOTS strategy. Presumptive TB cases are tested for sputum microscopy; negative cases that have other TB symptoms get

investigation support for other test (such as X-ray, FNAC, Biopsy). All TB cases are then registered under NTP and treat accordingly. Orientation on TB has also been conducted to raise awareness among factory owners and workers.

Results and lessons learnt: In the BGMEA working area through 208 orientation events, 10 377 and 10 351 workers and managers/owners of different garment factory were orientated on TB in 2013 and 2014 respectively. In 2013 and 2014, 619 and 838 TB cases were diagnosed and registered. Among them 283 and 362 were new smear positive, 133 and 168 smear negative and 176 and 255 were extra pulmonary TB case. Treatment success rate was 93.05 % and 95.05% among new smears positive case in 2012 and 2013 respectively. In 2013, 38 presumptive cases are given social support and 34 persons are diagnosed as TB whereas in 2014, 98 persons were diagnosed as TB against 161 social support. Regarding patient referral, in 2013, 593 patients are referred by BGMEA staff, 24 patients by Government Hospital and 2 patients by Government field staff. In 2014, 663 patients are referred by BGMEA staff, 159 patients by Government Hospital, 10 by private practitioners and 3 by cured TB patients.

Conclusions and key recommendations: Establishment of DOTS centres in workplaces, different orientation to factory workers and to the management authority, and social support to presumptive TB cases increased case notification, treatment adherence and treatment success rate.

OA-310-04 Improving case notification in the elderly and other vulnerable communities in Cambodia using chest X-ray and Xpert® MTB/RIF testing

M Chry,¹ K Mom,¹ C Andrew,² C Jacob,² L Gerstel³ ¹Cambodia Anti-Tuberculosis Association, Phnom Penh, Cambodia; ²Stop TB Partnership, Geneva, Switzerland; ³Royal Tropical Institute, Amsterdam, Netherlands. e-mail: rath@thecata.org.kh

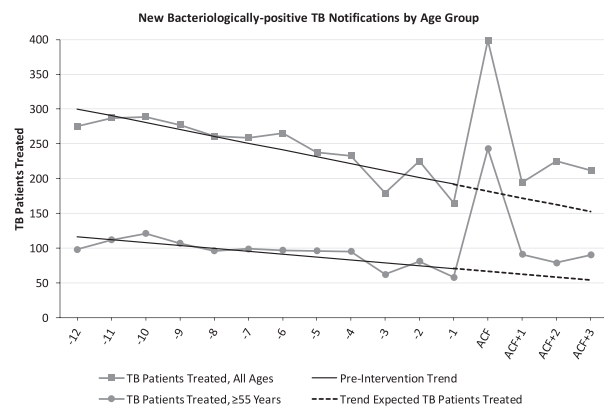
Background: Since 2000, the TB burden in Cambodia has been reduced by 50%. Despite this impressive achievement, the country still has one of the highest TB prevalence rates in the world (748 cases per 100 000 population in 2013). The elderly (aged ≥55 years) account for an estimated 50% of the TB burden, yet this group has low case notification rates owing to poor access to health services.

Methods: Active case finding (ACF) using mobile teams equipped with a chest X-ray (CXR) and GeneXpert machine was conducted in 4 operational districts. Staff set up ACF days at existing health facilities and screened people using a TB symptom questionnaire and CXR. Those with a positive screen were then tested on the Xpert MTB/RIF assay and detected patients were initiated on appropriate treatment. Village health support groups (VHSGs) mobilized the communities around each health facility to ensure high screening volumes during ACF days. Though the elderly were targeted, all

community members were eligible for screening. Project yield and TB notification data were analysed to assess the impact of activities on treatment initiation.

Results: Across four districts, 76 health facilities were visited by the mobile teams on ACF days, resulting in the screening of 9,260 individuals for TB symptoms and by CXR. 1756 (19.0%) individuals were then tested using the Xpert MTB/RIF assay, resulting in the detection of 324 (18.5%) MTB-positive patients. New bacteriologically-positive notifications increased +119.3% for all ages and +266.2% for those ≥ 55 years during the ACF quarters compared to trend expected notifications. The temporary ACF activities had a more lasting effect than anticipated, as notifications were above trend three full quarters post-intervention. When extending the post-ACF period to 12 months to capture this effect, new bacteriologically-positive notifications were +54.0% and +109.2% higher than expected for all ages and ≥ 55 years respectively. This translates into an estimated 361 TB patients of all ages and 263 patients aged ≥ 55 years being treated who would not have received care in the absence of the ACF intervention.

Conclusion: ACF using mobile teams was able to increase access to health facilities in vulnerable communities, particularly among the elderly, and to detect and treat many previously missed TB patients. In settings with low notification rates, targeted ACF interventions such as this should be prioritized to reduce the pool of prevalent TB patients.



OA-311-04 Exploration of methods of TB for internal migrants: the experience of China

J Li,¹ X Liu,¹ S Jiang,¹ H Zhang,¹ L-X Wang¹ ¹National Center for TB Control and Prevention, China CDC, Beijing, China. e-mail: lijun@chinatb.org

Background: Floating population in China is increasingly one of major challenges in TB control, with the number increased to 2360 million in 2012. Considering the low case detection, poor treatment adherence and high contagious risk among them, China had explored TB control mode for floating population from October 2006 to June 2012, totally covered 198 counties/districts and 75 cities in 29 provinces, supported by the Globe Fund and local government.

Interventions: Regarding health care services for floating population, free chest radiograph and sputum-smear microscopy examinations were provided in TB dispensaries, while health examination screening for TB in designated spots. Patients were given free first-line drugs, basic follow-up examinations, as well as transportation and nutrition subsidies during treatment course. Medical service time was prolonged. Group and individual psychological counseling were provided to target cases. With enhanced health service and TB surveillance system for floating population, TB dispensary monitored epidemic, traced cases referred by other health institutions, and provided health care services. DOT was conducted by primary health care center. Specific measures included establishing mechanism of inter-sector coordination and technical exchange, cross-area management procedure, hiring full-time health care staff, increasing health staff's subsidies of DOT, conducting training and health promotion, as well as cooperating with NGOs.

Results and lessons learned: 165 529 TB patients were detected and treated in total, of which 43.7% were smear positive cases. The case registered rate was increasing from 26.2/100 000 in 2007 to 71.4/100 000 in 2011, higher than the national average level. The rate of cases arrived in TB dispensaries was increased from 65.5% to 87.1%. The successful treatment rate was increased from 79.2% to 91.5%, while the default rate decreased from 16.1% to 2.9%. The total satisfaction rate of patients and acceptability rate of health staff regarding the control mode was respectively 78% and 89%. Critical to those effective outcomes were government commitment, sufficient financial support, well-constructed health system and quality control mechanism.

Conclusions: Significant achievements of TB control mode for floating population were observed in China: the case detection and treatment adherence had been well improved. This control mode should be enhanced and expanded nationwide with sustainable government commitment.

OA-312-04 Risk factors associated with acquisition of tuberculosis in two Colombian prisons

L Arroyave,¹ L López,² D Marin,¹ M P Arbeláez,¹ Y Keynan,³ Z Rueda² ¹Universidad de Antioquia UDEA, Medellín, ²Universidad Pontificia Bolivariana, Medellín, Colombia; ³University of Manitoba, Winnipeg, MB, Canada. e-mail: zulmaruedav@gmail.com

Background: Incarceration is associated with high incidence of tuberculosis (TB) and latent tuberculosis infection (LTBI). We wanted to measure the incidence of latent tuberculosis infection (LTBI) and identify risk factors associated with it.

Design/Methods: In a previous study, 829 male inmates from two prisons in Medellín and Itagüí, Colombia were evaluated for prevalence of LTBI, and 186 prisoners were negative to the first two step TST administration. We followed people with negative TST for two years. TST were administered according to CDC guidelines and

were not applied in persons with previous or current active TB, severe adverse event with prior TST administration, immunosuppressive treatment and administration of live vaccines (MMR, varicella or the live attenuated influenza vaccine) in the 4 weeks before TST application. A TST result of 10 mm induration and an increase of 6 mm between baseline and follow-up application was considered as a converter. The adjusted relative risk and their 95% confidence intervals were estimated using the binomial regression adjusting by standard errors.

Results: Among 120 people that we could follow, 100 remained incarcerated and 20 were released. The overall percentage of TST conversion over two years was 23.5% (28/119). The incidences of conversion were: in Prison One-34% (22/65), there was no conversion in Prison Two, and 30% (6/20) among people that were released (those converters were incarcerated in Prison One). The risk factors for LTBI conversion were history of contact with a TB case (RR: 1.56; 95%CI 1.51-1.61), inhaled drugs (RR: 1.31; 95%CI 1.26-1.37), BMI >25kg/m² (RR: 1.49; 95%CI 1.48-1.50), and being incarcerated in Prison One (RR: 1.11; 95%CI 1.08-1.14). During follow-up, 7 inmates developed active TB (six had a positive TST by two-step method and one had a previous negative TST).

Conclusion: Active TB transmission in prisoners is high, and it differed between prisons. The data suggests that some LTBI identified in the initial screening are actually active TB thus contributing to transmission. It is important to apply TST by two-step method and follow-up prisoners because of the high incidence of TB infection, and they benefit of the administration of isoniazid after ruling out active TB.

OA-313-04 Effectiveness of an alcohol intervention strategy among TB patients: a study from South India

B Thomas,¹ B Watson,^{1,2} E Senthil Kumar,¹ S Chandra,¹ A Deepalakshmi,¹ A Dhanalakshmi,¹ C Manogaran¹

¹Social and Behavioral Research, National Institute for Research in Tuberculosis, Chennai, ²Statistics, National Institute for Research in Tuberculosis, Chennai, India. Fax: (+91) 442 836 2528. e-mail: beenaelli09@gmail.com

Background: The influence of alcohol with regard to delays in seeking care and non-compliance for treatment has been well documented. There is an urgent need to develop a feasible, acceptable alcohol intervention strategy among TB patients to ensure successful treatment completion and a better quality of life. It is against this background that this study was conducted.

Methodology: This is a two-arm randomized controlled study in which 4 zones of the Chennai Corporation were randomly selected and allotted (2 each) to the experimental and control arms. TB patients (>18 years) registered from August 2013 to January 2014, under the RNTCP, were assessed using AUDIT scale (>8 to <20). The intervention consisted of 4 individual counseling sessions (0, 2, 4 and 6th month) conducted by trained interventionists. An intervention manual using

a community participatory approach was prepared to guide the sessions. This involved one to one counseling sessions and visual aids were used to explain facts about TB and the effects of alcohol use on TB treatment and management

Results: Of the total 872 registered TB patients, 298 (31%) were found to have AUD (alcohol use disorders). The number of TB patients in the experimental and control arms were 113 and 185 respectively. Percentage with favorable treatment outcomes (cured/completed treatment) was significantly higher ($\chi^2=20.8$, 1 d.f., $P < 0.001$) in intervention (87%) compared to the control group (62%). It was also observed that the overall adherence to TB treatment was significantly higher ($\chi^2=35.1$, 2 d.f. $P < 0.001$) among the intervention group when compared to the control group. Among the intervention group, 88% completed more than 2 intervention sessions. Percentage of patients with favorable treatment outcomes increased with the number of interventions attended ($\chi^2=43.3$, 4 d.f. $P < 0.001$). It was seen that the proportion with regular consumption of doses till the end of treatment increased with the number of interventions attended ($\chi^2=44.6$, 4 d.f. $P < 0.001$). Participants expressed interest towards the effectiveness of the interventions especially with regard to the visual aids that were used and the time taken for the sessions

Conclusion: Alcohol intervention among TB patients is effective in ensuring favorable treatment outcomes and TB treatment adherence. This intervention was feasible and acceptable to patients. This study suggests the need for trained counselors in TB care settings to ensure effective alcohol intervention strategies to ensure TB treatment compliance among TB patients with AUDs

OA-314-04 TB screening of hard-to-reach populations at household level with volunteer field workers in Umzinyathi, Kwa-Zulu Natal

D Turner,¹ S Shenoi,² R P Brooks,² M Ma,² L Ngubane¹

¹Umvoti AIDS Centre, Greytown, South Africa; ²Yale School of Medicine, New Haven, CT, USA. Fax: (+27) 033 413 4726. e-mail: derek@umvoti.co.za

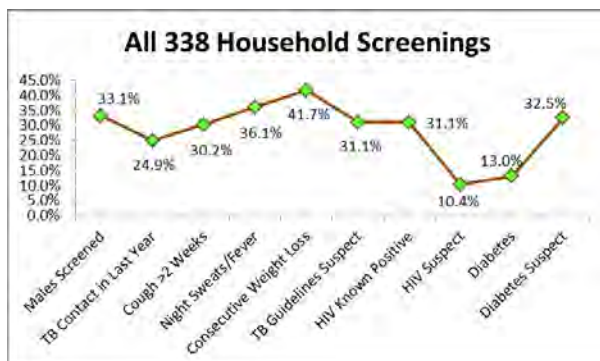
Background: South Africa is facing multiple issues in reaching deep rural populations with targeted TB investigation at a household level for those with recent TB contacts. Due to the nature of clinic based care options, many households are unable to access services, particularly men and non-ambulant household members, either due to costs involved, distance to facilities or stigma.

Intervention: We trained semi-literate community volunteers to screen for TB, HIV and Diabetes at a household level using a 10 question tick sheet covering major signs and symptoms as well as asking for known household TB contact in the previous year. The aim was to screen only households where the care givers knew family members to be ill or to have TB signs and symptoms. In all 37 care givers screened 338 people in 145 households over a six

week period, with the intention of reaching those who do not travel to centralised clinics, in particular men.

Findings: Of 219 people with no active TB, 31% of whom were male, 44 had had contact with a TB patient at household level in the previous year and 66 were screened positive as TB suspects. Known HIV prevalence was 25.8% with a further 9.3% showing multiple signs of HIV and Diabetes prevalence was 11.7% with a further 33% screened as suspects. Of 47 people screened who are known active TB cases, 44.7% were men, 85% had a TB contact in the previous year and 39 screened positive for all major signs and symptoms of TB treatment (cough, night sweats and/or fever and persistent weight loss).

Conclusion: The care givers were able to identify and screen households with active and suspected TB whilst gaining access to traditionally hard to reach population groups, with care givers screening high percentages of household members with multiple signs and symptoms of TB, HIV and Diabetes. For those with active TB, indicators suggest that the majority is likely to be still infectious, with high percentages of major symptoms in evidence, indicating adherence and conversion issues which are reflected in DoH statistics for the District. Results indicate that disclosure of status and willingness to screen is significantly higher than usually found in community case finding initiatives due to the non-threatening and informal screening process as well as the familiarity of the field worker with their community households.



OA-315-04 Early TB case detection in pre-trial detention centers (SIZOs) in Ukraine

S Leontyeva,¹ K Gamazina,² O Bogdanov,² M Gagarkin³

¹Organization for Appropriate Technology in Health, Kyiv,

²PATH, Kyiv, ³All-Ukrainian Penitentiary Network, Kyiv, Ukraine. Fax: (+380) 444 962 627. e-mail:

sleontyeva@oath.org.ua

Background and challenges to implementation: Over the past decade, Ukraine has improved TB care services in both the civil and prison systems. However, overcrowding in pre-trial detention centers (SIZOs) has rarely been prioritized, these facilities fall between the prison and civil TB care systems. In SIZOs, TB diagnosis is limited to digital CXR screening upon entry. Smear microscopy is

indicated if fluorography shows abnormalities. Follow-up care algorithms for detainees with presumptive TB are poorly developed and initiation of treatment is often significantly delayed.

Intervention or response: PATH in partnership with the All-Ukrainian Penitentiary Network and in coordination with the NTP and the State Penitentiary Service implemented a project "Increasing TB Case Detection in the Ukrainian Detention System" with support from TB REACH. The goal of the project was to improve the early TB diagnosis and increase the yield of bacteriologically confirmed TB patients among pre-trial detainees in 3 SIZOs in Ukraine, in the regions of Kherson, Mykolaiv and L'viv through systematic verbal screening for symptoms and risk factors of TB, followed by the sputum smear microscopy and further culture/DST, if indicated and establish prompt referral to timely treatment.

Results and lessons learnt: Across 12 months, 8361 detainees were verbally screened upon entry and then quarterly, resulting in the identification of 3280 (39.2%) individuals with suspected TB who were referred for further evaluation (smear microscopy, culture/DST). 58 bacteriologically confirmed TB patients were detected and a further 120 TB patients were clinically diagnosed. This translates into a TB prevalence of 1435 patients per 100 000 population, more than 10-fold higher than the national prevalence estimate. All TB patients were initiated on treatment in SIZO or in civil TB hospitals.

Conclusions and key recommendations: Early TB case detection among detainees, based on the verbal screening algorithm, resulted in the significant increase (178 TB cases comparing 40 during previous 12 months) of the number of TB cases detected and referred for immediate treatment. Active interventions to rapidly identify infectious patients and treat them are essential to interrupt TB transmission inside and outside the detention settings.

03. Placing the patient at the center of care

OA-316-04 Patient-centered TB treatment approach: a cluster randomized controlled trial in Armenia, 2015

N Truzyan,¹ V Petrosyan,¹ A Harutyunyan,¹

V Khachadourian,¹ M Thompson² ¹American University of Armenia, Yerevan, Armenia, ²University of North Carolina at Charlotte, Charlotte, NC, USA. Fax: (+374) 1051 2566.

e-mail: tnune@aia.am

Background: Tuberculosis (TB) remains a leading public health concern and an infectious cause for high rates of morbidity and mortality worldwide. Various approaches including patient empowerment, education and counseling sessions, and involvement of family members and community workers have been suggested for improving treatment adherence and outcome. This study, supported by Grand Challenges Canada, evaluated if an innovative

Conclusion: This new strategy can be applied in resource poor countries to reduce healthcare providers' workload, save time and financial resources that could be potentially used for other TB related services.

A C Carvalho,¹ L M P Oliveira,¹ L Isidoro,¹ V Trajano,¹
M L B C Mello,¹ T C Araujo-Jorge,¹ J S Garcia,^{1,2}
S C Cavalcante^{1,2} Oswaldo Cruz Institute (IOC), FioCruz, Rio
de Janeiro, RJ, ²Municipal Health Secretariat, Rio de Janeiro,
RJ, Brazil. Fax: (+55) 21 2562 1432. e-mail:
a.carvalho@libero.it

Design/Methods: From Nov 14, patients starting TB treatment at a public health clinic that assists Rocinha's community were invited to participate with their relatives. After written informed consent, they answered

Conclusion: These results indicate that TB is part of the community's daily life, is perceived as a serious illness, and although knowledge about appropriate treatment is good, modes of transmission are still confused. The interest of patients and families in learning more about the disease makes us hopeful about good acceptance and participation in educational activities that are being implemented. Figure: Word cloud of TB patients' response to the question "What worries you the most when you think about TB?" (www.wordle.net)



OA-318-04 Counselling is associated with improved adherence to early phase treatment for multidrug-resistant tuberculosis

B Sengupta,¹ K Roy,² A Dutta,³ S Sahoo³ ¹CARE India, New Delhi, India; ²CARE USA, Atlanta, GA, USA; ³Asian Institute of Public Health, Bhubaneswar, India. e-mail: bsengupta@careindia.org

Background and challenges to implementation: Compliance to Multidrug-resistant Tuberculosis (MDR-TB) treatment is a challenge to the patient and the health system for its duration and complexity. Programmatic Management of Drug-resistant TB (PMDT), India is implemented to address the MDR-TB problem. CARE India with support from Lilly MDR-TB partnership with PMDT provided psychosocial counselling support to the MDR-TB patients from 2011 in the DOTS Plus site of KS Roy TB Hospital in West Bengal to increase treatment adherence, which was evaluated through this study.

Intervention or response: The study included 265 patients from KS Roy TB Hospital as the Formally Counselling (FC) group and 223 from SCB Medical College, Orissa as the Not Formally Counselling (NFC) group; those initiated on treatment between January 2011 and June 2013. Data included age, gender, weight, MDR-TB suspect criteria, number of doses missed within first six months and days taken to undergo first sputum follow-up culture and start continuation phase from initiation.

Results and lessons learnt: The FCs were mostly diagnosed using suspect criterion B compared to A in NFCs; also had less males and had lower average age. Fifty-eight percent FCs ($n = 153$) did not miss a single dose of treatment to 32% ($n = 71$) NFCs; those missing more than 5 doses were 13% and 34% respectively. The adjusted risk of missing doses was 1.84 times more in absence of counselling (1.40 to 1.66, $P < 0.001$). The median number of days for first follow-up sputum culture was 103 days and 112.5 days in the FCs and NFCs respectively; the adjusted mean difference being 13.81 (6.40-21.39, $P < 0.001$). The median number of days to start continuation phase was 205 in FCs vs. 260 in NFCs, the adjusted mean difference being 41.32 (17.91-64.69, $P < 0.001$).

Conclusions and key recommendations: The results demonstrated the beneficial association between counselling and treatment compliance to Drug-resistant TB patients; hence the overarching recommendation is to mainstream counselling in the programme.

OA-319-04 Ambulatory vs. hospital-based treatment for MDR-TB under programmatic conditions

M Kaela,¹ N Ruswa,^{1,2} F Mavhunga,¹ A Zezai² ¹Ministry of Health and Social Services, Windhoek, ²KNCV Tuberculosis Foundation, Windhoek, Namibia. Fax: (+264) 61 252 740. e-mail: ncruswa@yahoo.com

Background and challenges to implementation: Namibia is Southern African country with a high incidence rate of TB. Patients with MDR TB in Namibia undergo

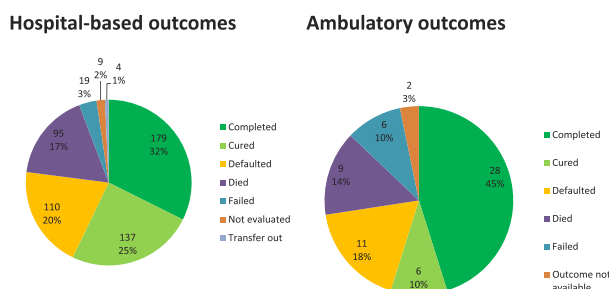
hospitalization in the intensive phase of treatment followed by one or more forms of ambulatory treatment. The WHO guidelines advocate for ambulatory care for MDR TB, but this has sparked local debate on the risks and feasibility. Grootfontein District in Namibia is home to the San bushman tribes who are disproportionately affected by MDR TB. Due to their nomadic lifestyles and social structures, hospital admission is viewed very negatively. The prolonged treatment for MDR TB was associated with high rates of loss to follow-up (45%).

Intervention or response: In 2010, after local consultations with patients and ACSM interventions, a decision was made to introduce a community based ambulatory care model for DR-TB in the Tsumkwe Constituency. No additional health workers were recruited, but the local clinic nurses and community health workers were responsible for patient treatment and monitoring, with technical support from district doctors and the national clinical committee. Final treatment outcomes for patients treated in this district between 2009 and 2012 were analysed and compared with those from other districts implementing a hospital-based intensive phase of treatment.

Results and lessons learnt: In 2010 and 2011, 62 patients with DR TB received regimens in line with WHO recommendations from the local clinic, but with no hospital admission. This included an injectable phase of at least 8 months, for which patients had to present daily at the clinic. In the same period 553 patients were treated nationally. Treatment success rates between the 2 groups were 55% and 57% respectively

Conclusions and key recommendations: There was no significant difference in MDR TB treatment outcomes between ambulatory care settings and traditional hospital-based treatment settings. This demonstrates that ambulatory treatment indeed has a place in countries like Namibia, with the additional benefit of cutting costs and maintaining stable families, especially among vulnerable populations.

Ambulatory vs. hospital-based MDR-TB treatment outcomes



OA-320-04 Introduction of out-patient care for DS-/MDR-TB patients in Tajikistan

I Leimane,¹ O Bobokhojaev,² M Makhmudova,³ Z Abdulloeva,³ S Verver¹ ¹KNCV Tuberculosis Foundation, The Hague, Netherlands; ²Republican Center of Protection of Population from TB of Republic of Tajikistan, Dushanbe, ³KNCV Tuberculosis Foundation, Dushanbe, Tajikistan. Fax: (+31) 70 358 4004. e-mail: ieva.leimane@kncvtbc.org

Background and challenges to implementation: Tajikistan is one of the 27 high burden MDR-TB countries with 108 new notified cases per 100 000 population. 10% of MDR-TB patients have XDR-TB. The number of (X) MDR-TB patients continues to rise. The majority of DS/MDR-TB patients are poor. Loss-to-follow-up of TB treatment is common, with a principal reason to migrate for employment. Patients are hospitalized for long period of time. Therefore, NTP decided to introduce patients' centered out-patient care model and piloted it in nine districts.

Intervention or response: In 2013, TB CARE I project provided TA to NTP to facilitate a shift from in-patient to out-patient treatment in PHC facilities. Local governments developed implementation plans for psycho-social support (PSS) and provided quarterly social packages to DS-/MDR-TB patients. A patients' support team was established at the NTP to provide PSS. Clinical staff, community activists and religious leaders were trained on outpatient care protocol, communication skills, and stigma reduction. A supportive supervision system was introduced during implementation including on-the-job training. The DS-/MDR-TB data of 9 districts were recorded in the Central TB Register and analyzed.

Results and lessons learnt: The proportion of registered DS-TB patients in out-patient care increased from 20% (115 out of 579) in 2013 to 58% (311 out of 536) in 2014. The proportion of DS-TB in-/out-patients who received PSS increased from 24% (45 out of 184 eligible) in 2013 to 74% (120 out of 162 eligible) in 2014. The proportion of registered MDR-TB out-patients almost tripled from 21% (11 out of 52) in 2013 to 58% (38 out of 66) in 2014. The number of MDR-TB in-/out-patients, who received PSS increased from 15 in 2013 to 118 in 2014. In 2014, among all registered MDR-TB patients 98% (65) received PSS. In 2013, 57 MDR-TB patients have been enrolled on out-patient treatment. No patients were lost-to-follow-up since then. We learned that, since little local government funding is available, PSS focus should be on MDR-TB patients.

Conclusions and key recommendations: This approach gave positive results and contributed to the sustainability of out-patients care and better adherence to treatment. The coordination of PSS from local government, collaboration among medical workers from the PHC and TB facilities, community activists and religious leaders are main factors of success. It is recommended to apply this model elsewhere.

OA-321-04 Patients' perceptions of interventions to improve MDR-TB treatment completion in the Philippines

T Tupasi,¹ A Garfin,² J Mangan,³ L Naval,¹ J Pancho,⁴ M Mantala,⁵ E Kurbatova,³ A Golubkov⁶ ¹Tropical Disease Foundation, Inc., Makati City, ²The National Tuberculosis Control Program, Department of Health, Manila, Philippines; ³U.S. Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, Atlanta, GA, USA; ⁴National Center for Pulmonary Research, Lung Center of the Philippines, Quezon City, ⁵Technical Assistance to the Countries (TASC) Project, Manila, Philippines; ⁶U.S. Agency for International Development, Washington, DC, USA. Fax: (+352) 265 7683. e-mail: bpy4@cdc.gov

Background: As part of an effort to improve treatment completion rates at programmatic management of drug-resistant tuberculosis (PMDT) treatment centers in the Philippines, a case-control study was conducted. One aim of this study was to describe patients' views on interventions that would affect adherence to treatment for multidrug-resistant (MDR) tuberculosis (TB).

Methods: In-depth interviews were conducted with patients who were lost to follow-up (cases) and patients who were continuing or had completed treatment (controls) between April and July of 2014 among patients with rifampicin-resistant TB who had initiated MDR TB treatment between July and December of 2012 at 15 PMDT treatment centers throughout the Philippines. Responses to open-ended questions were thematically analyzed.

Results: Interviews were conducted with 91 cases and 182 controls. Suggested interventions could be categorized as either approaches to improve adherence or approaches to remove barriers. The top three themes that emerged were: (1) the need for transportation assistance or improvements to the current transportation assistance program, (2) food assistance, and (3) difficulties patients encountered related to their anti-TB medications. These themes were identified by 63%, 60%, and 32% of participants (both cases and controls) respectively. Proposed improvements to the transportation assistance program included: providing funds to cover the full cost of transportation to and from treatment centers, providing funds for companions to accompany patients who are too weak to travel alone, and eliminating delays or interruptions in the National Tuberculosis Control Program-organized travel assistance program. Participants from both groups who advocated for food assistance suggested that it be provided at centers when patients receive treatment. Some noted food assistance would help lessen medication side effects and aid recovery. Participants from both groups who commented about medication difficulties expressed their hopes for medications with fewer side effects, medication that could achieve a cure in a shorter time, a smaller quantity of pills to ingest per dose, and treatment that would not inhibit activities of daily living.

Conclusions: Study findings point to the need for a more patient-centered approach within the PMDT strategy, specifically improvements in transportation assistance

and food support, and a need for simpler, less toxic regimens.

OA-322-04 Patient-centred M/XDR-TB care: what do patients in urban and rural Peru say?

S Mookherji,¹ K Alegria-Flores² ¹George Washington University, Washington, DC, ²University of North Carolina, Chapel Hill, NC, USA. Fax: (+1) 202 994 9193. e-mail: smookher@gwu.edu

Background: Controlling multidrug and extremely drug-resistant tuberculosis (M/XDR-TB) poses a grave challenge to public health, globally. Studies repeatedly show that effective M/XDR-TB management goes beyond strategies recommended in global TB control plans, uniformly pointing to patient-centred care as critical to progress in controlling the epidemic. We aim to describe patient-centred care in M/XDR-TB management in Peru, which presented a context where M/XDR-TB remains a persistent problem, even with increased capacity for diagnosis, decreased costs of treatment, and increased financial and human resources.

Design/Methods: We used a case-based study design, purposively selecting urban and rural sites with some of the highest M/XDR-TB prevalence in Peru, employing multiple qualitative data sources: 58 patient interviews, 5 provider focus groups, and observations in 8 facilities, which we compared for triangulation and verification. Current M/XDR-TB strategy recommendations, health systems factors, and social determinants were the primary parameters in the analytical framework. Our approach emphasizes patient voices to identify the current status and challenges in providing patient-centered care for M/XDR-TB.

Results: Overwhelmingly, patients were demoralized during the M/XDR-TB diagnosis process. Several factors contributed to fear, frustration, and depression, highlighting the crucial need for psychosocial support. Because CHWs and community outreach were available in one site and not the other, we could identify how these services made critical positive contributions to patient experiences. CHWs as part of M/XDR-TB management and care contributed to patient-centredness and to disease control by: 1) supporting patients to complete treatment by offering more convenient DOT and providing ongoing psychosocial support; 2) reducing primary transmission of M/XDR-TB and diagnosis delays with active contact tracing, case finding, and patient education.

Conclusion: Our findings reinforce that it is not direct observation of drug ingestion that is important for TB control, but the continuous support from the health system and community that can be conveyed through regular DOT contacts. Patients need interaction, not observation. If TB programs can provide the right kind of patient-centred DOT – flexible, personal, and convenient – patients say that psychosocial, economic, and motivational barriers to successful M/XDR-TB management are diminished.

OA-323-04 Adverse drug reactions and resultant health-related quality of life during multidrug-resistant tuberculosis treatment in South Africa

A Kelly,¹ B Smith,¹ Z Luo,² J Farley³ ¹Michigan State University, East Lansing, MI, ²Michigan State University, East Lansing, MI, ³Johns Hopkins University, Baltimore, MD, USA. e-mail: ana.kelly@hc.msu.edu

Background: Multidrug-resistant tuberculosis (MDR-TB) treatment has been described as “worse than the illness itself” due in large part to the high incidence of adverse drug reactions (ADRs) from treatment, yet little is known about the impact of such effects on patients’ lives. This cross-sectional, observational study examined the effect of patient-reported ADRs from MDR-TB treatment on health-related quality-of-life (HRQOL).

Design/Methods: Patients in the intensive phase of MDR-TB treatment were recruited from May – July 2014 from an outpatient clinic in Durban, South Africa. Patients were interviewed about the presence of 18 possible ADRs experienced during the last 30 days of treatment and the degree of bother (rated 1 – 4) of each. The EuroQOL group five-dimension questionnaire (EQ-5D) was used to produce a HRQOL utility score. Multiple linear regressions and partial correlations were used to determine the detriment in utility attributable to ADRs from MDR-TB treatment.

Results: The sample included 121 MDR-TB patients, 62 (51%) female, and 90 (74%) co-infected with HIV. Patients were on a standardized MDR-TB regimen with a median time-on-treatment of 4 months. Insomnia was the most common ADR, experienced by 83 (69%) of the patients with 57 (69%) reporting the highest degree of bother. Patients reported an average of 8.6 ± 4.1 ADRs. An increased number of total ADRs was associated with a reduction in HRQOL utility ($P < 0.001$). Six ADRs were significantly associated with a decrement in utility and explained 45% of the variance. Gastrointestinal symptoms—nausea/vomiting and bothersome (level 4) diarrhea—had the greatest effect size (-0.33), followed by ADRs affecting movement: bothersome peripheral neuropathy, arthralgia, and myalgia (-0.2 to -0.25) and lastly, tinnitus (-0.2).

Conclusion: In this study, one of the first to quantify the effect of ADRs on HRQOL during MDR-TB treatment, ADRs were common and demonstrated a substantial decrement in utility. These findings will enable clinicians to provide more patient-centered care as they are tasked with prioritizing ADR management in low-resource settings.

04. Law enforcement and awareness

OA-324-04 Mobile court operation for tobacco control in Bangladesh: a success story of enforcement

M A U Ahsan,¹ A M Alamgir Sikder,¹

S M Mahbubus Sobhan¹ ¹Ministry of Health & Family Welfare, Dhaka, Bangladesh. Fax: (+880) 2958 0255. e-mail: ahsan5965@gmail.com

Background: Mobile court is one of the popular court which moves to the place of occurrence and the Executive Magistrates, on the spot, impose penalty for the violation of provision of laws. Mobile court operation for the enforcement of tobacco control law is even popular in Bangladesh. However, the Executive Magistrates conduct mobile courts on almost 100 laws in the country, and also most of the time they are busy with heinous crime control laws, so it is challenging to move the court for tobacco control many times. Moreover the Ministry of Health does not have any Executive Magistrate specific for the enforcement of tobacco control law.

Intervention: National Tobacco Control Cell (NTCC), Ministry of Health & Family Welfare has undertaken to conduct mobile court on tobacco control law throughout the country during October 2014-March 2015. In the district level the Executive Magistrates work under the supervision of Deputy Commissioner (DC) of the respective districts. As the DC is the chairperson of the taskforce committee for tobacco control in the district level, NTCC took the opportunity to use the platform of the committee and managed to convince the DC to undertake the program. NTCC has already trained 187 executive magistrates on the tobacco control law. Civil Surgeon of the respected districts organize at least two the mobile court during the period and send a report to NTCC. Mobile court has been conducted in all 64 districts of Bangladesh.

Results and lesson learned: Within these six months executive magistrates conducted 252 mobile courts throughout the country. They have fined 1279 persons and 68 organizations for violation of different provisions of the tobacco control law. The total amount collected as fine was 1 515 940 BDT (19 690 USD). Almost all mobile court could able to earn a number of media coverage, which has a multiple effect of the program. A vast public awareness has done through the activity.

Conclusion: Mobile court is a proven instrument for enforcement of the provisions of the tobacco control law in Bangladesh. One mobile court can earn a multiple effect as it attracts huge media coverage.

OA-325-04 Evaluation of the first national tobacco control mass media campaign in China

X Jin,¹ Y Zhang,¹ W Chen,² W Zhao,¹ J Song¹ ¹Chinese Center for Health Education, Beijing, ²World Lung Foundation, Beijing, China. e-mail: yaya22nd@hotmail.com

Background: Tobacco use is the leading preventable cause of morbidity and mortality worldwide, yet the usage rate continues to increase in low- and middle-income countries (LMICs) such as China. Of over 1.3 billion smokers in the world, about one-third (360 million) lives in China, which accounts for 28% of the general population. In 2009, it was estimated that approximate 72% of nonsmokers in China were exposed to secondhand smoking (SHS), which was much higher than the worldwide average level (40% of children, 35% of women, and 33% of men). As a result, tobacco control in China has recently has garnered domestic and international interests for the diffusion of evidence-based policies and programs into the country to forestall the impending tobacco-induced epidemic. In 2013, the WLF collaborated with the Chinese Center for Health Education (CCHE), a national branch of the Chinese Ministry of Health (MOH), to implement the first national tobacco control mass media campaign in China. The campaign was expected to improve knowledge about health effects of smoking and SHS exposure and shape attitudes and behaviors toward tobacco control policies, particularly SFPs. Objective: To evaluate the effectiveness of the first national tobacco control mass media campaign piloted by Bloomberg Global Initiative, World Lung Foundation and Chinese Center for Health Education in 2013.

Methods: The campaign was adapted from materials originally produced in the UK, which depicts a hospital environment with secondhand smoke (SHS) to show how it affects everyone. It was broadcast on two national Television channels and seven provincial satellite networks for a 4-week period. A total of 3000 participants were selected to complete interviews through a stratified random sampling from ten provinces. The participants consisted of 1509 (50.3%) males and 1491 (49.7) females, 1161 (38.7%) smokers, and 1839 (61.3%) non-smokers.

Results: The campaign reached about 24% of the Chinese population and increased smokers' knowledge about the harmful effects of SHS exposure for non-smokers (57.4% vs. 68.5%, $P < 0.05$). Both smokers and non-smokers increased their knowledge that smoking leads to diseases other than lung cancer (Table). Although smokers exposed to the campaign were more likely to take actions to reduce smoking than those not exposed (17% vs. 8%, $P < 0.05$), the percentage was still low. The support for bans on smoking in public places increased after the campaign, especially among non-smokers and females. However, the support for bans on smoking in bars (43%) and restaurants (56%) were much lower than for bans in hospitals (97%), schools (96%), and public transport (89%).

Conclusions: The mass media campaign reinforced people's knowledge and attitudes about harmful health

effects of smoking and SHS exposure, increased people's desire to quit, and improved people's support for smoking bans in public places. Therefore, policymakers and the public health communities should dedicate more resources for health related mass media campaigns (Table).

Table Effects of mass media campaign exposure on knowledge, behaviors, and attitudes among smokers and non-smokers ($n = 3000$)

	No exposure ($n = 500$) %	Exposure ($n = 165$) %
Smoker[†]		
SHS leads to serious illnesses of important vital organ in non-smokers [†]	57.4	68.5
Smoking leads to lung diseases other than cancer [†]	74.2	81.2
Non-smoker[†]		
Smoking leads to lung diseases other than cancer [†]	74.2	81.2
SHS leads to lung cancer in non-smokers [†]	74.6	80.6

* Model adjusted for TVC exposure, number of cigarettes smoked, intention to quit, age, sex, education, weekly TV viewing, weekly surfing on computer, weekly surfing on mobile phone.

[†]Significant at $P < 0.05$.

[‡] Model adjusted for TVC exposure, age, sex, education, weekly TV viewing, weekly surfing on computer, weekly surfing on mobile phone.

OA-326-04 Review of the Global Adult Tobacco Survey, India, 2010: recommendations for the next round 2015–2016

G Chauhan¹ ¹Postgraduate Institute of Medical Education & Research, Chandigarh, India. e-mail: dr.ankursangwan@gmail.com

Background: The tobacco epidemic is currently a major cause of preventable disease and deaths globally, claiming the lives of nearly six million people a year, killing nearly half of the users. GATS (Global Adult Tobacco Survey) are monitoring process in response to WHO FCTC (Framework Convention on Tobacco Control) to track Tobacco Control indicators like tobacco prevalence (smoking and smokeless), exposure to second hand smoke, cessation, knowledge attitude and perceptions that are critical for control and policy development. As second round of GATS is proposed in 2015-16 it is high time to address the limitations and take suitable remedial actions for further improvements to quality of data.

Design/Methods: GATS 2009-10 has been analyzed and discussed with the researchers of PGIMER Chandigarh and implementers within the research framework including the objectives, indicators chosen, methodology, population and sample size, sampling method, study tool used, quality assurance and data analysis. The study tool was discussed with respect to questions which should be added, deleted or modified in order to improve response and data quality.

Results: Stratification of the population on basis of socio-economic status has not been included in GATS to

provide better understanding of its association with tobacco use. The inclusion criteria has not been expanded to include institutionalized people (i.e. residential, school and college students, army personnel etc), internally displaced persons, refugees and migrant population as they are more vulnerable to tobacco use. The reasons for initiation and continuation use, knowledge of people regarding provisions of COTPA, 2003, place for storage/disposal of tobacco products is missing. **Conclusion:** As India prepares for next GATS in 2015-16 it is pertinent to remove flaws identified in the prior round so as to make more efficient and effective tool for policy makers. As prevalence is not an appropriate indicator to measure tobacco burden due to influence of factors such as increase in life span/better cure/ diagnostics etc. Therefore incidence of tobacco use needs to be incorporated to reveal the desired impact of policy implementation.

OA-327-04 Making a tertiary health care institution a model tobacco-free educational institution: a case study from the Indira Gandhi Medical College in Shimla, India

R Chand¹ ¹Indira Gandhi Medical College, Shimla, India. e-mail: dr.rameshigmc@gmail.com

Background and challenges to implementation: Indira Gandhi Medical College and Hospital (IGMC) Shimla in Himachal Pradesh is one of the largest and oldest teaching institutions in Northern India having 872 bed strengths and more than 1200 daily OPD registration. One fifth of adults in the state are tobacco users. Indian tobacco control legislation (COTPA) bans smoking in public places and sale of tobacco products in and around an educational institution; however the implementation has been sub-optimal. The present case study enumerates the steps taken by the department of hospital administration to make IGMC- a model tobacco free educational institution.

Intervention or response: A high level institutional core committee for tobacco control was constituted. A strategic and comprehensive action plan was formulated. Department wise nodal officers were notified to ensure enforcement in respective departments and buildings. Circular was shared to all departments, students and employees association to comply with the law. Signages as specified under the law were displayed at all prominent places in campus. Several boards having anti-tobacco messages were displayed across the hospital campus, walls and also on OPD siip. Strict law enforcement was ensured, till date more than 300 violators has been punished and fine amount of Rs 54630/- has been collected.

Results and lessons learnt: There is an overwhelmingly positive response from all sections of peoples, employees, students, patients and visitors. The smoking has been literally banned throughout the campus. Department of hospital administration is doing regular monitoring of enforcement activities. The number of people seeking tobacco cessation services in the TCC is increased; from

January 1, 2014 till date 277 persons has seeked help from TCC to quit tobacco. There is no tobacco selling shop inside and within 100 yards of the premise. The institute qualifies for the model tobacco free educational institution.

Conclusions and key recommendations: IGMC and associated hospitals becomes a model for tobacco free educational institution in India demonstrating successful implementation of tobacco control policies. Other tertiary care health institutions and teaching hospitals in India or in similar settings in other countries can also be made tobacco free educational institutions.

OA-328-04 Building capacity for tobacco-free schools in Rural Maharashtra: the Salaam Mumbai model

D Patil,¹ D Chadha¹ ¹Salaam Bombay Foundation, Mumbai, India. e-mail: deepak.patil@salaambombay.org

Background and challenges to implementation: Tobacco is a significant public health risk faced by youth in rural India. In rural Maharashtra, as many as 45.4% of youth use tobacco. Tobacco use is commonly seen on school grounds across the state. India's tobacco control law, the Cigarettes and Other Tobacco Products Act (2003), imposes restrictions on the use of tobacco on school campuses and prohibits the sale of tobacco within 100 yards of school grounds.

Intervention or response: In 2008 the Salaam Bombay Foundation began a tobacco-free schools initiative in rural Maharashtra. Awareness meetings were held with the Direct of State Education and District Education Officers to build motivation to promote the tobacco-free schools programme. District-level workshops were held with Master Trainers for the Education Ministry. Master Trainers included training on tobacco-free schools as part of their regular training curriculum. Once trained, teachers conducted tobacco control initiatives with students. Steps were taken by teachers, students and administrators to meet the CBSC criteria. Salaam Bombay Foundation rewards schools for reaching levels of compliance with the criteria created by SBF in accordance with a education board. Bronze-level awards are given to schools reaching 4 out of 11 criteria. Silver-level awards are given to schools reaching 8 criteria. Gold-level awards are provided to school reaching all 11 criteria.

Results and lessons learnt: To date, 124 schools have reached the Bronze level of compliance, 56 schools have reached the Silver level, and 27 schools have reached the Gold level of compliance (full compliance with CBSC criteria).

Conclusions and key recommendations: Using the existing infrastructure of Maharashtra's rural teacher training programme has been a successful and efficient strategy for increasing compliance with tobacco-free schools criteria. Using a graded system to reward schools provides an incentive for schools to expand compliance and serves as a useful tool for measuring increases in compliance over time.

OA-329-04 Using litigation to protect and promote lung health

K Hashmi¹ ¹Society for Alternative Media and Research, Islamabad, Pakistan. e-mail: hashmi@ctcpak.org

Background and challenges: Tobacco use is chronic to lung health and Shisha affects direly. Shisha came to Pakistan in 2000 and in a decade's period, it became a profitable industry. Shisha cafes owners spent millions on their café's and ambiance attracted even non-smoker including youth to use shisha for fun. This perception attracted all age groups and families. In March 2011, the Government of Pakistan realizing the threat ordered crackdowns against Shisha Café's and take legal action in the light of Tobacco Control Law in Pakistan. Shisha cafes owners challenged the actions of authorities to court, filing different cases and alleging that law enforcement agencies action are 'malafide' and not be in the interest of public health.

Intervention or response: Assessing the environment, Society for Alternative Media and Research (SAMAR) to support Ministry of Health through a writ petition became a party in the cases. Over the period of four years, provided the court with facts on shisha as a tobacco product and relevant laws. SAMAR also did a mapping on shisha cafes, gathered evidence on breach of laws by visiting different cafes in different cities, taking photographic and other evidences to present in the court. The court dismissed this Petition and others and accepted SAMAR's Writ Petition No. 25011/2011 in a single order enforcement authorities to strictly enforce that Ordinance which is being be monitored by Provincial Home Department. Furthermore, the Court vide a reported Judgment ordered that smoking, including shisha, was ban in any public place, also declaring open spaces of restaurants a part of restaurant covered by the definition, hence, none allowed to smoke in any public place collectively.

Results and lessons learnt: Litigation is an important tool to promote lung health. Civil society is an important component of civil cases. During the 4 years period since 2010, all eight cases related to shisha were were dismissed/disposed in favor of tobacco control marking a 100% success rate. The litigation precedent in one province, set an example for other provinces to follow (Pakistan has four provinces). One province, Balochistan, also banned shisha products while other, Sindh province, is in process of enforcing tobacco control laws on shisha as well where SAMAR will be utilizing this experience.

Conclusions and key recommendations: Litigation can be a successful tool for promoting lung health by making other forms of tobacco more coherent with the laws.

OA-330-04 Population-level tobacco control communication program 'best buys' to support the changing public health landscape in low- and middle-income countries

T Turk,¹ N Murukutla,¹ S Mullin¹ ¹World Lung Foundation, New York, NY, USA. Fax: (+1) 212 542 8871. e-mail: tturk@worldlungfoundation.org

Background: WHO has identified the need for policy makers making investments in order to tackle risk factors for non-communicable diseases (NCDs), to assess interventions based on their: i) health impact; ii) cost-effectiveness; iii) cost of implementation; and iv) feasibility of scale-up, particularly in resource constrained settings. One of the four interventions identified by WHO as a "best buy" is a component of the MPOWER package designed to 'Warn about the dangers of tobacco use'. These include hard-hitting, population level, tobacco control campaigns, delivered through mass media delivery channels. The concept of best buys for tobacco control is explored through operational outcome surveys recently conducted in a number of LMIC settings.

Design/Methods: National, cross sectional post-intervention knowledge, attitude and behavioural (KAB) surveys of tobacco users were implemented in a number of LMIC settings following tobacco control communication campaigns. Key performance indicators included audience recall of campaign messages, and changes in knowledge and attitudes toward tobacco use including; personal risk perceptions, self-efficacy perceptions and behavioural intentions. Additionally, tobacco users were assessed according to the number of cessation attempts of 'campaign aware' vs. 'campaign unaware' audience segments as well as assessment of average cost per cessation attempt.

Results: Findings across LMIC settings identified generally high recall of the campaigns by both urban and rural audiences, with significant differences (<.95%) by campaign aware respondents in relation to a number of KAB indicators. Tens of millions of tobacco users made a quit attempt as a result of the campaigns at very low cost (less than 1 cent) per cessation attempt. Furthermore, campaign aware audience attitudes supported strengthened tobacco control policy initiatives. Following advocacy of findings, governments were more fully engaged in campaign implementation through the provision of matched funding and institutionalisation of approaches for tobacco and other NCD risk factors.

Conclusion: Best practice, population level, communication campaigns for tobacco control demonstrate through compelling evidence that they are interventions that can have significant public health impact and be highly cost-effective, inexpensive and feasible to implement in resource constrained settings of LMICs. Hard hitting communication campaigns warning about the harms of tobacco can be particularly cost-effective and provide best buys in highly populated LMICs, as a result of rapidly emerging media networks, relatively low-cost media rates and more fully engaged viewing audiences. Findings point to the need to urgently scale up mass

communication campaign activities to reduce the burden of tobacco related diseases in LMICs.

OA-331-04 Cost-effectiveness of tobacco control mass media campaigns in LMICs

N Murukutla,¹ T Turk,¹ N Negi,¹ S Mullin¹ ¹World Lung Foundation, New York, NY, USA. Fax: (+1) 212 542 8871. e-mail: nmurukutla@worldlungfoundation.org

Background: Tobacco consumption is a significant risk factor for non-communicable diseases, including lung diseases, that together are estimated to cost low- and middle-income countries (LMICs) close to 7 trillion USD in health care costs. Scalable and cost-effective strategies for tobacco control are therefore a critical public health priority. Population level mass media campaigns for tobacco control have been proven to reduce consumption and prevent tobacco uptake. To date however the cost-effectiveness and the return on investment of this approach has not been established in LMICs. Four recent tobacco control mass media campaigns in China, India, Senegal and Vietnam were studied for their cost-effectiveness.

Design/Methods: Household survey data measuring campaign impact was combined with campaign expenditure data to identify costs associated with campaign-attributable changes in knowledge, attitudes and behaviors. Logistic regression models, controlling for confounders, calculated differences between campaign aware and unaware respondents, and through extrapolation, the numbers of individuals in the populations reflecting campaign-attributable changes in knowledge, attitudes and behaviors. Sensitivity analyses with success rates ranging from 10 - 100% were performed for each outcome. Cost-effectiveness ratios were then calculated.

Results: Campaign awareness was associated with improved campaign-related knowledge in 7 million Chinese, 16 million Indians, 247 000 Senegalese, and 1 million Vietnamese. The cost per person to improve knowledge (at 50% campaign attributable) was lowest in India at US\$0.12 and highest in Senegal at US\$1.7. Campaign awareness was associated with increased quit attempts among 29 million Indian SLT tobacco users, 4 million Chinese, and 680 000 Vietnamese smokers, with costs per person (50% attributable) at US\$0.07, \$0.21, and US\$0.56 respectively, testifying to the relatively good returns on campaign budget expenditures. Return on investment in terms of life years saved will be presented.

Conclusion: This study highlights the large reach and cost-effectiveness of mass media campaigns in LMICs. Opportunities for future programme practice indicate that the rapid uptake of mass media such as television and social media, coupled with the more active viewing of television content by new adopters, provides an important and cost-effective channel of communication for behaviour change in LMICs.

05. Financing TB services

OA-332-04 'Value for money': it costs US\$ 90 to identify a TB patient in a community setting, India

M Rout,¹ P Banuru Muralidhara,¹ T Palorkar,¹ A Das,¹ B Entoor Ramachandran,¹ B Thapa¹ ¹The International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 114 605 4430. e-mail: bmprasad@theunion.org

Background: END-TB strategy is focused at community taking onus of Tuberculosis, prevention and care. Globally, many programmes are designed towards sensitizing and engaging community members. The Global Fund supported grant in Project Axshya in India adopted a strategy to engage community members through locally available Non-Government Organizations (NGOs) who are known in community for their other social-development including health. The activities of project were so designed that the organizations utilized the available resources for a maximum output in line with Global Fund – "Value for Money".

Intervention or response: NGOs (4 to 5) were identified in each of 300 districts of Project Axshya through sub-recipient partners. Members and volunteer of these organizations were trained on Tuberculosis to implement project activities. The activities/package included, (a) community meetings (b) mid-media activities (c) active case finding (d) tracking of referrals and sputum collection and transportation (SCT) and (e) retrieval of patients who lost to follow-up of the treatment. Rural Health Care Providers (RHCP) were also trained and engaged within community to identify presumptive TB person and provide diagnosis and treatment through DOTS.

Results and lessons learnt: Over 1200 NGOs, 10 000 volunteers and 19 000 RHCPs were identified and trained through the project. With the involvement of community, the project could offer package of TB services to 23 million populations during April 2013 to December 2014. Average cost for reaching one person is only US\$ 0.16. Through community intervention a total of 496 083 presumptive TB persons were identified and undergone diagnosis for TB and out of that 41 257 persons identified as having TB and >90% of them are on DOTS. 76% of the presumptive TB persons were provided sputum collection and transportation service. Around 3.8 million USD was incurred as expenditure for these activities, at an average cost US\$ 7.62 per presumptive TB patient identified and US\$ 91.6 per person identified as having TB.

Conclusions and key recommendations: This intervention has demonstrated that it costs ≈90 US\$ per person identified as having TB. It is worthwhile to interpret the amount spent not only at identifying TB patients but also efforts that were put forward towards generating awareness about TB in community. This community driven model could be expanded to reach the goal of END-TB strategy.

Table Cost per person identified as having TB in Project Axshya

Sl no	Indicator	Total
1	Number of TB presumptive referred for sputum examination in the reporting quarter	118,826
2	Sputum collected and Transported of presumptive TB person identified	377,257
3	Total presumptive TB person identified	496,083
4	Among presumptive TB person identified, number person identified as having TB	41,257
5	Overall Expenditures	US\$ 3,772,523
6	Cost per presumptive TB person identified	US\$ 8
7	Cost per TB patient identified	US\$ 91

OA-333-04 Assessment of costs related to community-based DOTS services: the FHI360/ TB CARE I experience in Mozambique

A Mataruse,¹ P Posse,² I Manhiça,³ S Machevo Chilundo,¹ Z Cuna,¹ A Abdula,¹ C Juliana,¹ E Oliveras¹ ¹FHI360 Mozambique, Maputo, ²Independent Consultant, Maputo, ³Mozambique National TB Control Program, Maputo, Mozambique. e-mail: amataruse@fhi360.org

Background: Community Based Direct Observed Treatment (CB-DOTs) is effective at improving presumptive case identification, referral to health services, diagnosis and treatment support. In Mozambique, CB-DOTs has been implemented since 2006, with more than 60 of 128 districts covered by 2012. A variety of CB-DOTS models have been used by the local NGOs implementing the strategy. Globally, evidence shows that CB-DOTs is more cost effective than health facility-administered TB control services with studies in Uganda, South Africa and Brazil showing cost savings. Evidence on cost-effectiveness in Mozambique is needed to ensure support for CB-DOTs and information on the relative cost effectiveness of different models is needed to determine how best to implement CB-DOTs. A cost-effectiveness analysis of NGOs implementing CB-DOTs was conducted in 2014

Design/Methods: Retrospective cost and results data were collected from 9 CB-DOTs NGOs for the period October 2011 to September 2013. An ingredients approach was used. Costs of personnel, supplies and equipment, training, and transport were captured. FHI360 and health facility costs were excluded. Costs were analyzed by component of care: identification, referral and follow-up of treatment. Costs were adjusted for inflation to 2013 and compared using the Incremental Cost Effectiveness Ratio (ICER). The ICER calculations were based on differences between costs per NGO divided by results. ICER was then compared to a gross domestic product. Cost-effectiveness was compared using the treatment success rate which is the sum of the completed treatment and cure rates

Results: The total average cost per patient to successfully complete TB treatment was US\$701, ranging from \$204 to \$1833 per partner. Both costs and efficacy varied widely across the NGOs. The costs per component of care were roughly equally distributed. The leading

contributors to costs were personnel (37%) and equipment (26%), though these too varied widely by NGO. With the exception of 2 partners who did not supply non-monetary incentives to volunteers, the cost per volunteer averaged \$134

Conclusion: The average cost of \$701 to successfully treat a TB patient is consistent with findings from other countries although it is twice the \$350/case threshold set by TB REACH. Given the range of cost-effectiveness, further analysis is needed to fully understand the factors that affect cost-effectiveness in the Mozambican context in order to guide CB-DOTs implementation.

OA-334-04 MDR-TB cost minimization study in Nigeria

B Musa,¹ A Kuznik,² A Habib¹ ¹Bayero University Kano, Kano, Nigeria; ²CELGENE, Warren, NJ, USA. e-mail: babamaiyaki2000@yahoo.co.uk

Background: In Nigeria, patients with multi drug resistant tuberculosis (MDR-TB) are treated in hospital facilities. However, the World Health Organization (WHO) also recommends home based treatment as a viable alternative. We compared the cost of facility (F) based MDR-TB care to home (H) based care from the perspective of the Nigerian national health system.

Design/Methods: We assessed the expected costs of the two MDR-TB treatment approaches using a decision-analytic model with a follow-up of 2 years. MDR-TB treatment outcomes were obtained from a systematic review of randomized clinical trials. The outcomes of interest included treatment success, treatment failure, treatment default, and mortality, and did not vary significantly between the two alternatives. Treatment costs included the cost of: drug therapy (F, H), hospital stay (F), nurse care (F, H), physician care (F), nursing facility (F), and transport to the health care provider (H). Finally, we estimate the potential cost savings associated with home based treatment for all patients starting MDR-TB treatment in Nigeria.

Results: The average expected total treatment cost for a Nigerian patient treated for MDR TB was estimated at US\$ 2957 based on the facility based model and \$1480 based on the home based care model, a potential saving of 50%. One of the major drivers of this difference is the significantly more intensive, and therefore more costly, nurse care in the hospital facility. In the year 2013, a total of 426 patients were initiated on facility based MDR TB treatment in Nigeria, thus, the potential savings associated with implementation of home based care is estimated at US\$ 629 202 per year.

Conclusion: In Nigeria, treatment of MDR TB using home based care is expected to result in similar patient outcomes at markedly reduced public health costs compared with facility based care.

OA-335-04 Post-diagnosis costs for patients living with TB and HIV and their households in South Africa

D Mudzengi,¹ S Sweeney,² T Kufa,^{1,3} P Hippner,¹ S Charalambous,^{1,2,3} A Grant,² G Churchyard,^{1,3}

A Vassall² ¹The Aurum Institute, Johannesburg, South Africa;

²London School of Hygiene & Tropical Medicine, London, UK;

³University of the Witwatersrand, Johannesburg, South Africa. e-mail: dmudzengi@auruminstitute.org

Background: The World Health Organization (WHO) has a new post-2015 strategy which aims to eliminate catastrophic costs for TB patients. In South Africa, TB affects the poorest; and many of those already suffering the economic hardship due to HIV. Previous studies, from other settings, suggest that the experience of the TB patient immediately post-diagnosis can cause considerable economic distress, particularly for those who are HIV positive. This study investigates the costs incurred by people being treated for TB, HIV and both conditions combined in South Africa.

Methods: This study focused on the post-diagnostic costs incurred by TB and HIV patients attending 18 primary health care clinics in the Ekurhuleni North sub-district, Gauteng, South Africa. The clinics were participating in a cluster randomised trial to evaluate a TB-HIV integration intervention. Data on direct and indirect patients' post-diagnosis costs were collected using structured questionnaires administered to trial participants within 6 months after HIV diagnosis or starting TB treatment. Data were captured in an electronic database and analysed in Microsoft Excel.

Results: The study enrolled 463 participants; 25% with TB and HIV combined, 11% with only TB and 65% with only HIV. Mean monthly post-diagnosis costs were highest for TB-HIV patients (\$118.23) when compared with TB only (\$83.58) and HIV only (\$45.82). While out-of-pocket expenses were high, income lost through job changes or missed work was also substantial, as patients felt unwell and/or sought care. Indirect costs accounted for 41% of TB-HIV, 46% of TB and 34% of HIV only; total costs.

Conclusion: Costs incurred by TB patients after diagnosis are often catastrophic, and are substantially higher for those co-infected with HIV, given the complex post-diagnosis trajectory. Better integration of care and social support to address both out-of pocket expenditure and income loss to this, most vulnerable group, is urgently required in South Africa; and elsewhere if global targets are to be met.

OA-336-04 Economic cost of patient centred tuberculosis treatment in Tanzania

A Mkopi,¹ F Van Leth,² N Range,³ F Lwilla,¹ S M Egwaga,⁴ A Schulze,⁵ E. Geubbels¹ ¹Ifakara Health Institute, Dar Es Salaam, Tanzania; ²University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; ³National Institute for Medical Research, Dar Es Salaam; ⁴National Tuberculosis and Leprosy Programme, Ministry of Health and Social Welfare, Dar Es Salaam, Tanzania; ⁵Swiss Agency for Development and Cooperation, Berne, Switzerland. Fax: (+255) 23 262 5312. e-mail: abdallah.mkopi@gmail.com

Background: In 2006, the National Tuberculosis and Leprosy Programme (NTLP) of Tanzania introduced a strategy known as Patient Centred Tuberculosis Treatment (PCT). We estimated the economic costs per HB-DOT patient treated under the PCT strategy in Tanzania from a societal perspective and compared this to a hypothetical scenario of health facility-based DOT (HF-DOT).

Design/Methods: This cross sectional study in one urban and two rural districts measured TB service delivery costs and both direct and indirect patient / treatment supporter costs using WHO guidelines. We used structured questionnaires to collect the required information.

Intervention: Patient Centred Tuberculosis Treatment (PCT); newly diagnosed patients are given the opportunity to choose either home-based DOT (HB-DOT) supervised by a non-medical person of their preference, or health facility-based DOT (HF-DOT) observed by a health worker.

Results: Average direct costs amounted to US\$4.8 and US\$5.2 per visit for a patient and a treatment supporter respectively. Indirect costs related to treatment or support were US\$61.0 and US\$57.5 per month for a patient and a treatment supporter respectively. Total economic costs for treating a new HB-DOT patient under the PCT strategy was US\$901.7, compared with US\$1211.1 for treating a new HF-DOT patient. Total costs incurred by patients and treatment supporters were higher than service delivery costs for the health system and NTLP.

Conclusion: The present study shows that compared to conventional DOT strategies, the PCT strategy is relatively less costly in terms of both service delivery costs and personal costs incurred by patients and treatment supporters. However, even under the PCT strategy the bulk of the economic burden is carried by TB patients and their treatment supporters. Therefore, intervention strategies to further reduce the costs to patients and treatment supporters are highly needed

OA-337-04 Cost of TB diagnosis and treatment packages in Viet Nam: estimates and projections, 2015–2020

K Vu Duy,¹ M Hoang Van,¹ H K Pham² ¹Hanoi Medical University, Hanoi; ²World Health Organization in Viet Nam, Hanoi, Viet Nam. e-mail: vuduykien@gmail.com

Background: Moving towards a sustainable financing mechanism for TB is reflected in the National TB

Strategy 2014-2020, vision 2030 approved by the Government in March 2014. In order to inform the policy to support the TB program, we conducted this costing study for TB diagnosis and treatment packages in Viet Nam.

Design/Methods: The costs of providing tuberculosis diagnosis and treatment packages in this study were estimated from the provider perspective. We considered different factors that impacted on the costs such as age group, types of TB, type of TB services and health facility levels. 1) To estimate the costs of providing TB diagnosis and treatment packages in Viet Nam, and 2) To project a needed annual budget for the TB programme in Vietnam during 2015-2020.

Results: At national level, the unit costs of diagnosis and treatment for a pulmonary TB AFB(+) ranged 97.2-171.1 US\$, a pulmonary AFB(-) ranged 158.7-272.7 US\$ and a extra-pulmonary TB case ranged 107.3-148.3 US\$. The unit costs for diagnosis and treatment of a MDR-TB case were very high for both children (ranged 1211.2-1580.2 US\$) and adults (ranged 1474.1-1849.6 US\$) at national level. At provincial level, the costs of diagnosis and treatment for a pulmonary TB AFB(-) ranged 92.8-157.9 US\$, for a pulmonary AFB(+) ranged 152.9-237.2 US\$, for a extra-pulmonary TB case ranged 98.7-130.7 US\$, and for a MDR TB case ranged 1202.8-1819.6 US\$. At district level, the costs of diagnosis and treatment for a pulmonary TB AFB(-) ranged 122.1-162.3 US\$, for a pulmonary AFB(+) ranged 51.2-101.7 US\$, for a extra-pulmonary TB case ranged 53.1-118.2 US\$, and for a MDR TB case ranged 1568.2-2391.2 US\$. The annual budget needed for TB program was about 15-19.8 million US\$ in 2015, then increased about 21-29.8 million US\$ in 2020. The annual revenue of the Health Insurance (HI) Fund in Vietnam is about 1.85 billion US\$. This budget is equal to about 1 % of the annual revenue of the HI fund.

Conclusion: This study provides the cost estimation for TB diagnosis and treatment in Viet Nam 2015-2020. As the donor exit policies in the coming time, TB diagnosis and treatment should be covered under Health Insurance programme in order to maintain the crucial TB services for Vietnamese.

OA-338-04 TB-related dissaving was common and correlated with incurring catastrophic costs in TB-affected households in Peruvian shantytowns

T Wingfield,^{1,2,3} M Tovar,^{1,4} D Huff,^{1,5} J Lewis,^{1,6} R Montoya,¹ D Boccia,^{1,6} C Evans^{1,2,4} ¹Asociación Benéfica PRISMA, Lima, Peru; ²Imperial College London, London; ³North Manchester General Hospital, Manchester, UK; ⁴Universidad Peruana Cayetano Heredia, Lima, Peru; ⁵Tulane University, New Orleans, LA, USA; ⁶London School of Hygiene & Tropical Medicine, London, UK. e-mail: tom.wingfield@ifhad.org

Background: The World Health Organization's (WHO) post-2015 global TB control policy states that no TB-affected family should incur catastrophic costs. However, measuring catastrophic costs may be operationally

difficult for National TB Programs. Dissaving is a proxy measure of financial shock but its correlation with catastrophic costs is not yet known and is a priority research question for the WHO Global TB Programme Task Force. We aimed to evaluate the association of TB-related dissaving with catastrophic costs to inform post-2015 TB control policy.

Methods: Consecutive TB patients diagnosed by the Peruvian National TB Program in 32 contiguous shantytown communities of north Lima, Peru, were invited to participate in the study. Patient households' total TB-related costs (lost income plus direct out-of-pocket expenditure) and dissaving variables (Figure) were recorded throughout treatment. A composite dissaving index in arbitrary units was derived by principal component analysis (PCA) from all dissaving variables. Catastrophic costs were defined as total costs of $\geq 20\%$ of the annual income of the same household, as previously defined in the study setting.

Results: 312 TB patients were invited to participate, of whom 282 were recruited and had costs and dissaving data available for analysis. The specific dissaving variables that best explained the PCA-derived dissaving score in this setting were: missing scheduled payments, starting a new job, selling or pawning household items, undertaking small scale fundraising activities, and being asked to eat elsewhere. Patients with greater than average dissaving were significantly more likely to: incur catastrophic costs, be poorer, have a lower education level, to have greater food insecurity, and have longer symptom duration prior to diagnosis (Figure). There was a significant positive correlation between increasing total costs as a proportion of annual income and dissaving score (Spearman's correlation coefficient 0.26, $P < 0.0001$).

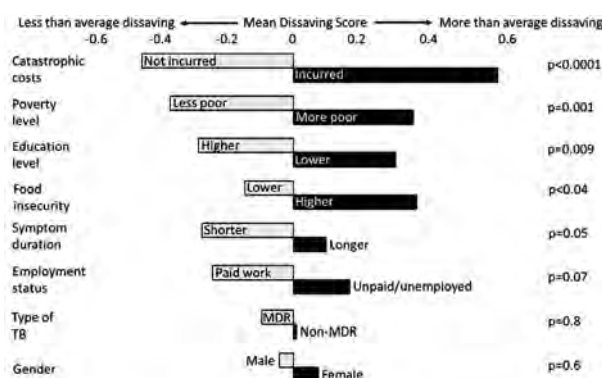


Figure: TB-related dissaving score by socioeconomic and health variables. The dissaving score is measured as a continuous variable in arbitrary units with the overall dissaving score of the patient cohort being 0 units. P values represent the association of dissaving score with each variable by Student's T test. These results followed a similar pattern of significance in univariable linear regression with the dissaving score as the dependent variable. On multiple regression analysis with stepwise exclusion of non-significant variables, only incurring catastrophic costs (OR 2.4 [95%CI=1.4-4.0]) and being poorer (OR 1.8 [95%CI=1.1-3.0]) remained associated with greater than average dissaving. The dissaving variables that contributed to the score were household members; leaving education, using savings, taking out a loan (be it formal or informal), taking a new job, taking a second job, being asked to move out, being asked to eat elsewhere, selling household items, missing a scheduled payment, and undertaking small-scale fundraising activities due to TB (e.g. buying ingredients to prepare food that will then be sold to friends, family, colleagues, and others for a small profit).

Conclusions: In this setting, dissaving was associated with incurring greater and catastrophic costs, and belonging to more vulnerable patient households. This

evidence supports the use of dissaving variables and/or a dissaving score as a proxy for catastrophic costs that may be adapted to local settings.

OA-339-04 Are TB patients in Republic of Macedonia at risk for catastrophic health expenditures? Results of a cross sectional-study

D Gudeva Nikovska,¹ F Tozija^{1,2} ¹Faculty of Medicine, University SS Cyril and Methodius, Skopje, ²National Institute of Public Health, Skopje, Macedonia, Yugoslav Republic. Fax: (+389) 2317 7983. e-mail: dgnikovs.ka@gmail.com

Background: Republic of Macedonia (RM) has developed a comprehensive TB control program over the past decade, funded by both Governmental funds and more comprehensively with the generous funding from Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria (GFATM) since 2006. In turn, this is reflected in the incidence numbers, showing that TB is on constant decrease and reaching the MDG#6 (with incidence of 25.9/100 000 in 2006 to 15.2/100 000 in 2014, that classifies RM as low incidence country). TB diagnostics, treatment and follow-up is free of charge for all population, regardless of the insurance status. However, not all the population benefitted from implementation of activities, the highest rates still being notified in the north-west part of the country and in certain ethnic groups, mostly affecting the age group 25-54.

Design/Methods: Nested case-control study was conducted on a sample of 605 households (HH); face-to-face interviews were conducted, using selected modules from World Health Survey questionnaire. Cases are TB patients registered Jul, 2012 – Jun, 2013 ($n = 315$) and controls HH in their neighborhood ($n = 290$). Data were analyzed with SPSS 19.0, utilizing logistic regression to measure predictive value of most important SDH.

Results: Analyzed by groups of respondents, the mean value of costs for treatment were higher in controls, with exception of costs for transport that are significantly higher in TB cases ($t = 6.548$, $df = 483$, $P < 0.01$), which is most likely associated with the regional distribution of TB dispensaries around the country where TB patients seek care. Statistically significant differences are noted by place of residence, costs being higher among TB patients living in rural areas (t -test = -2.145 , $df = 125$, $P = 0.034$) and in the North-West region (t -test = 1.212 , $df = 7$, $P < 0.001$). Of particular importance is the share of costs for health care in TB patients in the total HH expenditures, amounting to 55-70%, a percentage that certainly implies catastrophic health expenditures for these HH that were already identified as of lower socio-economic status.

Conclusions: High share of expenditure on healthcare in the total HH expenditures, particularly among TB patients residing in rural areas implies not only catastrophic health expenditures, but also existence of certain degree of inequity in access for this socially disadvantaged population stratum. The findings needs further exploration of the underlying causes, particularly due to

the fact that treatment of TB is free of charge under provisions of the National TB control program, especially notified regional differences in expenditures that imply inequities in access to health care of certain vulnerable groups.

06. MDR-TB: trials, cohorts and predictors

OA-340-04 Bedaquiline prevents acquired resistance to second-line drugs

N Lounis,¹ A Diacon,² A Pym,³ B Van Baelen,¹ R Van Heeswijk,¹ M Haxaire-Theeuwes,¹ B Dannemann,⁴ K Andries¹ ¹Janssen Research and Development, Beerse, Belgium; ²Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, ³Medical Research Council and Kwazulu Research Institute for Tuberculosis and HIV, Durban, South Africa; ⁴Janssen-R&D, LLC, Titusville, NJ, USA. e-mail: nlounis@its.jnj.com

Background: Study C208/2 (NCT00449644) was a randomized, double-blind, placebo-controlled Phase II study where patients diagnosed with MDR-TB or pre-XDR-TB were treated for 24 weeks with bedaquiline (BDQ) or placebo, combined with a preferred MDR-TB background regimen (BR) consisting of ofloxacin (OFX), kanamycin (KM), pyrazinamide (PZA), ethionamide (ETO) and cycloserine followed by BR only for up to 18 more months. Treatment response defined as sustained culture conversion was assessed over 120 weeks. The role of BDQ in preventing acquired resistance to second-line drugs was assessed.

Methods: Drug susceptibility tests (DST) for OFX, KM, ETO, EMB, streptomycin (SM), capreomycin (CM), and para-aminosalicylic acid (PAS) were performed on 7H11 agar (proportion method) and for PZA in the MGIT960 system. The minimal inhibitory concentration (MIC) for BDQ was determined on 7H11 agar. Acquired resistance to a specific drug was defined as a change from susceptible at baseline to resistance at any post-baseline visit.

Results: In the final analysis, baseline and post-baseline DST results were available for 11 of the 66 mITT patients in the BDQ group and 30 of the 66 mITT patients in the placebo group. In the placebo group, 16/30 (53%) acquired resistance to at least 1 additional TB drug. Acquired resistance developed to OFX (7 out of 26 patients with a susceptible isolate at baseline), EMB (6/15), SM (1/5), PZA (2/11), ETO (2/27), KM (1/24), and CM (1/24). The response rate was 56% (7/16) in patients who acquired resistance and 79% (11/14) in patients who did not. Evolution towards pre-XDR or XDR-TB was observed in 8 of 66 (12%) patients: 6 progressed from MDR-TB to pre-XDR-TB and 2 from pre-XDR-TB to XDR-TB. In the BDQ group, 2/11 patients (18%, 1 responder, 1 non-responder) acquired resistance to at least 1 additional TB drug. Acquired resistance to SM was found in 1 patient out of 2. Acquired resistance to EMB and CM was identified in one additional patient (out of 4 and 8, respectively). A 4-fold increase in BDQ MIC due to a

mutation in Rv0678 gene occurred in 1 (failing patient) out of 10 with post-baseline isolates. None of the patients in the BDQ group progressed from MDR to pre-XDR-TB or from pre-XDR-TB to XDR-TB.

Conclusion: Despite the limited number of paired samples, addition of BDQ to the preferred MDR-TB background regimen decreased development of resistance and halted the progression from MDR-TB to pre-XDR-TB and from pre-XDR-TB to XDR-TB.

OA-341-04 Efflux-pump-mediated acquired resistance to bedaquiline in a clinical trial

K Andries,¹ N Coeck,² C Villellas,¹ B Van Baelen,¹ N Lounis,¹ L Rigouts,² B Dannemann,³ P Alexander⁴ ¹Janssen Research and Development, Beerse, ²Institute of Tropical Medicine, Antwerp, Belgium; ³Janssen-R&D, LLC, Titusville, NJ, USA; ⁴Medical Research Council and KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, South Africa. e-mail: kandries@its.jnj.com

Background: Study C209 was an open-label Phase II study where patients diagnosed with MDRH&R-TB, pre-XDR-TB or XDR-TB were treated with bedaquiline (BDQ) for 24 weeks combined with an individualised MDR-TB background regimen for up to 120 weeks. The majority had confirmed infection with an MDRH&R-TB strain (93/174 or 53.4%), with 44 (25.3%) and 37 (21.3%) infected with a pre-XDR-TB strain or XDR-TB strain, respectively.

Methods: Acquired resistance was defined as an at least 4-fold increase in BDQ MIC on 7H11 agar in any post-baseline isolate (week 24 or later), compared to the MIC of the corresponding baseline isolate.

Results: Twenty-four patients included in the efficacy analysis who received BDQ had paired isolates from baseline and from week 24 or later. Nineteen paired isolates were genotypically identical (by MIRU-VNTR) and 12 of these had ≥ 4 -fold increases in BDQ MIC. In all these 12 post-baseline isolates, mutations were identified in Rv0678. Mutations in this regulatory gene lead to overexpression of the MmpS5-MmpL5 efflux pump and 2- to 8- fold increases in BDQ MIC. When analysing the effect of MIC increases on treatment response, 5 of the 12 patients (41.7%) with ≥ 4 -fold increases in BDQ MIC were responders at endpoint, while 3 of the 7 patients (42.9%) with < 4 -fold increases in BDQ MIC were responders at endpoint (final analysis). When considering absolute values, 9 of the 12 patients with increased MICs had a post-baseline BDQ MIC of ≥ 0.25 $\mu\text{g/ml}$, and 3 had an MIC < 0.25 $\mu\text{g/ml}$. Nine of 13 patients (69.2%) with post-baseline BDQ MICs ≥ 0.25 $\mu\text{g/ml}$ were responders at endpoint, while 4 of 11 patients (36.4%) with post-baseline BDQ MICs < 0.25 $\mu\text{g/ml}$ were responders at endpoint. BDQ MIC increases occurred more frequently in XDR-TB patients (7/37, 19%) and pre-XDR-TB patients (4/44, 9%) than in MDRH&R-TB patients (1/93, 1%), and more frequently in patients with a background regimen interruption of at least 2 weeks (4/34, 12%) than in those without such interruption (8/140, 6%).

Conclusions: Having pre-XDR-TB or XDR-TB and treatment non-adherence increased the risk of acquired resistance to BDQ. Treatment of MDRH&R-TB patients involved less risk. However, no clear relationship was observed between this low-level, efflux-based acquired resistance to BDQ and treatment response (sputum culture conversion) at endpoint. Based on these data, increases in BDQ MICs due to mutations in Rv0678 may not necessarily translate into clinical resistance.

OA-342-04 Comparison of 2- and 6-month culture conversion as early predictors of multidrug-resistant TB treatment success: multicentre study of MSF programmes

M Bastard,¹ E Sanchez,¹ H Khamraev Atadjan,² Z Tigay,³ A Hayrapetyan,⁴ M Kamene Kimenya Mariita,⁵ S Khurkhumal,^{6,8} T Dlamini,⁷ F Varaine,⁹ M Bonnet^{1,10}

¹Epicentre, Paris, France; ²Tashkent Pediatric Medical Institute, Nukus, ³Chief Doctor of Republican TB Hospital, Nukus, Uzbekistan; ⁴National Tuberculosis Control Office, Yerevan, Armenia; ⁵Programmatic Management of Drug Resistant Tuberculosis, Nairobi, Kenya; ⁶National Tuberculosis Program, Soukumi, Georgia; ⁷Ministry of Health TB National Control Program National Manager, Mbanane, Swaziland; ⁸National Tuberculosis Program, Soukumi, Abkhazia, Georgia; ⁹Médecins Sans Frontières, Paris, ¹⁰Unité Mixte Internationale UMI233-U1175, Institute of Research for Development, Montpellier, France. e-mail: mathieu.bastard@geneva.msf.org

Background: An early treatment efficacy indicator for multi-drug resistant TB (MDR-TB) could lead to better treatment success through earlier treatment adaptation and potentially be in the evaluation of treatment efficacy. We evaluated the values of 2 and 6-month culture conversion to predict final treatment outcomes using data from seven MSF drug-resistant TB programs.

Methods: Confirmed MDR-TB patients starting treatment from 2001 to 2011 with available results on follow-up culture and a treatment outcome assigned were included in the study. Proportion of patients converted at month 2 and 6 of treatment was assessed and performances of these indicators to predict treatment success were assessed. We also fitted a random-intercept logistic model to adjust the estimates for potential confounders.

Results: A total of 1445 MDR-TB patients were included in this study: 57.1% male, median age of 32 years [IQR 24-42], 82.2% previously treated cases. Profiles of baseline resistance were as follow: 66.6% were resistant to H and R only, 31% had additional resistance to injectables or fluoroquinolones and 2.4% had both resistance to injectables and fluoroquinolones. A total of 319 (22.1%) and 709 (49.1%) patients converted at 2 and 6 months, respectively. Two-month culture conversion had a positive predicted value (PPV) of 75.5% (95%CI 70.5-80.2), sensitivity of 27.7% (95%CI 24.8-30.8) specificity of 86.5% (95%CI 83.4-89.1) and negative predicted value (NPV) of 44.2% (95%CI 41.3-47.2) against final treatment outcome. At

6 months, culture conversion had a PPV of 74.9% (95%CI 72.0-77.6), 81.6% (95%CI 78.8-84.1) sensitivity, 58.7% (95%CI 54.5-62.7) specificity and 67.9% (95%CI 63.6-72.0) NPV. These performances did not differ strongly by baseline resistance profiles. After adjustment on gender, age, body mass index, baseline resistance profile and being previously treated, culture conversion at month 2 and 6 remained a strong predictor of treatment success (aOR=2.22, 95%CI 1.65-2.98 and aOR=6.18, 95%CI 4.78-7.98, respectively). The association was even stronger when excluding defaulters.

Conclusions: Although 2 and 6 months culture conversion had similar PPV for treatment success, only 28% of patients who succeed treatment converted by 2 months compared to 82% at 6 months. The 6-month culture conversion is probably a better predictor of the final treatment outcome for MDR-TB. However, performances found in this study are substantially lower than those reported in literature.

OA-344-04 Subgroup analysis of patients receiving bedaquiline as part of a multidrug-resistant tuberculosis treatment regimen

A Pym,¹ A Diacon,² F Conradie,³ S Tang,⁴

B Van Baelen,⁵ N Lounis,⁵ M Haxaire-Theeuwes,⁵

B Dannemann⁶ ¹Medical Research Council and Kwazulu

Research Institute for TB and HIV (K-RITH), Durban,

²Division of Medical Physiology and the Department of Science and Technology/National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research and Medical Research Council Centre for Tuberculosis

Research, Cape Town, ³Clinical HIV Research Unit,

Department of Medicine, Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg, South

Africa; ⁴Tuberculosis Department, Beijing Chest Hospital,

Capital Medical University, Beijing Tuberculosis and Thoracic

Tumor Research Institute, Beijing, China; ⁵Janssen Infectious

Diseases BVBA, Beerse, Belgium; ⁶Janssen Research &

Development LLC, Titusville, NJ, USA. Fax: (+27) 31 203

4702. e-mail: alexanderpym@hotmail.com

Background: C209 was a Phase 2, open-label, single-arm trial (NCT00910871) of bedaquiline (BDQ) as part of an individualized background regimen (BR). The 120-wk sputum culture conversion rate (missing=failure) was 72% in 205 newly diagnosed or pre-treated adults with confirmed sputum-smear positive pulmonary MDR-TB, pre-extensively or extensively drug resistant (pre-XDR or XDR) TB. All patients (pts) received BDQ for 24 wks (400mg qd for 2 wks, 200mg tiw for 22 wks) with a BR according to WHO guidelines continued for up to 120 wks (final assessment).

Methods: Treatment response (sustained culture conversion at 120 wks) was investigated for subgroups according to baseline characteristics of individual patients (gender, age, race), disease severity (radiology, body mass index, serum albumin, time to culture positivity, smear grade), drug resistance (previous drug use, extent of resistance) and the BR received.

Table Sputum culture conversion rates at 120 wks

Subgroup	Responders* n/N (%)
Sex	
Male	94/132 (71)
Female	54/73 (74)
Age (years)	
18–45	115/160 (72)
>45–65	31/43 (72)
>65	2/2 (100)
Race [†]	
American Indian	5/6 (83)
Asian	70/84 (83)
Black/African American	39/67 (58)
White	34/48 (71)
Lung cavitations	
None or <2cm	57/70 (81)
≥2cm in one lung only	73/108 (68)
≥2cm in both lungs	18/27 (67)
Extent of resistance to <i>M. tuberculosis</i> strain	
MDR-TB [‡]	68/93 (73)
Pre-XDR-TB	31/44 (71)
Fluoroquinolone resistant	23/31 (74)
Second-line injectable [§] resistant	8/13 (62)
XDR-TB	23/37 (62)
Previous use of second-line drugs	
Newly diagnosed	23/28 (82)
Non-newly diagnosed	125/177 (71)
Background regimen at baseline	
Fluoroquinolones	127/180(71)
Pyrazinamide	108/152 (71)
Second-line injectable [§]	137/191 (72)
Linezolid	9/12 (75)
Baseline pyrazinamide susceptibility	
Susceptible	25/38 (66)
Resistant	96/135 (71)
Baseline albumin grade	
Grade 0	126/167 (75)
Grade 1	10/15 (67)
Grade 2	12/22 (55)
Grade 3	0/1 (0)
Baseline body mass index (kg/m ²)	
<18	35/49 (71)
≥18–<20	40/59 (68)
≥20–<25	57/77 (74)
≥25	16/20 (80)
Median time to positive signal in MGIT at baseline (days)	
≤10	49/72 (68)
>10	99/133 (74)
Baseline AFB score	
0	34/38 (90)
Scanty	44/60 (73)
1	32/42 (76)
2	22/34 (65)
3	16/31 (52)

*Responder = culture conversion.

[†]Race based on FDA template.[‡]Excluding pre-XDR-TB and XDR-TB;[§]Amikacin, kanamycin and capreomycin;

MDR-TB = multidrug-resistant TB; XDR-T = extensively drug-resistant TB; AFB = acid-fast bacilli.

Results: Overall, 45% of pts had MDR-TB, 22% pre-XDR-TB, 18% XDR-TB and in 15% with at least MDR-TB the extent of further resistance could not be determined. At baseline; 88% used fluoroquinolones

(49% ofloxacin; 32% levofloxacin), 78% ethionamide or prothionamide, 74% pyrazinamide, 74% aminoglycosides and 12 pts used linezolid (5 were pre-XDR and 4 XDR). Conversion rates were 73%, 71% and 62% in pts with MDR-TB, pre-XDR-TB and XDR-TB, respectively (Table). All pts with XDR-TB at baseline who sputum culture converted at some point and who completed the trial ($n = 23$) remained culture negative at treatment end or after treatment-free follow-up (16/23, median duration 5.4 months). Of the linezolid users ($n = 12$), 9 were responders (75%), 2 were non responders (17%) and 1 pt withdrew consent but had culture converted at discontinuation. This conversion rate was comparable to that of the overall study. In a multivariate analysis of the subgroup data, the conversion rate was significantly lower in pts who previously used second-line drugs and in pts with higher baseline AFB score.

Conclusion: Addition of BDQ to an MDR-TB regimen in heavily pre-treated pts resulted in durable conversion rates at 120 wks, irrespective of infection sub-type. In the majority of pts with XDR-TB, 6 months of BDQ administration followed by continuation of an individualized BR was sufficient both to convert the sputum culture and prevent short-term relapse.

OA-345-04 Twelve-month outcomes of patients initiating drug-resistant tuberculosis treatment at a decentralized outpatient clinic in Johannesburg, South Africa

K Hirasen,¹ R Berhanu,² D Evans,¹ K Schnippel,² L Long,¹ S Rosen,^{1,3} I Sanne^{1,2,3,4} ¹Health Economics and Epidemiology Research Office, Johannesburg, ²Right to Care, Johannesburg, South Africa; ³Center for Global Health & Development, Boston, MA, USA; ⁴Clinical HIV Research Unit, Johannesburg, South Africa. e-mail: khirasen@heroza.org

Background: Treatment success rates for drug-resistant (DR) TB in South Africa are poor, due in part to high rates of loss to follow-up (LTFU). In 2011, South African guidelines expanded to include decentralized, outpatient DR TB care to improve treatment access; however, the concern was that outpatient treatment would lead to increased LTFU. Sufficient data have now accrued to allow analysis of rates of LTFU and death and to identify factors associated with LTFU during the first 12 months after treatment initiation at a decentralized, public sector DR-TB treatment site in Johannesburg.

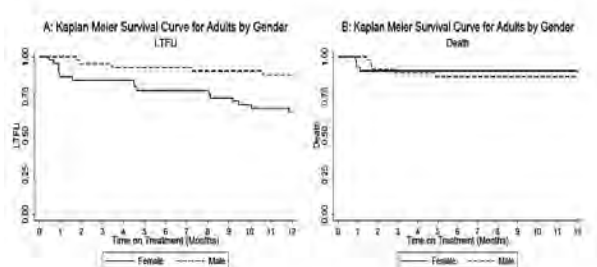
Methods: Prospective observational cohort analysis of adults (≥ 18) who initiated treatment for rifampicin resistance from March 2013 to March 2014. LTFU was defined as a treatment interruption ≥ 2 months. Factors associated with LTFU were identified using Cox hazards models to produce hazard ratios (HR). Person time was calculated from DR-TB initiation until either a final outcome reported or 12 months of follow-up occurred.

Results: 134 patients enrolled in the study; 32 were excluded from analysis (28 transferred; 4 drug sensitive). Of the 102 remaining, 49 (48%) were male, median age 37 (IQR 29–44). 84 (82%) were HIV-infected, with a median CD4 count of 113 cells/mm³ (IQR 35–262), and 40/84 (48%) were on antiretroviral therapy (ART) at

baseline. Pulmonary and extrapulmonary TB occurred in 90 (88%) and 12 (12%), respectively; 33/69 (48%) were smear positive at baseline. At 12 months, 10 patients (11%) had died, 25 (28%) were LTFU, and 55 (61%) remained on treatment. Females had a significantly higher risk of LTFU than males (aHR 3.82; 95%CI 1.06-13.83) but lower risk of mortality (HR 0.78; 95%CI 0.22-2.78). There was no association between LTFU and drug resistance pattern, employment status, or HIV status. All deaths occurred before 6 months of treatment whereas LTFU persisted throughout the 12 months.

Conclusion: At this decentralized DR-TB treatment site, 12-month LTFU and mortality were high. Mortality occurred early in treatment which is consistent with previous findings. Being female was associated with a higher risk of LTFU but a lower risk of mortality. The high risk of LTFU among females is a finding that differs from results of other DR-TB and HIV treatment programs and warrants further study.

Figure1. Kaplan Meier survival curves for adults by gender at a DR TB outpatient clinic. A: Loss to follow-up (LTFU) and B: all-cause mortality



OA-346-04 Mortality during XDR-TB treatment in South Africa, 2007–2009: a retrospective cohort analysis

N Ndjeka,¹ S S Dlamini,¹ N Bantubani,² K Schnippel³ ¹TB Control and Management Cluster, Pretoria, ²TB HIV Investigative Network of KwaZulu Natal (THINK), Durban, ³Witswatersrand University, Johannesburg, South Africa. Fax: (+27) 866 046 792. e-mail: ndjeka@esnet.co.za

Background: Between 2007 and 2014 approximately 7000 extensively drug resistant (XDR-) TB cases were diagnosed in South Africa of which 4567 received treatment. Treatment success is low (15-20%) and mortality high (50-60%) among XDR-TB patients.

Design/Methods: In 2011-2012, a retrospective review of patient files, clinic and electronic DR TB registers for XDR-TB patients registered for treatment in South Africa between 2007 and 2009 was conducted. During the study period, XDR-TB treatment was provided on an inpatient basis until sputum culture conversion in specialized, centralized hospitals. XDR-TB treatment regimens were individualized based upon resistance test results but often included capreomycin and para-aminosalicylic acid (PAS); moxifloxacin was not commonly used until late in the period.

Results: 543 XDR-TB patients were registered during the period. Median age was 35 (IQR: 27-43), 49.4% were

male. Two (of 9) provinces, KwaZulu Natal and Eastern Cape, accounted for 64% of cases. HIV status was reported for 79.6%; of patients with known status, 61.6% ($n = 266$) were HIV-positive and patient outcomes had not been evaluated or reported for 128 (23.6%); these patients were excluded from the outcome analysis. 241 of the 415 with outcomes died during treatment (58.1%), 10.4% were lost to follow-up, 14.7% on treatment or failed treatment, and 11.3 % were successfully treated. Positive baseline smear microscopy was a predictor of mortality relative risk (RR) 1.58 (95%CI: 1.25 to 2.00); having negative sputum culture at 6 months was a negative predictor of mortality (RR: 0.37, 95%CI: 0.25 to 0.53). HIV-positive patients were also at higher RR for mortality (1.24, 95%CI: 1.02 to 1.52), even when controlling for smear positive status (aRR:1.29, 95%CI: 1.02 to 1.62). Antiretroviral therapy for HIV coverage was high (91.6%) and therefore was not statistically significant (results not shown). Treatment with capreomycin, PAS, or moxifloxacin did not significantly affect RR of mortality.

Table Relative risk^{*†} of mortality during XDR-TB treatment by patient and treatment characteristics, XDR-TB patients with treatment outcomes registered in South Africa from 2007 to 2009

	Count / sample (%)	Relative risk (95%CI)	Adjusted relative risk [†] (95%CI)
All patients	241/415 (58.1%)		
Male	206/413 (49.9%)	0.88 (0.75–1.04)	0.90 (0.72–1.12)
HIV-positive	206/346 (59.4%)	1.24 (1.02–1.52)	1.29 (1.02–1.62)
Age category			
0–24 years	68/408 (16.7%)	0.84 (0.65–1.10)	1.08 (0.79–1.46)
25–39 years	187/408 (45.8%)	0.91 (0.76–1.10)	0.86 (0.68–1.10)
40–54 years	126/408 (30.9%)	REF	REF
≥ 55 years	27/408 (6.6%)	0.89 (0.62–1.27)	0.96 (0.56–1.65)
TB disease			
Previous TB reported	287/415 (69.2%)	0.90 (0.76–1.06)	1.01 (0.79–1.29)
Smear positive at initiation	209/344 (60.8%)	1.58 (1.25–2.00)	1.61 (1.25–2.07)
Culture negative at 6 months	133/239 (55.7%)	0.37 (0.25–0.53)	0.36 (0.24–0.55)
Treatment regimen			
Moxifloxacin	125/403 (31.0%)	0.86 (0.71–1.05)	1.06 (0.85–1.33)
Capreomycin	341/403 (84.6%)	0.97 (0.77–1.23)	0.94 (0.71–1.24)
PAS	342/403 (84.6%)	0.87 (0.70–1.07)	0.87 (0.67–1.13)

^{*} Relative risk calculated using Poisson regression with robust standard errors.

[†] Adjusted for baseline smear status (positive or negative) and HIV status (positive or negative).

XDR-TB = extensively drug-resistant tuberculosis; CI = confidence interval; HIV = human immunodeficiency virus; PAS = para-aminosalicylic acid.

Conclusion: XDR-TB continues to claim a lot of lives. Low treatment successful completion rate and high

mortality are still key features of this condition. Introduction of new medicines which have high rates of early smear and culture conversion is imperative to reduce mortality from XDR TB.

OA-347-04 Mortality among patients treated for multidrug-resistant tuberculosis in nine countries, 2005–2010

H Kirking,¹ M Yagui Moscoso,² M Van Der Walt,³ T Tupasi,⁴ O Demikhova,⁵ T Dalton,¹ E Kurbatova,¹ The Global Petts Investigators¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Peru Ministry of Health, Lima, Peru; ³South Africa Medical Research Council, Pretoria, South Africa; ⁴Tropical Disease Foundation, Manila, Philippines; ⁵Central Tuberculosis Research Institute of the Russian Academy of Medical Sciences, Moscow, Russian Federation. e-mail: hrj7@cdc.gov

Background: Worldwide, an estimated 5% of tuberculosis cases are multidrug-resistant tuberculosis (MDR-TB), which is associated with increased mortality and can be treated only with prolonged, poorly tolerated regimens. To identify opportunities to reduce MDR TB-related mortality, we investigated predictors of mortality in a multinational prospective observational cohort study of patients undergoing treatment.

Design/Methods: During 2005–2008, adults (≥ 18 years) were enrolled at the start of treatment for MDR-TB in Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, Thailand, and Taiwan. Patients were followed up until end of treatment or end of observation on June 30, 2010. Patients who did not follow study protocol and those without data on outcome or time until outcome were excluded. The survival distribution was estimated using the Kaplan Meier method. Predictors of death were ascertained by using multivariate Cox proportional hazards regression modeling.

Results: In total, 1550/1761 (88%) patients were included. An estimated 84.7% of patients survived past two years (95%CI 82.6%–86.9%). Independent predictors of mortality included HIV infection (adjusted hazard ratio [aHR]: 1.8; 95% confidence interval [CI]: 1.1–2.8), body mass index of <18.5 kg/m² (aHR: 2.7; 95%CI: 2.0–3.8), and baseline resistance to ≥ 1 second-line injectable drugs (aHR: 2.2; 95%CI 1.5–3.2) or fluoroquinolones (aHR 2.2, 95%CI 1.4–3.5).

Conclusion: Among patients with MDR-TB, 2 treatable conditions—HIV and low BMI—were associated with mortality. Data from future investigations of interventions for these conditions may help to increase survival rates.

07. Many paths to the same END TB strategy

OA-348-04 How did we perform? An assessment of global investment effectiveness in sub-Saharan Africa against key tuberculosis control performance indicators

K G Koura,¹ F Boillot,¹ V Schwoebel,¹ A Trebucq¹

¹International Union Against Tuberculosis and Lung Disease, Paris, France. e-mail: kgkoura@theunion.org

Background: While the DOTS strategy provides the technical framework for tuberculosis control since TB was declared a public-health emergency in 1990, Global Fund (GF) grants eventually provided low-income countries in sub-saharan Africa (SSA) with substantial additional resources to accelerate progress. Additional components like Performance Based Funding (PBF) and partnership were expected to provide powerful additional incentives to accelerate progress. As the horizon for the Millennium Development Goals comes close, we examined the trends in TB notifications and treatment success in SSA, looking whether the implementation of GF grants accelerated increases in these indicators.

Design/Methods: We consolidated country data for the WHO-Afro region, obtained from the Global Health Observatory from 1995, when countries regularly reported to WHO. We compared data from the 1995–2003 period—before countries accessed to GF grants—to those from the 2004–2012 period when GF support eventually matured. We compared time series for notified new cases (total and smear-positive) and treatment success rates, with the null hypothesis that GF grants did not accelerate trends. We tested statistical significance of change by segmented regression analysis after adjusting for first order auto-correlation using STATA.

Results: We observed no progress acceleration for the 3 selected indicators after GF grants were implemented ($P > 0.1$). Surprisingly, case notification of new smear-positive cases slowed down after 2003. Progress in notification of all new cases and treatment success slowed down from 2008.

Conclusion: As prevalence surveys increasingly suggest that the TB burden in SSA is underestimated, the failure of the GF to boost progress in TB control is alarming. Documentation to assess the magnitude of GF disbursements is not easily accessible but the hypothesis they substantially increased funding is reasonable. In countries with limited health care access, the StopTB strategy focused on care supply may have reached its limits. A scope for the End TB strategy broadened to the demand side, with emphasis on research to find how to transform resources into results is a logical development. Substantial resources that only the GF has proved able to mobilize and sustain will remain necessary. To face the challenge, the GF may need to adjust its approaches beyond its current funding model and to clarify the impact on results of its partnership model and the incentives it delivers.

OA-349-04 Reaching missed tuberculosis cases: lessons learnt using screening tools used in Ghana's 2013 National Tuberculosis Prevalence Survey

F Bonsu,¹ I Law,² R Gockah,¹ Z Wagaw,¹
N N Hanson-Nortey,¹ M Tadolini,² E Owusu-Dabo,³
I Onozaki² ¹National TB Control Programme, Ghana Health Service, Accra, Ghana; ²World Health Organization, Geneva, Switzerland; ³RESEARCH, Kumasi Centre for Collaborative Research (KCCR), Accra, Ghana. e-mail: zalebachew@gmail.com

Background: Low Tuberculosis case notification rate is a challenge for Ghana Tuberculosis control. It is believed existing screening tools may partly be an important underlying reason. We examined the various screening tools used during a prevalence survey and determine proportion of survey tuberculosis cases that would have been detected using routine symptom screening (coughing two weeks or more) and Acid-Fast Bacilli smear microscopy as first diagnosis. The aim of this study is to determine proportion of cases that are missed under routine programmatic conditions and evaluate the sensitivity of screening tools used during the survey.

Design/Methods: A nationwide, clustered-sampled, stratified (urban/rural), cross-sectional survey, was conducted in 2013. All consenting participants were screened for tuberculosis using: chest X-ray examination and a symptom based screening of cough of two-week duration. Individuals identified with an abnormal chest X-ray or cough symptoms of more than two weeks duration were eligible for sputum examination. All spot and morning sputum specimens collected from suspects were examined by Acid-Fast Bacilli smear microscopy and liquid culture (MGIT).

Results: Among 67 757 eligible individuals, 61 726 697 (91.1%) participated in the survey. Of which 8298 (13.4%) participants were eligible for sputum examination. A total of 202 tuberculosis cases: 64 smear positive and 138 smear negative culture positive were identified. Smear microscopy detected 31.7% (25.3, 38.1) of cases while 68.3 % (61.9%, 74.7%) of survey tuberculosis case were smear negative culture positive. Based on the survey finding sensitivity of symptom screening was 40.6 % (33.83, 47.37). From the total 167 surveys tuberculosis cases who had X-ray examination 92.1 % (89, 96.2) had abnormal Chest X-ray. Among the total survey cases only 20.3 % (14.8, 25.9) were symptom positive and smear positive pulmonary tuberculosis.

Conclusion: Close to 80% of survey cases would have been missed if survey was conducted using routine programmatic screening tools and diagnosis. The study underscores the importance of digital X-ray as a screening tool for improved and early tuberculosis case detection as found in other studies. GeneXpert and culture diagnosis will exclude Non-Tuberculosis Mycobacteria (NTM) among notified tuberculosis cases.

OA-350-04 Impact of Ebola virus disease outbreak on tuberculosis case management in Guinea

H Traore,¹ A M Bangoura,² D Adjoua,¹ C Diallo,¹
T Kazadi³ ¹Population Services International, Conakry,
²Programme National de Lutte Antituberculeuse, Conakry,
Guinea; ³Population Services International, Washington, DC,
USA. e-mail: htraore@psiguinee.org

Background: Guinea is the epicenter of the Ebola Virus Disease (EVD) outbreak since March 2014. This impacted the control of many diseases including tuberculosis (TB). The Global Fund asked PSI and The National TB Program to look at what is EVD's impact on TB screening/treatment and address the issue

Design/Methods: The project conducted a meta-analysis of 8 activity reports (2013 and 2014) from The National TB Program and Partners against TB in Guinea. Data was analyzed in Epi InfoTM7.

Results: The impact of EVD affected the continuity of care of TB in Guinea. Compared to 2013, PSI found there was a 16% decrease (30% in Middle Guinea) in the average number of patients screened for TB and 6% in the average number of TB patients on care at the Conakry TB Center (CAT la Carrière). This caused a reduction in case management activities in 22% ($n = 68$) of TB Screening Centers (TSC), mainly in the forest region due to fear of health workers contacting EVD, EVD deaths among health workers, and reassigning health care providers to EVD treatment activities. Monitoring activities were difficult to implement, and the supervision of 12% of all prefectures ($n = 33$) were reached in Guinea. Moreover, a third ($n = 15$) of TSC in the forest region experienced stock outs of TB supplies and drugs, and the effectiveness of implemented education activities and tracing of TB defaulter cases were compromised.

Conclusion: The results show that EVD had a major impact on TB screening and treatment in Guinea. To address the problem, PSI/Guinea, the Global Fund TB Principal Recipient, in collaboration with the National TB Program, developed a plan to mitigate the effects of EVD by focusing on: strengthening capacity of TSC providers by integrating EVD prevention modules into TB training curricula; the implementation of prevention and EVD infection control measures within TSC; and sensitization of EVD awareness coupled with TB defaulter case tracing at the community level. This mitigation plan should strengthen the capacity of 247 health and community workers, and equip 68 TB TSCs with EVD prevention kits to ensure continuity of care and follow-up TB activities. The selected interventions will increase TSC's patient attendance, and better equip health care providers to deal with the EVD epidemic while ensuring quality care for TB patients.

OA-351-04 From road map to road: comprehensive tuberculosis management and identification of 'missing' private patients in urban Karnataka, India

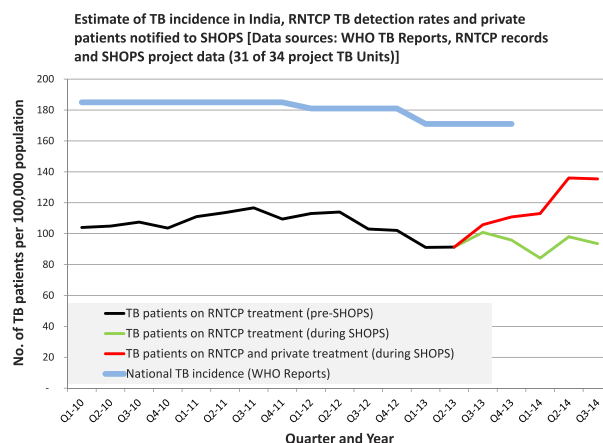
O George,¹ H Gururaj,² R Ganesan,¹ R Swamickan,³ M Benezet⁴ ¹Abt Associates Inc., New Delhi, ²Karnataka Health Promotion Trust, Bengaluru, ³USA Agency for International Development, New Delhi, India; ⁴Abt Associates Inc., Bethesda, MD, USA. Fax: (+91) 112 653 5172. e-mail: oommen.geo@gmail.com

Background: The need to identify and manage 'missing' tuberculosis (TB) patients is urgent. Global strategies promote comprehensive urban TB interventions which include engagement of private health care providers (PHCP). While the 'why' and 'what' are alluded to, the 'how' has largely eluded resource-strapped TB programs. India needs cost-effective, innovative ideas to engage its dominant private sector in TB prevention and care.

Intervention: The USAID-funded Strengthening Health Outcomes through the Private Sector (SHOPS) project in India developed a private provider interface agency (PPIA) model to demonstrate impact in 42 towns of Karnataka. The PPIA engaged the Revised National TB Control Program (RNTCP), PHCP and communities to synergistically effect stakeholder collaboration and result in comprehensive care for TB patients. The model covered a population of 16.8 million, focusing on 1.1 million living in 663 urban slums. SHOPS mapped and engaged urban slum communities, and qualified and unqualified health providers. Access to certified diagnostic tests was enabled through sputum sample transportation and dialogue with RNTCP. TB patients in slums were offered in-person care and support; others had access to a telephone 'Careline' counseling and adherence support service. Community-level patient support groups aided patients and families live with TB and fostered treatment compliance.

Results: The intervention halved delays in TB diagnosis and treatment initiation among new smear positive patients from intervention slums. Treatment compliance among 1409 RNTCP and 371 private patients receiving in-person support by the PPIA was 95% and 97% respectively. Completed cohorts showed that 94% of 128 privately treated patients had successful outcomes. In the 18 months of intervention, PHCP notified 6342 TB patients to SHOPS, while PPIA referrals from slums added 1499 more patients. Children made up 18% of patients known to SHOPS (11% were less than 5 years of age). SHOPS reported more than 40% additional private TB patients by the end of the project.

Conclusions: A comprehensive urban-TB model demonstrated the potential to identify and effectively manage 'missing' TB patients through inter-sectoral coordination, especially through engagement of private providers and by respecting patient choices. The model established ways to improve TB detection under RNTCP, identify additional private patients, reduce delays and improve treatment outcomes.



OA-352-04 Modelling health system costs to support decision making for MDR-TB diagnostics in Cape Town

R Dunbar,¹ P Naidoo,¹ I Langley,² N Beyers¹ ¹Desmond Tutu TB Centre, Cape Town, South Africa; ²Liverpool School of Tropical Medicine, Liverpool, UK. Fax: (+27) 219 389 719. e-mail: rdun@sun.ac.za

Background: Improving multidrug-resistant tuberculosis (MDR-TB) control requires access to accurate and rapid diagnostics for drug susceptibility testing. New molecular diagnostic tests for tuberculosis (TB) such as Xpert MTB/RIF (Xpert) hold the promise of improving TB and multidrug-resistant (MDR) TB diagnosis. Whilst accurate data are readily available from laboratory and demonstration studies, many operational questions remain and are most readily answered through modelling.

Methods: South Africa moved from a smear and culture based algorithm for diagnosis of TB to an Xpert-based algorithm. The Witness package was used to model all aspects of both algorithms to reflect the diagnostic pathways, including the laboratory procedures, as close to reality as possible, based on information and data collected during the PROVE IT (Policy Relevant Outcomes from Validating Evidence on Impact) study. Routine operational data was used to validate the model. The model was used to assess the effect of operational changes on yield and laboratory costs.

Results: Routine data showed a declining trend in the yield of TB cases identified over time in both algorithms. A binomial regression analysis showed no significant difference in yield between the algorithms when the time effect was taken into consideration, with a risk difference of 0.2% (95%CI -1.8% to 2.3%) ($P = 0.818$) in the Xpert-based algorithm. Total TB diagnostic costs were increased by 43% from \$440,967 in the smear-culture-based algorithm to \$632,262 in the Xpert-based algorithm. The cost per patient diagnosed with TB increased by 158% from \$49 in the smear/culture-based algorithm to \$125 in the Xpert-based algorithm. The total cost per MDR-TB case diagnosed was decreased by 3%, from \$205 in the smear-culture-based algorithm to

\$199 in the Xpert-based algorithm. The model was used to demonstrate the effect of an optimised algorithm, increased case-finding and other operational changes on TB yield and laboratory costs.

Conclusion: This study used a combination of operational data and discrete event simulation to answer important operational questions that could not be readily addressed through other methods. Modelling is an attractive and viable option to guide policy makers in making decisions about the implementation of new diagnostic tools and algorithms.

OA-353-04 Social protection and TB: an ecological analysis

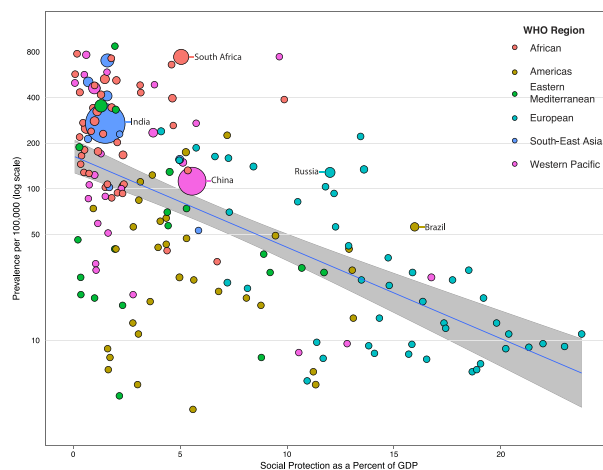
A Siroka,¹ K Lonnroth,² N Ponce¹ ¹University of California, Los Angeles, Los Angeles, CA, USA; ²World Health Organization, Geneva, Switzerland. e-mail: asiroka@gmail.com

Background: Pillar Two of the End TB Strategy stresses the need for social protection programs that aim to alleviate poverty. Without progressive policies in areas outside of the medical sphere it will be impossible to achieve the ambitious goals set forth in the End TB Strategy. There is a limited amount of research on the relationship between social protection and TB. Reeves et al. show the inverse relationship between social protection and TB in European nations with sizeable social protection systems and secure welfare mechanisms. This paper builds upon this work by analyzing this association with a global purview.

Design/Methods: We aim to show the association between levels of social protection, measured as the percentage of GDP spent on social protection programs and national TB prevalence, incidence, and mortality rates. Social protection data, which covers the years 2000 – 2012, were obtained from the International Labor Organization's (ILO) Social Protection Department. TB burden rates are from the World Health Organization's Global TB database. The full model includes national-level factors that could also influence TB rates. These include GDP per capita, HIV rates, and the strength of the health system. Further control variables are population density, percentage of foreign-born residents, and TB treatment success rate among new cases. This last control variable is meant to represent the strength of the national TB treatment program. To account for the clustering of data points within countries we used a country-level fixed effects model.

Results: In multivariate models, social protection levels were significantly inversely associated with all three measures of TB burden. This was formally tested using a joint significance test of social protection and its squared term. The association is especially strong in setting with low levels of social protection spending (as a percentage of GDP). For example, moving from 0% to 1% of GDP in social protection spending within a country is associated with an 18.33 person per 100 000 decline in the TB prevalence rate.

Conclusion: Due to the ecological nature of this study we cannot show a causal relationship between social protection levels and TB rates. This work could influence funding agencies, such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, as well as national treatment programs to increase their funding of programs outside of the medical sphere.



OA-354-04 Four degrees of separation: the influence of social and provider networks in the steps to diagnosis of active tuberculosis in Urban Uganda

J Sekandi,^{1,2} S Zalwango,¹ R Kakaire,² L Martinez,² A Kizza,² A Ezeamama,² N Kiwanuka,¹ CC Whalen² ¹Makerere University School of Public Health, Kampala, Uganda; ²University of Georgia, Athens, GA, USA. e-mail: jsekandi@musph.ac.ug

Background: Delay in tuberculosis (TB) diagnosis adversely affects patients' health outcomes and prolongs transmission in the community. The steps taken by active TB patients to seek a diagnosis are not well understood.

Design/Methods: Using retrospective cohort design, TB patients on treatment for three months or less and aged ≥ 18 years were enrolled from three public clinics in Kampala, Uganda, between March and July 2014. Structured face-to-face interviews and network analysis were used to evaluate information about patients' social and health provider networks. Steps, or degrees of separation, were defined as the number of contacts a patient made to seek help since recognition of symptoms to the time of final diagnosis. Social contacts included family members, friends and coworkers. Health providers included public and private hospitals, private clinics, public health centers, pharmacies, village health workers and herbal healers. Descriptive and step sequence analyses were performed, followed by Cox regression analyses to determine factors associated with steps and time to final TB diagnosis. Hazard ratios and 95% confidence intervals were calculated to represent the likelihood of timely TB diagnosis.

Results: Of 294 TB patients, 58% were male and median age was 30 (IQR; 24-38) years. The median number of

steps was 4 (IQR: 3, 7) corresponding to 70 (IQR: 28,140) days to diagnosis. New patients had more steps and time to diagnosis compared retreatment patients (5 vs. 3, $P < 0.0001$; 84 vs. 46 days $P < 0.0001$). Fifty-eight percent of patients first contacted persons in their social network. The first step to seeking care accounted for 41% of the patients' time to diagnosis while visits to non-TB providers and TB providers (without a TB diagnosis) accounted for 34% and 11% respectively. New TB patients vs. retreatment (HR: 0.66, 95%CI: 1.11, 1.99), those who first contacted a non-TB provider vs. contacting social network (HR: 0.72 95%CI: 0.55, 0.95) and HIV seronegative vs. seropositive patients (HR: 0.70, 95%CI: 0.53, 0.92) had a significantly lower likelihood of a timely final diagnosis.

Conclusion: On average, there were four steps or degrees of separation between the onset of symptoms in a TB patient and a final diagnosis. The patients' social and provider networks influenced their respective diagnostic pathways. Most delays occurred in the first step, representing the patients' initial decisions to seek help, or through interactions with non-TB providers. TB control programs should strengthen community education and TB screening as well as continuing medical education to health providers to ensure timely diagnosis of TB.

OA-355-04 Households receiving a TB-specific social protection intervention in Peruvian shantytowns placed more importance on social than economic support

R Montoya,¹ M Tovar,^{1,2} D Huff,^{1,3,6} T Wingfield,^{1,4,5} E Ramos,² J Lewis,^{1,3} D Boccia,^{1,3} C Evans^{1,2,4} ¹Asociación Benéfica PRISMA, Lima, ²Universidad Peruana Cayetano Heredia, Lima, Peru; ³London School of Hygiene & Tropical Medicine, London, ⁴Imperial College London, London, ⁵North Manchester General Hospital, Manchester, UK; ⁶Tulane University, New Orleans, LA, USA. e-mail: tom.wingfield@ifhad.org

Background: Social protection forms part of a key pillar in the World Health Organization's post-2015 global TB control strategy. However, evidence concerning TB-specific social protection is limited and it is unclear whether social and/or economic support will have the most impact on TB control. During the pilot of a Community Randomized Evaluation of a Socioeconomic Intervention: to Prevent TB (CRESIPT), we assessed acceptability of a TB-specific social protection intervention and evaluated feedback on the differential importance of social vs. economic support in TB-affected households.

Methods: 282 TB patients diagnosed by the Peruvian National TB Program in 32 shantytown communities of Lima, Peru, were recruited to the study. Patients were randomly allocated to the comparison arm (standard of care from the Peruvian NTP) or supported arm (standard of care plus the social protection intervention). The social protection intervention consisted of economic support and social activities. Social activities included household visits and participatory community meetings for infor-

mation, mutual support, stigma reduction and empowerment. Economic support was provided through conditional cash transfers throughout treatment to reduce TB vulnerability, incentivise and enable care through mitigation of TB-related costs. A mixed-methods approach collected quantitative/qualitative feedback in focus group discussions and exit questionnaires with all participants.

Results: 135 patient households were randomised to the support arm of whom 115 have had final follow up to date. 8/135 (6%) recruited patient households did not engage at all with the intervention and thus did not receive any conditional cash transfers. 890/1157 (80%) potential conditional cash transfers were made. Patient households ranked the social activities of the social protection intervention higher than the economic support (Figure). 88/92 (96%) patient households with data reported that they would participate again in the intervention if a household member fell ill.

Conclusion: In this setting, there was good uptake and acceptance of the novel TB-specific social protection intervention including conditional cash transfers. However, TB-affected household feedback suggested that the social activities of the intervention were perceived to be more important than the economic support. This evidence should be considered in future planning of social protection interventions incorporated into TB control strategies.

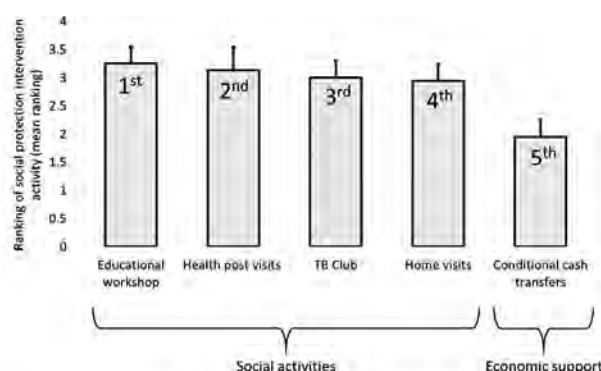


Figure: Patient household (n=115) feedback of ranking of importance of CRESIPT social and economic activities. This data was gathered at the final follow-up visit at the end of the patient's treatment and involvement in the intervention. Overall ranking of importance of each activity is indicated inside the corresponding column.

08. The molecular basis of PZA resistance: from bench to bedside

OA-356-04 Mutations in *gyrA* and *gyrB* among fluoroquinolone- and multidrug-resistant *Mycobacterium tuberculosis* isolates

J-Y Chien,^{1,2} S-T Chien,³ C-J Yu,¹ P-R Hsueh¹ ¹National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, ²Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, ³Chest Hospital, Ministry of Health and Welfare, Tainan, Taiwan. e-mail: jychien@ntu.edu.tw

Background: To evaluate the correlation between mutations in the *gyrA* and *gyrB* genes and the level of resistance to ofloxacin (OFX) and moxifloxacin (MFX) in isolates of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB).

Design/Methods: Using minimum inhibitory concentrations (MICs) measured by the broth microdilution method, we categorized the isolates into OFX-susceptible (MIC ≤ 2 mg/L), low- (MIC 4-8 mg/L) and high-level (MIC ≥ 16 mg/L) OFX-resistant isolates, and MFX-susceptible (MIC ≤ 0.5 mg/L), low- (MIC 1-2 mg/L) and high-level (MIC ≥ 4 mg/L) MFX-resistant isolates.

Results: Of 111 isolates, mutations in the *gyrA* gene were found in 30.2% of OFX-susceptible isolates, 72.5% of low-level OFX-resistant isolates and in 72.2% of high-level OFX-resistant isolates, and in 28.6% of MFX-susceptible isolates, 58.1% of low-level MFX-resistant isolates and in 83.9% of high-level MFX-resistant isolates. Compared with OFX-susceptible isolates, low- and high-level OFX-resistant isolates had a significantly higher prevalence of mutations at *gyrA* codons 88-94 (9/53, 17.0% vs. 26/40, 65.0% and 13/18, 72.2%, respectively; $P < 0.001$) and a higher prevalence of the *gyrB* G512R mutation (0/53, 0.0% vs. 1/40, 2.5% and 3/18, 16.7%, respectively; $P = 0.006$). Similarly, compared with MFX-susceptible isolates, low- and high-level MFX-resistant isolates had a significantly higher prevalence of mutations at *gyrA* codons 88-94 (7/49, 14.3% vs. 16/31, 51.6% and 25/31, 80.6%, respectively; $P < 0.001$) and a higher prevalence of the *gyrB* G512R mutation (0/49, 0.0% vs. 0/31, 0.0% and 4/31, 12.9%, respectively; $P = 0.011$). D94G and D94N mutations in *gyrA* and the G512R mutation in *gyrB* were correlated with high-level MFX resistance while the D94A mutation was associated with low-level MFX resistance. We also found that the prevalence of those mutations was higher among fluoroquinolone-susceptible East Asian (Beijing) and Indo-Oceanic strains than among fluoroquinolone-susceptible Euro-American strains.

Conclusion: Mutations at codons 88-94 of the *gyrA* gene and the G512R mutation in the *gyrB* gene were associated with resistance to OFX and MFX, although the level of resistance was not equally affected by those mutations. Our finding that the prevalence of *gyrA* and *gyrB* gene mutations was higher among fluoroquinolone-susceptible East Asian (Beijing) and Indo-Oceanic strains than among fluoroquinolone-susceptible Euro-American

strains imply that molecular techniques to detect FQ resistance may be less sensitive in areas with a high prevalence of those strains.

OA-357-04 Identification of *pncA* gene regions associated with high-level pyrazinamide-resistant TB in China

D Li,^{1,2,4} Y Hu,^{1,2,3} J Werngren,⁴ M Mansjo,⁴ S Hoffner,^{3,4} B Xu^{1,2} ¹School of Public Health, Fudan University, Shanghai, ²School of Public Health, Fudan University, Shanghai, China; ³Microbiology and Tumor Biology Center, Karolinska Institutet, Stockholm, ⁴The Public Health Agency of Sweden, Stockholm, Sweden. e-mail: yhu@fudan.edu.cn

Background: A mutation in the *pncA* gene is a major mechanism of pyrazinamide (PZA) resistance. However, the mutations are highly diverse and scatter over the full length of the 561 bp of the *pncA* gene. This may complicate the development of rapid molecular diagnosis. The present study aimed to investigate the genetic characterization of pyrazinamide resistant M. TB isolated from China as well as to analyze its relationship to the minimum inhibitory concentration (MIC), in attempt to search for the valuable hotspot regions associated with high-level PZA resistance.

Design/Methods: A population-based multi-center study was carried out in 4 Chinese counties. Pulmonary TB cases registered in the local TB health facilities from 2011 to 2013 were enrolled in the study. Mutations in the *pncA* gene were identified by whole gene sequencing. MIC test for *pncA* mutated isolates were performed on the mycobacterial growth indicator tube (MGIT) 960 platform according to the standard manufacturer protocol.

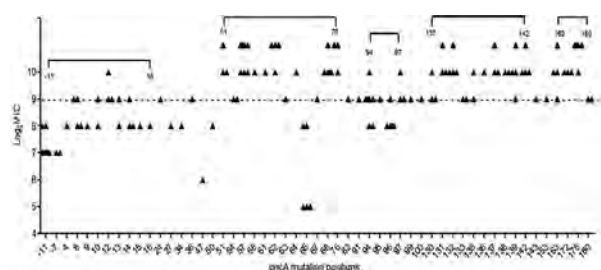


Figure: The MICs of PZA in isolates with genetic mutations of *pncA*. The distribution of MIC was presented by symbols for each isolate and the symbols above the dotted line indicating the high level of PZA resistance (MIC > 500 mg/L). MIC showed the same value in this figure if it was above 1024 mg/L.

Results: Of 912 cases enrolled within the studied period, 878 were culture positive and 136 isolates had the nonsynonymous *pncA* mutation including 133 with Single Nucleotide Polymorphism (SNP) and 3 with the large fragment insertions or deletions. Of the 147 PZA resistant isolates, we identified 131 *pncA* nonsynonymous mutation, with a sensitivity of 89.1% (95%CI: 83.05%-93.19%) and a specificity of 99.3% (95%CI: 98.41%-99.71%) to detect the PZA resistance. Besides, all 133 SNP distributed between position -11 and position 180 of *pncA* gene and concentrated in five regions with statistically different MIC level distributions ($P < 0.001$): 73.2% (71/97) isolates with high-level MIC (MIC > 500 µg/ml) and 95.1% (58/61) isolates with

extreme high-level MIC (MIC $\geq$ 1024 μ g/ml) had the mutation at three regions (position 51 to 76, position 130 to 142 and position 163 to 180); 72.2% (26/36) isolates with MIC between 128 to 500 μ g/ml were observed to have the mutation in the other two regions (position 94 to 97 and position -11 to 16).

Conclusion: The specific regions of *pncA* gene have approved their value for the molecular rapid diagnosis of PZA resistance in M.TB, especially for three regions to define the high PZA resistance.

OA-358-04 Prevalence of common and rare *Mycobacterium tuberculosis* resistance-conferring mutations in Uganda

W Ssengooba,^{1,2} F Cobelens,^{1,3,4} D Lukoye,^{3,5} G W Kasule,⁵ M Joloba,^{2,5} B De Jong^{6,7} ¹Academic Medical Center, Amsterdam Netherlands; ²Makerere University College of Health Sciences, Kampala, Uganda; ³Amsterdam Institute of Global Health and Development, Amsterdam, Netherlands; ⁴KNCV Tuberculosis Foundation, The Hague, Netherlands; ⁵Ministry of Health National TB program, Kampala, Uganda; ⁶Institute of Tropical Medicine, Antwerp, Belgium; ⁷New York University, New York, NY, USA. Fax: (+256) 414 533 033. e-mail: willyssengooba@gmail.com

Background: Understanding the circulating *Mycobacterium tuberculosis* (MTB) resistance mutations is vital for better TB control strategies, especially in early stages of second-line TB treatment programme introduction.

Design/Methods: We performed whole genome sequencing on 112 rifampicin and/or isoniazid-resistant isolates from two drug resistance surveys done in Uganda. We compared MTB strain lineages with drug resistance, previous TB treatment and HIV-infection. We screened for common and rare drug resistance mutations and their relation with MTB-lineage and HIV-infection.

Results: 73 (65.2%) patients were male, median age was 35 years (IQR; 26-45), 33 (29.5%) were HIV-infected and 77 (68.8%) were previously treated for tuberculosis. Phenotypic mono-resistance to rifampicin (RIF) was 6 (5.0%), to isoniazid (INH) 67 (60.0%) and 39 (35.0%) were MDR-TB. MTB lineages were L2 (East-Asian) 4.5%, L3 (East-African-Indian) 17.8% and L4 (Euro-American) 77.7%. Of the 70 sequencing results available to date, drug resistance mutations were found in 42.9% for RIF, 80% for INH, 28.6% for ethambutol (EMB), 19% for pyrazinamide (PZA), and 17.1% for streptomycin (STR). The most prevalent first-line mutations per drug were RIF *rpoB*.S450L 47% (present in 92% of MDR), INH *katG*.S315T 75% and *inhA*.pro-15T 20%, EMB *embB*360 70%, STR *rpsL*.K43R 58% and pyrazinamide *pncA*.V180F 23%. Only two patients had RIF compensatory mutations, *rpoC*.N698S and *rpoC*.V483A, both with *rpoB*.S450L mutation against a L4 background. One MDR-TB patient had kanamycin/amikacin resistance *rrsk*.R468S. There was an unusual QRDR *gyrA*.T80A mutation in 48% of the TB patients, mostly in L4 (89%) and among previously treated patients. None of the other mutations were associated with HIV, previous treatment or MTB lineage.

Conclusions: Among tuberculosis patients in Uganda, resistance is mainly due to common *Mycobacterium tuberculosis* resistance mutations, and mostly to first-line treatment. PZA resistance was found in 52% of MDRs, while injectable resistance is low, and the unusual *gyrA* mutation unlikely confers fluoroquinolone resistance.

OA-359-04 Construction and validation of a three-color single-tube assay for the detection of resistance to first- and second-line anti-tuberculosis drugs

M De Vos,¹ J Rice,² N Ismail,³ B Kreiswirth,⁴ T Dolby,⁵ P Van Helden,¹ R M Warren,¹ L Wangh² ¹Stellenbosch University, Cape Town, South Africa; ²Brandeis University, Waltham, MA, USA; ³National Institute for Communicable Diseases, Johannesburg, South Africa; ⁴University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA; ⁵National Health Laboratory, Cape Town, South Africa. e-mail: margab@sun.ac.za

Background: The Genotype® MTBDRplus line probe assay and the Xpert® MTB/RIF assay, currently endorsed by the WHO only provide evidence for resistance to isoniazid and/or rifampicin. These data are insufficient to ensure optimal treatment of MDR-TB when resistance extends beyond those first line drugs. Moreover, treatment of MDR-TB in the absence of comprehensive drug susceptibility testing promotes the emergence of XDR-TB. Therefore there is a critical need for a convenient, single-tube diagnostic technology that can test all known mutations conferring TB drug resistance. The present report describes such a reaction for first- and second-line antibiotics.

Design/Methods: Using a combination of multiplexed LATE-PCR and Lights-on/Lights-off probe technology we have constructed a three color single tube assay to screen and identify mutations in seven genetic targets known to confer resistance to first-line (rifampicin and isoniazid) and second-line (fluoroquinolone, aminoglycoside/polypeptide and ethionamide) antibiotics. The assay was evaluated on DNA extracted from well characterized clinical *M. tuberculosis* isolates harboring all known mutation types in *inhA* and *eis* promoters, *rpoB*, *katG*, *gyrB*, *gyrA*, and *rrs* genes. This comprises a total of 44 possible allelic variants in a multitude of possible combinations. One thousand blinded DNA samples have been collected to evaluate the diagnostic performance of the assay.

Results: Analysis of 81 resistant isolates generated a library of signatures reflecting all of the known mutations in *inhA* and *eis* promoters, *rpoB*, *katG*, *gyrB*, *gyrA*, and *rrs* genes. Each unique mutation had its own, highly reproducible fluorescent signature which was distinct from that of pan-susceptible laboratory strain, H37Rv, as well as all other isolates with different mutations at the same or different codons.

Conclusion: This study demonstrates that a single tube multiplexed assay can simultaneously distinguish different mutations that confer resistance to rifampicin, isoniazid, ofloxacin, moxifloxacin, amikacin, kanamycin, capreomycin and ethionamide in less than three

hours. This assay is currently being validated with 1000 DNA samples. Automation of this methodology will enable clinicians to optimise treatment of drug resistant TB thereby ensuring improved outcomes. This study is funded by the NIH R01 A1099532.

OA-360-04 Association between genotypic and phenotypic pyrazinamide resistance in INH and RMP mono-resistant and MDR-TB isolates

M Whitfield,¹ E Streicher,¹ L Scott,² W Stevens,² S Sampson,¹ P Van Helden,¹ R M Warren,¹ A Van Rie^{3,4}
¹Stellenbosch University, Tygerberg, ²National Health Laboratory Services, South Africa, Johannesburg, South Africa; ³University of Antwerp, Antwerp, Belgium; ⁴University of North Carolina at Chapel Hill, NC, USA. e-mail: mwhit@sun.ac.za

Background: Pyrazinamide (PZA) plays an integral part in anti-tuberculosis treatment. PZA will likely remain an important component of treatment regimens for drug-susceptible and multidrug-resistant tuberculosis (MDR-TB) because of its distinctive mode of action. However little is understood about the prevalence of PZA resistance with rifampicin (RIF) and isoniazid (INH) mono-resistant cohorts.

Methods: A total of 87 isolates that were INH mono-resistant, 391 isolates RIF mono-resistant and 370 MDR-TB isolates according to the MTBDRplus line probe assay were identified from a culture bank housed at Stellenbosch University, South Africa. The *pncA* gene was sequenced for all isolates including up- and downstream regions. Isolates were phenotypically tested using the BACTEC MGIT 960 PZA drug susceptibility test (DST) at a concentration of 100µg/ml. INH or RIF mono-resistant were subjected to culture based phenotypic DST (BACTEC 960 SIRE kit) to confirm INH or RIF mono-resistance, respectively.

Results: 79 (90.8% - 95%CI 99.1%) of the 87 INH mono-resistant isolates were found to be wild type for *pncA*; 318 (81.5% - 95%CI 93.2%) of the 391 RIF mono-resistant isolates were found to be wild type for *pncA*; and 184 (49.7% - 95%CI 96.4%) of the 370 MDR-TB isolates were found to be wild type for *pncA*. All isolates with a wild type *pncA* genotype were confirmed as PZA sensitive using the PZA DST. A total of 62 different mutations were identified in the *pncA* gene.

Conclusion: A clear increase in PZA resistance is observed from INH mono-resistance (9.2%) to RIF mono-resistance (18.5%) and finally to MDR-TB (50.3%). This question's the utility of PZA in the WHO recommended standardised MDR-TB treatment regimen. The development of simplified routine diagnostic methods for PZA susceptibility will be essential if new treatment regimens continue to rely on the inclusion of PZA.

OA-361-04 Genotypic testing using next-generation sequencing is superior to phenotypic testing for pyrazinamide susceptibility testing

S Omar,¹ N Ismail,¹ A W Dreyer,¹ N Ismail¹ ¹National Institute for Communicable Diseases, Johannesburg, South Africa. e-mail: shaheedvo@nicd.ac.za

Background: Pyrazinamide (PZA) is an important drug for the treatment of *Mycobacterium tuberculosis* infection, with efficient sterilization ability. This pro-drug is converted to pyrazinoic acid by the enzyme pyrazinamidase (encoded by the *pncA* gene) produced by the organism. Phenotypic testing is technically challenging and often produces unreliable results due to dependence on media-specific conditions. The genes of interest (*pncA*) together with other genes (*rpsA* and *panD*) are molecular markers for PZA resistance. Development of a rapid, reliable molecular assay for determination of resistance is difficult as the mutations associated with resistance are spread across the entire length of the *pncA* gene. We determined the value of whole genome sequencing (WGS) using the next-generation method for the determination of PZA resistance from isolates collected in high-burdened TB South Africa.

Design/Methods: A total of 860 *M. tuberculosis* isolates collected from a province in South Africa, a subset of a larger national survey, were included in this study. All isolates were phenotypically tested for PZA drug susceptibility using the BD BACTEC 960 mycobacterial detection system and the BD MGIT 960 PZA kit. WGS was performed on the Illumina MiSeq instrument with libraries prepared using Nextera XT chemistry. The modified Wayne's test for pyrazinamidase activity was performed on all PZA resistant isolates by either method. All test methods were performed at the National Tuberculosis Reference Laboratory, South Africa.

Results: Of the 860 isolates tested, PZA resistance was prevalent at 3.37% phenotypically and 2.44% genotypically. Resistance associated mutations were only found in the *pncA* gene and none in the *rpsA* or *panD* genes. Agreement between the phenotypic method and WGS was 99% for susceptible isolates and 55% for resistant isolates. Pyrazinamidase activity testing showed greater agreement with WGS compared to MGIT-based phenotype; 91% for PZA resistant and 100% for PZA susceptible (McNemar; $P = 0.5$) compared to 52% and 20% (McNemar; $P = 0.03$) respectively for the MGIT-based phenotypic method. This implies an approximate 50% false resistant rate when using the phenotypic method.

Conclusion: The phenotypic method lead to a significant number of false PZA resistance. Molecular PZA susceptibility testing by WGS is a more accurate tool for this important drug compared to the phenotypic method, thereby improving benefit to TB patients.

OA-362-04 Large pncA gene deletions in *Mycobacterium tuberculosis*: a novel mechanism of pyrazinamide resistance

E Streicher,¹ R Van Der Merwe,¹ S Sampson,¹ A Dippenaar,¹ M Whitfield,¹ N Da Camara,¹ P Van Helden,¹ P Arnab² ¹Biomedical Sciences, Stellenbosch University, Tygerberg, South Africa; ²King Abdullah University of Science and Technology, Thuwal-jeddah, Saudi Arabia. e-mail: lizma@sun.ac.za

Background: PZA has been used for the treatment of TB for the past 50 years and therefore its continued use in new and second line-treatment regimens requires accurate drug susceptibility testing to ensure optimal treatment. PZA susceptibility testing is currently not done routinely due to the complexity of the culture based methods. Molecular methods offer a rapid means to identify mutations in the pncA gene which have been previously associated with PZA resistance. This study aimed to investigate the failure to PCR amplify the pncA gene in selected clinical isolates using the recently reported DNA sequencing method to detect pncA mutations.

Design/Methods: A convenient sample set of 669 clinical strains with various drug susceptibility profiles and representing different strain lineages of *Mycobacterium tuberculosis* were sequenced using the Illumina HiSeq sequencing platform. An in-house pipeline was used to align sequencing reads to the reference *M. tuberculosis* H37Rv genome and identify SNPs, insertions and deletions. Deletions were confirmed by Sanger sequencing. A phylogenetic tree was constructed to investigate the relatedness of strains.

Results: Whole genome sequence analysis identified 23 clinical isolates in which the pncA gene was either partially or completely deleted. Six different deletion boundaries were identified, of which the deleted area ranged from 298 to 17133 bp in length. Two isolates showed mixed infections where the deletion was absent in one strain and present in another. Phylogenetic reconstructions confirmed clonality of strains with identical deletions.

Conclusion: This study adds to the complexity of the molecular basis of PZA resistance. The absence of part of or the entire pncA gene in clinical isolates needs to be considered when using molecular methods to determine PZA resistance. This study also highlights that non-essential genes can be deleted without compromising the ability of these strains to transmit. However, an in vitro growth deficit was observed in isolates harbouring these deletions.

OA-363-04 Virtual sequencing of the entire pncA gene target in a single tube using Late-PCR and Lights-On/Lights-Off probes to predict PZA susceptibility

B Kreiswirth,¹ J Rice,² L Wangh,² M Whitfield,³ R M Warren,³ J Posey,⁴ P Bifani,⁵ S Marras¹ ¹PHRI - Rutgers University, Newark, NJ, ²Brandeis University, Waltham, MA, USA; ³Stellenbosch University, Tygerberg, South Africa; ⁴U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁵Novartis Institute, Singapore, Malaysia. e-mail: kreiswba@njms.rutgers.edu

Background: Pyrazinamide (PZA) is a key first line antibiotic to treat tuberculosis and it has become a critical drug in recent clinical trials with experimental agents. Historically, phenotypic testing for PZA resistance has been problematic and in most settings the drug is used empirically with no laboratory support. Genotypic analysis of resistance has revealed over 371 mutations in pncA, the vast majority are non-synonymous and correlate with PZA resistance. Importantly, sequencing data also revealed that a wild-type pncA gene correlates with PZA susceptibility. We have developed a LATE-PCR assay using Lights-On/Lights-Off probes to distinguish the wild type drug susceptible pncA gene sequence from all strains that have non-synonymous genetic alterations.

Design/Methods: LATE-PCR is used to amplify a 685 base long amplicon encompassing the entire coding region of the pncA gene, including the upstream flanking sequence. Following amplification, the temperature of the reaction is lowered to 25°C resulting in the coating of the single-stranded DNA templates with 35 Lights-On/Lights-Off fluorescent probes labeled in three colors. The probes are then melted off of the target and the resulting fluorescent signature reveals the presence/absence of mutations, which are all distinguished from a highly reproducible wild-type profile. Total time per assay 3.5 hrs.

Results: The assay, run in triplicate, has been tested against a blinded panel of 206 DNA samples isolated from 103 in vitro resistant PZA mutants in the CDC1551 background, and 103 PZA resistant and susceptible clinical mutants. Among the 206 DNAs, 196 (95%) samples were correctly genotyped as wild type (susceptible) or mutant (presumed non-susceptible). One susceptible isolate with a wild type pncA was incorrectly called mutant and 9 isolates with mutations were incorrectly called wild type.

Conclusion: We have successfully designed and tested a single closed-tube assay that is able to identify and distinguish the wild type pncA gene from strains with any genetic alterations and provide an accurate and rapid method to predict a PZA susceptible strain. Additional refinements will improve identification of the rare synonymous mutations in pncA and the few non-synonymous that were not correctly scored as PZA resistance. Supported by NIH Grant #R21AI106551.

09. HIV and lung health

OA-364-04 CD4 count and risk of incident tuberculosis in HIV-infected individuals: a dose-response meta-analysis

W-C Lo,¹ S-C Pan,^{1,2} H Fu,¹ H-H Lin¹ ¹Institute of Epidemiology and Preventive Medicine College of Public Health, National Taiwan University, Taipei, ²Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. e-mail: nicholaslo0114@gmail.com

Background: The CD4 count level is an indicator for the risk of tuberculosis among HIV-infected individuals, but the dose-risk relation remains unclear. We systematically reviewed and meta-analyzed literature to examine and quantify the dose-response association between CD4 count level and risk of tuberculosis among HIV-infected individuals.

Design/Methods: Prospective cohort studies were searched for in PubMed until April 2014. Three independent reviewers conducted abstract and full-text review and extracted relevant information. Quality of included studies was assessed using Newcastle-Ottawa scale. Data were pooled using dose-response random-effects models. When nonlinear effect was identified, the generalized least squares cubic spline model was used for dose-response analysis. Subgroup analysis was performed stratifying by the status of antiretroviral therapy (ART) use.

Results: We identified 27 prospective cohort studies, which included 141,894 HIV-infected individuals with the follow-up period ranging from 6 to 72 months. In the pooled analysis, the risk of tuberculosis increased with decreasing CD4 count: the summary relative risk (RR) was 1.41 [95% confidence interval (CI) 1.30-1.54, I² = 77.5%] per 100 cell/ μ o decrease in CD4 count. Non-linear association was noted with Pnon-linearity = 0.005. Dose-response analysis suggested that the risk of tuberculosis increases rapidly with declining CD4 count when the level of CD4 count was below 350 cell/ μ o (Figure 1a). When stratifying by the status of ART use, the rise of tuberculosis risk with declining CD4 count was faster in those with partial (<57%) or no ART (Figure 1b). Even among those with ART, the risk of tuberculosis still increased with declining CD4 count, suggesting that delaying the initiation of ART might increase tuberculosis risk (Figure 1c).

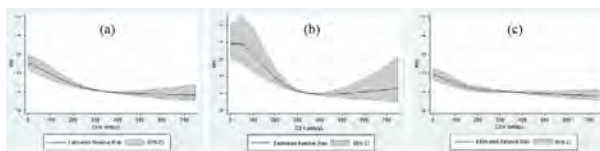


Figure 1. Non-linear dose-response curve of CD4 level and adjusted relative risk of TB based on different status of ART. (a) all studies included in meta-analysis (n=27). (b) partial or no participants under ART (n=11). (c) studies with all participants under ART (n=16). Restricted cubic splines were performed in a random-effects dose-response model. The solid line and the grey bands represented the estimated relative risk and the 95% CI respectively.

Conclusion: This dose-response meta-analysis of prospective studies revealed a nonlinear inverse association

between CD4 count and active tuberculosis risk. Information from this analysis could help determine the potential benefits of early ART initiation on reducing tuberculosis risk.

OA-365-04 Synergic effect on survival of streptomycin and an intensified anti-tuberculosis regimen in HIV-infected patients with tuberculous meningitis

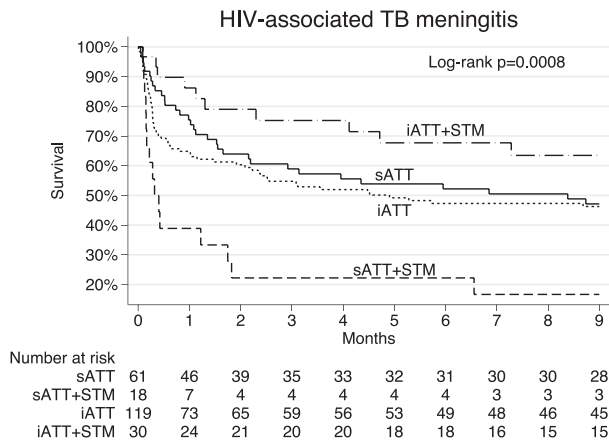
G Alvarez-Uria,¹ M Midde,¹ R Pakam,¹ P S Yalla,¹ P K Naik¹ ¹Rural Development Trust Hospital, Bathalapalli, India. e-mail: gerardouria@gmail.com

Background: The mortality of tuberculous meningitis (TM) in HIV infected patients is extremely high, and there has not been any major therapeutic breakthrough in the last decades.

Design/Methods: This is an observational study from a cohort study in Anantapur, India. We compared the mortality during the first nine months after TM diagnosis of 228 HIV-infected patients treated with a standard anti-tuberculosis therapy (sATT) (79 patients), an intensified ATT (iATT) (119 patients) and an iATT with streptomycin (iATT+STM) (30 patients). The sATT included rifampicin, isoniazid, ethambutol and pyrazinamide. The iATT included levofloxacin, ethionamide, pyrazinamide and double dosing of rifampicin and isoniazid, and was given only during the hospital admission (median 7 days, interquartile range 6-9). Univariate and multivariate analyses were performed using Cox regression proportional hazard models. Continuous variables that did not have a linear relationship with the log-hazard were transformed using restricted cubic splines.

Results: The mortality was similar in patients who received the sATT and the iATT. However, patients in the iATT+STM had significant lower mortality risk than patients in the sATT group (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.24 to 0.93), and the mortality difference at nine months was 23.3% (95%CI 2.1 to 44.5). After adjusting for other covariates, the mortality hazard of the iATT+STM vs. the sATT remained statistically significant (adjusted HR [aHR] 0.2, 95%CI 0.09 to 0.46). Other factors associated with mortality were being previously treated of tuberculosis (aHR 3.23, 95%CI 1.68 to 6.24), low albumin concentrations (aHR 0.74 per increase of 1 g/dl, 95%CI 0.58 to 0.95) and low CD4+ lymphocyte concentrations. The risk of death increased exponentially only with CD4+ lymphocyte concentrations below 100 cells/ μ l. High C-reactive protein concentrations were not associated with mortality in a subgroup of patients who received the iATT (with or without STM).

Conclusions: In this observational study in a resource-poor setting, the use of iATT with STM resulted in a clinically important reduction in mortality compared with the standard of care in HIV infected patients with TM. The results of this study deserve further research.



OA-366-04 One third of in-patients diagnosed with HIV-associated TB in Khayelitsha, South Africa, have mycobacteraemia associated with high mortality

S Janssen,^{1,2} C Schutz,² A Ward,^{2,3} R Burton,³ R Wilkinson,² M Grobusch,^{1,2} T Van Der Poll,^{1,2} G Meintjes² ¹Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; ²Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, ³Khayelitsha Hospital, Khayelitsha, South Africa. e-mail: s.janssen@amc.nl

Background: Mortality in patients with HIV-associated tuberculosis (TB) remains high despite availability of effective therapy, particularly amongst patients ill enough to require hospitalisation. We investigated prevalence and prognostic significance of TB mycobacteraemia in association with sepsis biomarkers.

Design/Methods: We conducted a prospective cohort study at Khayelitsha Hospital in Cape Town, South Africa. Hospitalized HIV-infected patients with CD4 counts <350 cells/uL that were diagnosed with, or had high clinical suspicion of TB on admission were selected randomly. At enrolment, sputum and blood cultures (BC) for TB, and sputum and urine Xpert were performed when specimens could be obtained. We restricted analyses to patients with microbiologically proven TB, who had a TB BC performed and did not have a BC positive for other pathological bacteria. Clinical characteristics and biomarkers in mycobacteraemic patients were compared to TB cases with negative TB BC. We used Cox proportional hazard models to assess the association of mycobacteraemia with time to death, adjusted for pre-specified co-variables (sex, age, antiretroviral therapy (ART) status, CD4 count, HIV viral load and haemoglobin).

Results: From January-September 2014 142 individuals were recruited, 116 had a discharge diagnosis of TB. Mycobacteraemia was found in 33% ($n = 39$). 73 microbiologically confirmed cases with a TB BC result were included in subsequent analyses. Of them, 53% were male; median age was 35 years (interquartile range (IQR) 28-43) and median CD4 count 59 cells/ μ L (IQR 17-102). Mycobacteraemia was found in 53%; 28% ($n =$

11) of mycobacteraemic patients died within 12 weeks, vs. 17% ($n = 6$) of patients with negative TB BC. Mycobacteraemic patients had elevated plasma concentrations of procalcitonin (median 4.4 vs. 0.8 ug/L, $P < 0.005$), CRP (median 176 vs. 105 mg/L, $P 0.02$) and D-dimer (1.3 vs. 1.1 mg/L, $P 0.09$), when compared with TB BC negative patients. Haemoglobin and lactate concentrations were not different between groups, but mortality was associated with higher lactate (median 2.9 vs. 1.7 mmol/L, $P = 0.003$). Mycobacteraemia independently predicted mortality. Older age, female sex and defaulting ART were also independently associated with mortality (Table).

Conclusion: In hospitalized patients with HIV-associated TB, mycobacteraemia was present in one-third, and independently predicted of mortality. Mycobacteraemia was associated with elevations of biomarkers that also characterize bacterial sepsis.

Table: Time to death in patients with microbiologically confirmed TB

Variable	Crude HR	95% CI	P value
Univariate analysis			
Mycobacteraemia	1.77	0.66-4.79	0.26
Female sex	2.23	0.82-6.03	0.11
Age (per 10 years increase)	1.93	1.31-2.83	0.001
CD4 count (per 100 cells/uL increase)	0.57	0.26-1.24	0.15
HIV viral load (per 100 000 copies/mL increase)	1.00	0.95-1.04	0.89
Haemoglobin (per 1 g/dL increase)	1.05	0.85-1.30	0.66
ART status			
ART naïve vs on ART	0.81	0.25-2.65	0.73
Default vs on ART	2.12	0.64-6.95	0.22
Multivariate analysis			
Mycobacteraemia	4.69	1.15-19.19	0.03
Female sex	3.50	1.12-10.96	0.03
Age (per 10 years increase)	3.03	1.76-5.23	<0.001
CD4 count (per 100 cells/uL increase)	0.92	0.40-2.09	0.84
HIV viral load (per 100 000 copies/mL increase)	0.97	0.92-1.03	0.37
Haemoglobin (per 1 g/dL increase)	0.93	0.73-1.17	0.52
ART status			
ART naïve vs on ART	1.11	0.29-4.31	0.88
Default vs on ART	4.73	1.15-19.52	0.03

OA-367-04 Low implementation of Xpert® MTB/RIF among HIV-TB co-infected adults: a survey of 19 low/middle-income countries from the IeDEA Consortium

K Clouse,¹ M L Lindegren,¹ M Yotebieng,² N Dung,³ A Omondi,⁴ D M Zannou,⁵ G Carriquiry,⁶ A Pettit¹

¹Vanderbilt University School of Medicine, Nashville, TN, ²The Ohio State University College of Public Health, Columbus, Ohio, USA; ³National Hospital of Tropical Diseases, Hanoi, Viet Nam; ⁴Academic Model Providing Access To Healthcare (AMPATH), Eldoret, Kenya; ⁵Université d'Abomey-Calavi, Cotonou, Benin; ⁶Instituto de Medicina Tropical Alexander von Humboldt, Ingenieria, Peru. e-mail: kate.clouse@vanderbilt.edu

Background: The World Health Organization (WHO) recommends Xpert MTB/RIF (Xpert) as the initial TB diagnostic for HIV-infected individuals but there are limited data describing real-world implementation of Xpert. We present Xpert implementation data from a large, global network of HIV treatment sites.

Methods: We conducted an observational cohort study among HIV-infected adults enrolled in HIV care/antiretroviral (ART) program sites participating in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium and clinically diagnosed with TB from 2012-2014. Data were collected on HIV-TB co-infected adults (age ≥ 18) regardless of ART status using a standardized electronic form. TB case validation was performed at sites by file review. We provide proportions for categorical variables and medians and interquartile ranges (IQR) for continuous; we use log-binomial models to estimate adjusted risk ratios (aRR) and 95% confidence intervals (95%CI) for unfavorable TB treatment outcome (death, default, failure, or undocumented).

Results: Twenty-two participating sites in 19 low/middle income countries provided data on 2780 patients; we excluded 283 (10.2%) missing Xpert utilization data, leaving 2497 participants. A majority was male (60.1%). At TB diagnosis, median age was 35 years (IQR: 29-42) and median CD4 count was 115 cells/ μ l (IQR:38-245). Of 2497 patients, 123 (4.9%) had a documented Xpert result; the remainder either did not have Xpert performed (70.2%) or had no recorded Xpert results (24.9%). Among 123 with Xpert performed, 75 (61.0%) were positive, 48 (39.0%) were negative, and none were invalid. Rifampicin resistance (RIF-R) was identified in 15 (20.0%) of Xpert-positive TB cases. Overall, 1626 (65.1%) TB cases were not bacteriologically confirmed by Xpert, AFB smear, culture or other nucleic acid amplification test. Adjusted for age, sex and CD4 at TB diagnosis, cases that had no documentation of an Xpert test or result were more than twice as likely to have an unfavorable treatment outcome than cases with an Xpert test (aRR:2.12, 95%CI: 1.14-3.92).

Conclusions: Use of Xpert for TB diagnosis among HIV co-infected patients in care in this global network is low. A majority of TB cases in this analysis had no documentation of Xpert testing on file, which was associated with unfavorable treatment outcomes. Future

operational research must address implementation challenges of Xpert in order to adhere to the WHO recommendations.

Multivariate analysis of factors associated with unfavorable TB treatment outcomes* among HIV/TB co-infected patients (N=2497).

	n (%)	Crude RR (95% CI)	Adjusted RR** (95% CI)
Xpert result documented**			
No	504 (27.6)	2.15 (1.20, 3.86)	2.12 (1.14, 3.92)
Yes	10 (12.8)	1	1
Age at TB diagnosis			
18-29 years	109 (24.9)	0.98 (0.80, 1.20)	0.92 (0.73, 1.16)
30-39 years	202 (25.4)	1	1
40 years and older	203 (30.2)	1.19 (1.01, 1.40)	1.18 (0.99, 1.41)
Sex			
Female	210 (26.3)	1	1
Male	304 (27.5)	1.04 (0.90, 1.22)	0.95 (0.81, 1.13)
CD4 value at TB diagnosis			
<50 cells/mm ³	163 (34.5)	1.74 (1.33, 2.26)	1.73 (1.33, 2.26)
50-199 cells/mm ³	160 (26.1)	1.31 (1.00, 1.72)	1.31 (1.00, 1.72)
200-350 cells/mm ³	56 (19.9)	1	1
>350 cells/mm ³	42 (18.1)	0.91 (0.64, 1.31)	0.90 (0.63, 1.30)

RR, risk ratio; CI, confidence interval; n (%) show proportion with an unfavorable outcome in each category

Adjusted model includes all variables listed.

*Unfavorable outcomes include death (190, 7.6%), default (93, 3.7%), failure (5, 0.2%) or undocumented (226, 9.1%). Favorable outcomes include cured (558, 22.4%) or completed treatment (831, 33.3%). Transfer (105, 4.2%) and still on-treatment (68, 2.7%) outcomes were excluded. 422 participants (16.9%) were missing outcome data (no response was provided), including all participating sites in Central and South America, and were excluded from this regression analysis.

**Documentation of Xpert test and result recorded in patient medical file.

OA-368-04 Wide variations in compliance with tuberculosis screening guidelines and tuberculosis incidence between antiretroviral therapy clinics, Ivory Coast

A Auld,¹ M Blain,¹ K Ekra,² J Kouakou,² R Shiraishi,¹ M Tuho,³ V Ettiègne-Traoré,³ T Ellerbrock¹ ¹Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Centers for Disease Control and Prevention, Abidjan, ³Ministry of Health, Abidjan, Ivory Coast. e-mail: aauld@cdc.gov

Background: In Ivory Coast, tuberculosis (TB) is a common cause of death among antiretroviral therapy (ART) enrollees. In accordance with World Health Organization (WHO) guidelines, Ivorian guidelines recommend screening for TB and initiation of treatment for active TB before ART initiation. Compliance with these guidelines can reduce TB-related morbidity and mortality during ART.

Design/Methods: In a retrospective cohort study, 34 from 78 ART facilities with at least 50 ART enrollees were randomly selected using probability-proportional-to-size sampling; at these facilities 3682 adults (≥ 15 years old) starting ART during 2004-2007 were randomly selected. Controlling for survey design, TB screening compliance, prevalence of active TB at ART initiation, and incidence of TB during ART were evaluated.

Results: At ART initiation, median age was 36 years, 67% were female, and median CD4 count was 135 cells/ μ l. Among all 3682 enrollees, 73 (2%) were on TB treatment at the time of referral to the ART clinic. Among the 3609 not on TB treatment, 1,263 (36%) were documented to receive some TB screening before ART initiation; 21% were screened for cough, 21% for weight loss, 18% for fever, 18% for TB contacts, and 12% for night sweats. All five TB screening questions were

administered to only 11% of patients. Among the 1,263 screened, 111 (11%) were diagnosed with TB and started TB treatment before ART initiation. No associations between patient characteristics and probability of being screened were noted. However, TB screening compliance varied widely by ART facility from 0–100%. At ART initiation, WHO stage IV was more common among patients taking vs. not taking TB treatment (63% vs. 19%, $P < 0.001$). TB incidence during ART was 3.04 per 100 person-years but varied widely by ART facility from 0/100 person-year to 13.1/100 person-years.

Conclusion: Compliance with TB screening guidelines was low. No evidence that clinicians were selectively screening patients with more advanced disease was found. Rather, facility-level factors such as training programs, or patient-to-provider ratios might explain facility variations in TB screening compliance. Targeting under-performing sites with improvement activities is needed. Facility variations in TB incidence warrant further research; they could reflect facility differences in TB screening or diagnostic practices, documentation, or TB risk possibly related to infection control practices or local community TB incidence.

OA-369-04 Routine implementation of 6-month isoniazid preventive therapy among HIV-infected patients in seven pilot sites in Zimbabwe

K Takarinda,^{1,2} R Choto,² A D Harries,^{1,3} T Apollo,² C C Musanhu⁴ ¹International Union Against Tuberculosis and Lung Disease, Paris, France; ²Ministry of Health and Child Care, Harare, Zimbabwe; ³London School of Hygiene & Tropical Medicine, London, UK; ⁴World Health Organization Country Office, Harare, Zimbabwe. e-mail: ktakarinda@theunion.org

Background: Isoniazid preventive therapy (IPT) is recommended for HIV-infected individuals because of their susceptibility to tuberculosis (TB). As from December 2012, Zimbabwe piloted the roll-out of IPT to HIV-infected patients enrolled at 10 public-sector antiretroviral therapy (ART) clinics. We therefore set out to determine the extent of non-completion of IPT and the associated factors in order to inform the scale-up of IPT countrywide.

Design/Methods: This study was a retrospective cohort study and data were abstracted from patient records for all HIV-infected patients enrolled on IPT between 31 December 2012 and 01 March 2013 in 7 of the 10 IPT pilot sites. Descriptive statistics were calculated using univariate analysis and factors associated with non-completion of IPT were established using multivariate logistic regression.

Results: Of the 578 patients, 466 (81%) completed the 6 month IPT course. Of the 112 patients who failed to complete IPT, 69 (60%) were lost to follow-up, 30 (27%) stopped treatment but with undocumented reasons and 8 (7%) developed adverse reactions and /or TB. In multivariate analysis, patients on ART were 93% less likely [adjusted odds ratio (AOR) = 0.09, 95% confidence interval (CI) = (0.03-0.28)] not to complete IPT

compared to pre-ART patients. Having ≥ 1 documented default visits from ART in the year prior to commencing IPT [AOR = 5.25, 95% CI = (2.10-13.14)] was associated with five-fold higher risk of non-completion in comparison to timely attendance of review visits in the past year. Patients who received IPT drugs for ≥ 2 months upon initiation of IPT were 48% less likely not to complete IPT [AOR = 0.52, 95% CI = (0.28-0.95)] when compared to those who received one month's supply of IPT drugs upon initiation of IPT.

Conclusion: The completion rate of IPT in Zimbabwe was high, and therefore expansion of IPT countrywide is feasible. Patients with a previous history of defaulting ART and those in pre-ART care have a higher risk of non-completion and hence require close monitoring to ensure they complete their treatment. Though dispensing a month's supply of isoniazid prophylaxis in the first month of treatment is recommended for close patient monitoring, this was linked with non-completion of treatment and may require synchronisation with ART drug pick-up times to achieve better IPT completion rates.

OA-370-04 The effect of antiretroviral therapy on chronic lung disease in vertically HIV-infected children and adolescents

G Mchugh,¹ J Rylance,^{2,3} E Majonga,^{1,4} J Metcalfe,⁵ T Bandason,¹ H Mujuru,⁶ K Kranzer,⁴ R Ferrand^{1,4}

¹Biomedical Research and Training Institute, Harare, Zimbabwe; ²University of Liverpool, Liverpool, ³Liverpool School of Tropical Medicine, Liverpool, ⁴London School of Hygiene & Tropical Medicine, London, UK; ⁵University of California San Francisco, San Francisco, CA, USA; ⁶University of Zimbabwe, Harare, Zimbabwe. e-mail: graceandandre@gmail.com

Background: HIV infection is a recognised cause of chronic lung disease. We conducted a cross-sectional study to investigate whether antiretroviral therapy (ART) reduces morbidity associated with chronic lung disease. We report findings comparing older children and adolescents with HIV receiving ART and a frequency aged matched group of children who have been newly diagnosed with HIV

Design/Methods: HIV- infected older children and adolescents (age 6-16years) on ART for at least 6 months and newly diagnosed ART- naïve HIV-infected children and adolescents underwent clinical examination including spirometry, shuttle walk testing and pulse oximetry. Laboratory examinations included CD4 count and HIV viral load testing.

Results: 200 participants on ART, median age 11 years (IQR 9-12), 104 (52%) male, mean age of diagnosis was 5 years old were recruited along with 385 ART naïve participants, median age 11 years (IQR 8-13) of whom 186(48%) were male. The median CD4 count in the treated group was 729 cells/ μ L (IQR 479-935) compared to 375cells/ μ L (IQR 215-599) in the untreated group ($P = 0.01$). Of those who had results available, 26% of ART naïve participants showed either obstruction or restriction on spirometry with poor reversibility.

Similarly, 25% of ART experienced participants showed either obstruction or restriction, again with poor reversibility. ART naïve $n = 385$ ART experienced $n = 200$, P value Age, Y, median (IQR) 11(8-13) 11(9-12) 0.67 Sex –male (%) 48 52 0.37 CD4 Count, cells/ μ L, median (IQR) 375(215-999) 729(479-935) 0.01 History of pulmonary tuberculosis (%) 5 38 <0.01 Cough (%) 53 15 <0.01 Breathless (%) 18 6 <0.01 Smokers in Household (%) 25 21 0.32 MRC Dyspnoea score ≥ 2 (%) 16 14 0.58 SpO₂ <88% (%) 14 1 <0.01 Respiratory Rate >30/min (%) 5 3 0.28 $\geq 5\%$ desaturation post exercise (%) 27 12 <0.01 FEV1 z score, mean(sd) –0.73 (1.40) –0.73 (1.20) 0.99 FVC z score, mean (sd) –0.63(1.35) –0.79(1.24) 0.22 FEF 25%-75% Z score, mean (sd) –0.19 (1.13) –0.08 (1.20) 0.34

Conclusion: Although ART naïve group reported a higher rate of symptoms, there was no difference in lung function between the two groups. While ART improves immune status, it appears to have little impact on improving lung function in children with longstanding HIV infection. Interventions to treat and reduce the significant burden of chronic lung disease are required.

OA-371-04 Patient characteristics and contribution to overall caseload from three different TB case-finding strategies in Blantyre, Malawi

P Macpherson,^{1,2} E Webb,³ A Choko,⁴ M Nliwasa,^{3,4,5} A Mdolo,⁴ J Mpunga,⁶ L Chiume,⁴ L Corbett^{3,4} ¹University of Liverpool, Liverpool, ²Liverpool School of Tropical Medicine, Liverpool, ³London School of Hygiene & Tropical Medicine, London, UK; ⁴Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, ⁵University of Malawi, Blantyre, ⁶Ministry of Health of Malawi, Lilongwe, Malawi. e-mail: p.macpherson@liverpool.ac.uk

Background: In high HIV-TB burden settings, slow progress towards targets indicates that more proactive TB case-finding strategies are required. Community-wide interventions may affect subsequent health-seeking behavior, as well as providing diagnosis.

Design/Methods: Between January 2011 and August 2014, electronic records including mode of detection (passive case finding, HIV-TB screening, or community-wide active case-finding (cwACF) were collected from all registering TB patients in 11 facilities in Blantyre, Malawi. cwACF used 6-monthly door-to-door enquiry for TB symptoms and smear microscopy in 3 informal settlements (total adult population 114 450). Multinomial logistic regression was used to compare characteristics of individuals registering for TB treatment by mode of detection.

Results: Overall, 10 240 adults were registered with TB, with 9308 (90.9%) identified through passive case finding, 144 (1.4%) through cwACF and 785 (7.7%) through HIV-TB screening. Overall smear-positive case-notification rates increased by 38% in the first year for communities provided with cwACF (230/100 000 in 2010 to 316/100 000 in 2011) and by 11% for non-cwACF communities (144/100 000 in 2010 to 160/100 000 in 2011). Adults identified through cwACF (com-

pared to passive case finding and HIV-TB screening respectively) were younger (median age: 32y vs. 34y vs. 35y; $P = 0.046$) were as likely to be men (58% vs. 60% vs. 59%; $P = 0.718$), were less likely to be HIV positive (59% vs. 73% vs. 86%; $P < 0.001$), but had similar rates of taking antiretroviral therapy if HIV-positive (67% vs. 68% vs. 65%; $P < 0.490$). On age- and sex-adjusted analysis, HIV prevalence remained significantly lower in adults with TB identified through cwACF (RR: 0.52; 95%CI: 0.36-0.74) and highest in adults identified through HIV-TB screening (RR: 2.33, 95%CI: 1.87-2.90) compared to self-presenting patients.

Conclusion: In this large citywide comparison, patient characteristics differed substantially under three different TB case-finding strategies. Passive case-finding remained the dominant mode of detection, but cwACF identified greater proportions of HIV-negative patients, and showed additional major indirect benefits in addition to the direct yield, likely from a lasting impact on health-seeking behaviour. Combined TB case-finding strategies are likely to have complementary benefits.

10. Using media for communication on TB

OA-372-04 Mass media communication campaign, a solution for reaching the unreachable: an experience from six states in India

S Pandurangan,¹ S Mohanty¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 11 46 05 40 30. e-mail: sripriya14@gmail.com

Background: TB remains one of the India's greatest public health challenges and accounts about 300 000 deaths per year. Lack of awareness about tuberculosis is one of the main reasons for huge TB burden in the country. The Union, through the project Axshya conducted a mass media campaign to improve the awareness level among the general population in six states of India. The campaign was conducted through a combination of mid-media, static media and mass media campaign in the program states. The first round of campaign was conducted in March 2012 and the second was in the month of December 2012. This paper presents the level of exposure of the IEC campaign in increasing the knowledge about early diagnosis of Tuberculosis and its treatment services in different localities. Methodology: Two rounds of cross sectional community based survey was conducted adopting multistage systematic random sampling in 30 districts of 6 states of India. The estimated sample size was 2426 from 30 districts in the 6 states considering 5% change in two years. A structured pretested questionnaire was administered to capture information on media exposure and awareness.

Results: Nearly 60 % of the general population in urban areas reported that they had seen or heard any mass media or mid-media or static media campaign on TB

during the last one year. In rural areas nearly one third population reported the same. Under mass media, the exposure of TV Commercial in comparison to radio commercial and radio jingles is nearly five times higher in both the areas i.e. rural and urban. Around 50% respondents reported that they have seen TV commercial on TB in the last one year whereas in rural areas only 26% reported so. Overall, nearly one third respondents reported to have watched TV Commercial and only 6.6% reported to have heard radio commercial/jingle on TB during the reference period.

Conclusion: This study highlights the reach of IEC campaigns in urban and rural areas. The influence of mass media campaign is seen more in urban areas than in rural areas. This study emphasizes the need for designing suitable campaigns to reach out to rural areas.

Table Exposure to campaign in program areas

Campaign exposure	Total	Urban	Rural
Exposed to any campaign activity	42.2	59.9	34.0
Exposed to Mass Media (TVC & Radio)	34.9	51.1	27.5
Exposed to TVC	33.8	50.3	26.1
Exposed to Radio	6.6	11.4	4.4
Exposed to Mid Media			
(Street theater/ Mobile van)	14.0	22.3	10.4
Exposed to street theater	9.3	16.1	6.1
Exposed to activation car activity	6.7	9.9	5.3
Exposed to Static Media			
(Hoarding/Poster/wall painting)	18.1	29.5	12.8
<i>n</i>	2551	807	1744

OA-373-04 Are TB-related issues still not an agenda for Indian media? Analysis of TB-related news content in the last year

S Satapathy,¹ S Chadha¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: Sachi.Satapathy@theunion.org

Background: The responsibility of TB control needs to move from doctors to medical administrators and politicians and most importantly solutions should be found by involving all stakeholders –from health care professionals and policy makers to the people and communities. This is where role of media paramount importance. The studies have been made from 15 April 2014 to 15 April 2015 to find out how national print media in India have flashed the issue of TB to analyse what is the present media interest on the issue and how and what more can be done to address the gap if any.

Design/Methods: The newspapers of one year (Feb 2014-Feb 2015) have been scanned to review the nature of articles and accordingly a classification has been made on the basis of news from government, civil society, private practitioner, community, editorial piece, event, TB patients, drugs and controversies and an attempt has been made to find the knowledge, interest of media on this issue.

Results: Government (govt.) related program and launch of govt. led initiatives have got highest coverage in the national media (39%) of all the news on tuberculosis in India followed by corporate partnership issue (28%) and

celebrity involvement/engagement (16%). The news on new research, drugs, and initiatives has been covered by 3 media houses once in whole last year. The worrying factor is that issue of tuberculosis-diabetes linkages issue, which is going to hit the country like India in coming years has so far not become a media interest in the country. The local edition of national newspapers have tried to focus issue of city specific TB cases, how elders in a particular states have become great contributors to tuberculosis, prisoners' infected on TB, private providers issues in some point of time. It shows that the main agenda of the tuberculosis control program as being strategized in Stop TB partnership has not so far become an issue for media.

Conclusion: The research on media interest shows that mainstream media are not so far open up their spaces for tuberculosis issues as required to reach out to communities. This requires to strategize and make a plan to engage media houses in an innovative campaign strategy to achieve the desired objective.

OA-374-04 Building partnerships with community radio for TB control: a field report from India

A Srinivasan,¹ N Krishnan,¹ R Ananthakrishnan¹ ¹REACH Resource Group for Education and Advocacy for Community Health, Chennai, India. e-mail: anupamasrinivasan.reach@gmail.com

Background: Community-owned and operated media are uniquely positioned to disseminate information about TB, thereby improving awareness of the disease among communities. Community radio stations (CRS) in India have been broadcasting programmes on health since their inception in the early 2000s. CRS have unique relationships with their local communities who are active listeners and often contribute to the process of creating content.

Intervention: As part of countrywide efforts to involve civil society in TB control activities through Project Axshya, CRS have been trained to produce high-quality radio programming on TB. Their primary mandate is to address gaps in knowledge on TB and connect people to local services. All CRS chosen as partners participate in an intensive workshop and receive a customized toolkit with talking points about different TB topics as well as mentoring support through the project period. CRS are linked with District TB Officers and NGO partners in their respective locations. In addition, CRS are mandated to organize regular community meetings that feature live broadcasts and Q & A sessions with public health providers.

Results: In five years, 40 stations have produced and broadcast 550 original episodes on different TB-related topics. Repeat broadcasts have attempted to enhance listenership and ensured over 900 hours of programming on TB on air. 120 community meetings have been held, providing listeners with an opportunity to interact directly with local service providers. Through their interactions with listeners, CRS have focused on two

key messages: that TB is curable and that high quality, free TB services are available.

Conclusion: While community radio faces considerable competition from private and commercial radio stations, it remains one of the few sources of credible health information in remote, hard-to-reach areas as is evident from the example of Kerala-based stations serving primarily tribal populations. However more research is required to understand the exact nature of CRS listenership and thereby customize programmes on TB for local communities. Through this intervention, CRS have built mutually rewarding relationships with district and state TB centres, with potential for long-term partnerships. This intervention has demonstrated the potential of CRS as a medium for social mobilization and sustained advocacy on TB.

OA-375-04 Keeping TB alive in the public domain through sustained media engagement: a report from India

A Srinivasan,¹ R Ananthakrishnan,¹ N Krishnan,¹ S Prasad² ¹REACH-Resource Group for Education and Advocacy for Community Health, Chennai, ²Lilly MDR-TB Partnership, New Delhi, India. e-mail: anupamasrinivasan.reach@gmail.com

Background: Public health issues continue to find limited space in newspapers in India. Given that newspapers remain a trusted source of health information in India, improving the frequency and quality of reporting on TB is imperative. This can help meet the knowledge gap on TB and give readers access to accurate information on symptoms, diagnosis and treatment.

Intervention: The media engagement programme was initiated in 2010 to improve the quality and frequency of media reporting on TB, particularly among local language media. Through annual fellowships programme, 62 mid-career journalists have received fellowships to investigate TB-related issues. All Fellows participate in an intensive orientation, learning about the science of TB and identifying locally relevant TB stories. In addition, Fellows, current and former, receive resources on TB and have access to key leaders in the TB community. The best reporting on TB is recognized through annual awards presented on World TB Day. Most recently, a pilot initiative has involved former Fellows as media trainers at journalism schools, thereby giving students an introduction to reporting on TB.

Results: In all, 62 Fellows have written 257 stories on different aspects of TB, all published in leading dailies and magazines. 46% of Fellows have continued to report on TB beyond the Fellowship period and 36% have demonstrated interest in improving their capacity to report on TB. In addition, over 10% of Fellows have voluntarily expanded their mandate to advocacy, such as lobbying for inclusion of TB in political manifestos. 23 journalists have received awards for effective reporting on TB. 92 journalists have received regular resources and information on TB. 15 resources have been published including a comprehensive FAQ, an introduction to

ethical reporting on TB and an overview of World TB Day themes. Overall, the initiative has engaged journalists based in 13 states in India and generated reporting on TB in at least seven different languages.

Conclusion: This initiative has drawn attention to the necessity of sustained engagement with the media if TB is to remain alive in the public domain. The Fellowship programme has demonstrated the long-term impact of investing in building the capacity of local language media. This process of engaging media in a sustained manner can potentially be replicated in other high-burden countries where there is limited reporting on TB.

OA-376-04 TB in the spotlight: media fellowships as a model for raising public investment in TB in India

A Buragohain,¹ A Jacob,¹ P Lal¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 11 46 054 430. e-mail: aburagohain@theunion.org

Background: India's devastating TB burden – over 1.5 million new patients annually – is overwhelmingly borne by the country's poor and marginalised communities giving rise to a popular conception of TB as “a disease of the poor.” Despite being one of India's greatest public health challenges, TB lacks attention in the public domain. Media reports on TB tend to be infrequent and reflect news of organisations working in TB control. Realities of the programme and patients on the ground are almost completely absent from mainstream media and consequently the public imagination.

Intervention: A media fellowship was designed to promote reporting on TB, through which reporters and researchers were invited to report on contemporary practices around TB in India and the ways in which it constituted “a disease of the poor.” The budget of USD 10 000 for the fellowship was drawn from the WHO DOTS Expansion TB and Poverty sub-working group secretariat, which was housed at The Union South-East Asia Office between 2008 and 2014.

Methodology: Through a national call for applications, applicants were asked to submit a letter of editorial support and propose at least two story ideas for investigation. Field visits were stipulated as a necessary component. After a screening process, nine regional and national journalists from across India were selected. They were linked to technical staff at The Union for access to the research and resource persons to develop the focus of their stories. Each fellowship included a stipend of USD 800.

Results: A total of 24 in-depth feature articles/ episodes were completed by 9 journalists over 9 months. Chronicling issues of access and quality of TB care in India, these were published/broadcast in leading media outlets and gained significant traction. Topics ranged from Non-clinical barriers to TB treatment (stigma, psychosocial support, malnutrition); TB as an occupational health hazard (weavers, miners, bidi rollers); to TB in special zones (refugee colonies, urban slums).

Conclusion: The reports thus produced were unique in highlighting the broader issues of human development – the structural and socio-political conditions – that influence the condition for TB treatment in India. Several of the fellows continue to report on TB today, attesting to returns beyond the duration of the intervention. A focus on the complex realities of TB care on the ground was informative both for public health advocates and raising public consciousness on TB.

OA-377-04 Promoting evidence-based reporting on lung health diseases and enhancing visibility in news media

R Dwivedi¹ ¹Citizen News Service - CNS, Lucknow, India.
Fax: (+91) 522 235 8230. e-mail: rahul@citizen-news.org

Background and challenges to implementation: As Citizen News Service (CNS) specializes in evidence based health reporting, it strides to identify structural barriers by engaging with affected populations; and listen, learn and document their voices along with national and international health experts on a range of lung health diseases; and getting news stories published through CNS syndication in order to enhance more visibility on lung health issues.

Intervention or response: CNS facilitates a Health Writers' Network that connects health writers/ reporters, particularly from the developing nations, and hosts online dialogue and debate on a range of cross-cutting priority health issues for building the understanding and sensitivity of CNS Health writers around lung health issues. With support from the Union, CNS develops issue brief on specific lung health issue each month to share with health writers and help them in developing evidence based news stories with inputs from issue brief, health experts and affected people. The news stories get published in newspapers, websites and widely disseminated through social media with specific hashtag (#Lunghealth). Apart from this CNS also organizes 'Media Dialogues' on specific issues engaging journalists of English and vernacular languages at local level with a view to increase sensitive reporting on lung health diseases.

Results and lessons learnt: In the last two year CNS has circulated around 36 issue briefs on specific lung health diseases, among health writers which have generated more the 500 news stories from various Asian and African countries mainly. CNS has also organised more than 40 media dialogues on the health issues, which have generated more than 400 news items in print and online media in vernacular and English languages at local level. Apart from these news stories CNS also documents 'Best Practices in Programmatic Management of Drug Resistance Tuberculosis' (PMDT) from 14 sites in India, Voices of unheard – Report on Childhood TB and Voices from the Field of Childhood Pneumonia

Conclusions and key recommendations: CNS strongly believes that it is critically important to ensure evidence based health reporting and engagement with affected

population to identify structural drivers and specific linkages between health and development issues.

OA-378-04 Use of commercial marketing and mass media tools for TB health promotion and education

M Villapando,¹ E B Generoso,¹ C Cotingting¹

¹Communication for Health Advancement through Networking and Governance Enhancement (CHANGE) Project, Makati, Philippines. e-mail: crystle.cotingting.change@grey.com

Background: Among the barriers associated with poor utilization of TB diagnosis and treatment services in the Philippines include misconceptions and social stigma surrounding TB, the unpopularity of visiting public health facilities and the tendency of Filipinos to self-medicate. Past TB communication strategies relied more heavily on interpersonal communication at the local health center, overlooking mass media.

Intervention: Under the USAID/Philippines-supported CHANGE project, two television campaigns were developed using a commercial marketing perspective. The target audiences of the campaigns were mostly from lower socioeconomic classes (Class D, E). The first campaign, a brand ambassador campaign, employed a likeable, credible entertainment personality to deliver the message that TB is curable. The message was set to upbeat music and comedic tones, in contrast to previous, more somber campaigns. The second TV ad employed the classic side-by-side / split-screen styles (i.e. Brand X vs. Y campaigns) to contrast successful recovery with the Directly Observed Treatment-Short Course against the deteriorating condition of one resorting to ineffective remedies. The ad sought to encourage seeking consultation when suspecting TB. Both ads underwent a series of pre-testing for message comprehension and acceptability before airing. The campaigns were aired in two phases, averaging 20 spots per week over a 15-week period for the first phase and for 14 weeks, in a "flighting" scheduling pattern that created the semblance of continuous airing, for phase two. An external research firm was employed to conduct a nationwide evaluation of the campaign with a survey of 2000 respondents.

Results: At the end of the campaign, a majority (54%) of those who had experienced at least one TB symptom now sought consultation, an increase from the baseline of 45%. A significant decrease from 42% to 34% in agreement to the statement, "TB is very contagious, so we should keep away from people with TB" indicated softening of attitudes towards people with TB, aiding to the objective of alleviating stigma. Ninety-six percent of people reached were now aware that TB is curable vs. 91% prior to the campaign. Of those interviewed, 70% were able to correctly identify the ads' key messages.

Conclusions: The results indicate that both ads had successfully communicated the key messages, demonstrating that mass media is a viable vehicle to encourage better health seeking behavior and practices.

POSTER DISCUSSION SESSIONS

01. Extra-pulmonary tuberculosis: detection and treatment

PC-700-04 Pott's disease: epidemiological aspects, diagnosis and prognosis in Ouagadougou

G M E Badoom Ouedraogo,¹ A Kabre,¹ K Boncounou,¹ G Ouedraogo,¹ A R Ouedraogo,¹ S Zabsonre,¹ M Ouedraogo¹ ¹Centre Hospitalier Universitaire Yalgado Ouedraogo, Burkina Faso. e-mail: gisebad@yahoo.fr

Background: Tuberculosis spondylitis or Pott's disease corresponds to the appearance of an infectious tubercular process on one or several disco-vertebral joints. The purpose of this study was to specify the epidemiological, diagnosis, therapeutic and prognosis aspects of Pott's disease at the University Teaching Hospital Yalgado Ouedraogo of Ouagadougou.

Methodology: This study was retrospective in nature. It involved 103 patients and was carried out over a period of 6 years in the Department of Neurosurgery.

Results: The average age of participants was 46.2 years. Men were more affected, the sex ratio was 1.6. Most patients (73%) were from disadvantaged social and professional groups. Spinal pain was the most common reason for consultation in 93 cases (90.3%). An average delayed patient consultation period of 10 months was noted. The lumbar spine was most affected in 54.4% of cases. The results of the tuberculin skin test were positive in 91.35% of cases. Even though no culture was made, a sputum examination for acid-fast bacilli was positive in 4.8% of cases. The treatment consisted in a 9-month antituberculosis chemotherapy associated or not to an orthopedic (12 cases) and/or surgical treatment (1 case). The evolution was good in 61% of cases and sequelae were observed in 37% of cases. In 1.9% of cases, evolution resulted in the death of the patient.

Conclusion: Pott's disease continues to be a public health problem because it affects a young working population. Antituberculosis chemotherapy is the primary method and often a sufficient one in treating the disease. However, surgery is still an option especially in a context where complications are frequent at the diagnosis stage.

PC-701-04 Detection of multidrug-resistant tuberculosis in extra-pulmonary specimens by line probe assay: experience from a National Reference Laboratory

R Singhal,¹ J Anand,¹ M P Bhalla,¹ G Kumar,¹ A K Verma,¹ J Arora,¹ V Myneedu,¹ R Sarin¹ ¹National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India. e-mail: drritugo@gmail.com

Background: Extra-pulmonary tuberculosis (EPTB) accounts for 10-15% of all cases. GenoType MTBDRplus; Line probe assay (LPA) is used as primary test for the detection of multi-drug resistant tuberculosis (MDR-TB) in pulmonary cases by National Programme in India. As

no experience is available on direct testing of EP samples using MTBDRplus, present retrospective study was conducted to determine its utility in these pauci-bacillary samples.

Materials and methods: The present retrospective study was conducted in Department of Microbiology, National Reference Laboratory under Revised National TB Control Programme. 644 EP samples from presumptive MDR-EPTB patients were received from 1st January 2014 to 31st August 2014. The samples were subjected to smear microscopy and processing as per RNTCP guidelines. Processed smear positive specimens were subjected to LPA and smear negatives were inoculated in MGIT 960 culture. Positive tubes identified as *M. tuberculosis* were subjected to LPA.

Results: Majority of patients (407/ 644; 63.2%) were in 15-35 years followed by 124/644; 19.3% in 36-60. Pediatric and geriatric patients were 90/645; 14.0% and 23/645; 3.6% respectively. Male: female ratio was 1:1. Commonest sample was fine needle aspiration (FNA) of lymph nodes (349/ 644; 54.2%), followed by pleural fluid (255/644; 39.6%), majority being exudative (157/ 255; 61.6%). Other samples included biopsies (12/645; 1.9 %), ascitic fluid (10/644; 1.6%), CSF (8/644; 1.2%), synovial tissue (4/644; 0.6%), urine (2/644; 0.3%), bone tissue (2/644; 0.3%) and one each of abscess (1/664; 0.15%) and endometrial aspirate (1/664; 0.15%). Total of 185; 28.7% samples were smear positive, of which 167; 90.3% gave valid results directly from sample in an average turn-around time of 3.3 days. 35/185 (20%) cultures were positive for mycobacteria of which 1 was non-tuberculous mycobacteria and remaining were *M. tuberculosis*. Total of 32/220 (15.8%), 10(5%) and 15(6.8%) strains were MDR, rifampicin mono-resistant and INH mono-resistant respectively. Commonest mutation in rifampicin and isoniazid were missing wild type with specific mutation S531L (33; 76.7%) in *rpoB* and missing wild type with specific mutation in S315T1 in *katG* 26; 57.8% respectively.

Conclusion: Genotype MTBDRplus is a useful rapid test for detection of MDR-TB in smear positive EP-TB samples. It is essential to perform structured studies to generate validation data of test against reference standard methodology.

PC-702-04 Predictors of success factors of extra-pulmonary tuberculosis treatment using the DOTS strategy in Dr. Cipto Mangunkusumo Hospital, Jakarta

T Kamelia¹ ¹Pulmonology Division, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Fax: (+62) 878 8159 7886. e-mail: tellybahar@gmail.com

Background: Extrapulmonary tuberculosis (EPTB) is a common presentation found in Indonesia, besides Tuberculosis (TB). We found that there were only few researches on EPTB in Indonesia, especially regarding the success of EPTB treatment using the DOTS strategy and its predictor factors. We aim to determine predictors of TB treatment success factors such as age, sex, diabetes

mellitus, HIV and anti-tuberculosis records. We also want to determine the success rate of EPTB treatment using DOTS strategy which is administered for a minimum of 9 months in our institution.

Design/Methods: A retrospective cohort study was conducted on medical records from January 1st, 2008 to December 31st, 2012. Medical records were taken from Dr. Cipto Mangunkusumo Hospital, one of the top national referral hospitals in Indonesia. A total of 542 patients of EPTB were identified, 193 patients were pure EPTB while 279 had mix of pulmonary TB and EPTB. Seventy records were not eligible due to incomplete data.

Results: The majority of patients were female (52.3%) and age 18-60 years old, mean 31,34 + 11,64 years old, (95.9%). The most common site of EPTB were lymph (56.9%). There are 61, 66% of EPTB patients who received treatment for <9 months. In bivariate analysis, successful treatment of EPTB among age of 18-60 years rated 49.7% (OR 2.97, 95%CI 0.59 to 15.09, $P = 0.313$). In patients treated for ≥ 9 months, success rate was 94.6%. Successful treatment of EPTB among female rated 55.4% (OR 1.77, 95%CI 1.00 to 3.13, $P = 0.05$). Successful treatment using DOTS strategy among patients with diabetes mellitus rated 33.3% (OR 1.96, 95%CI 0.48-8.06, $P = 0.546$) and the rate in patients that had past antituberculosis medication was 55,6% (OR 0.74, 95%CI 0.28-1.96, $P = 0.717$). Successful treatment in EPTB patients among HIV-seropositive rated 32,1% (OR 2.59, 95%CI 1.33-5.04, $P = 0.007$). In multivariate analysis, EPTB with HIV co-infection factor had OR 2.59, CI 95% 1.33-5.04, $P = 0.005$, for the success rate. EPTB among HIV-seropositive patients had lower therapy success rate using DOTS strategy and were associated with unsuccessful therapy and poor prognosis.

Conclusion: HIV was a predictor factor that may decrease therapy success rate of EPTB using DOTS strategy. Success rate of extrapulmonary TB treatment using DOTS strategy for minimum 9 months was good (94.6%) in our institution.

Table 3. Success Rate of Extrapulmonary Tuberculosis Therapy with DOTS Strategy

DOTS Result	Therapy ≥ 9 months	<9 months	Total
Successful	70 (94,6%)	24 (20,2%)	94 (48,7%)
Unsuccessful	4 (5,4%)	95 (79,8%)	99 (51,3%)
Total	100%	100%	100%

PC-703-04 Epidemiology of extra-pulmonary tuberculosis in Golestan Province, Iran, 2005-2012

S Rafiee,^{1,2} H R Kamalinia² ¹Golestan University of Medical Sciences, Gorgan, Iran. e-mail: soheil_rafiee@yahoo.com

Background and challenges to implementation: Almost one-fifth of golestan tuberculosis cases (1:4.9) are extrapulmonary; unexplained slower annual case count increases have occurred in extrapulmonary tuberculosis (EPTB), compared with annual case count increases in pulmonary tuberculosis (PTB) cases. We describe the

epidemiology of EPTB by means of national tuberculosis surveillance data in golestan province. This review is limited to reported public health surveillance system data and is not a clinical case review. Our goal is to describe EPTB epidemiology, compare the incidence and characteristics of EPTB with those of PTB, and suggest possible factors that are contributing to the increased proportion of EPTB-attributable tuberculosis cases.

Intervention or response: National tuberculosis cases reported from 2005 to 2012 were classified as either EPTB or PTB. EPTB encompassed lymphatic, pleural, bone and/or joint, genitourinary, meningeal, peritoneal, and unclassified EPTB cases. We excluded cases with concurrent extrapulmonary-pulmonary tuberculosis and cases of disseminated (miliary) tuberculosis. Demographic characteristics, drug susceptibility test results, and risk factors, including human immunodeficiency virus (HIV) status, were compared for EPTB and PTB cases. We analyzed tuberculosis cases reported from January 1, 2005, through December 31, 2012. Cases were categorized by major disease site, reported as either PTB or EPTB. The PTB group comprised cases with PTB listed as the only disease site

Results and lessons learnt: Among 6879 cases, 79.55% were PTB and 20.45% were EPTB, including pleural (26.3%), lymphatic (24.8%), bone and/or joint (13%), genitourinary (6.7%), meningeal (4.6%), peritoneal (4.2%), and other types of EPTB (20.4%) cases. Compared with PTB, EPTB was associated with female sex (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.2-1.6) and foreign birth (OR, 0.68; CI, 0.5-1), almost equally associated with HIV status (OR, 1.1; CI, 1.1-1.1). Slower annual decreases in EPTB case counts, compared with annual decreases in PTB case counts, from 2005 through 2012 have caused EPTB to increase from 24.03% of tuberculosis cases in 2005 to 19.78% in 2012.

Conclusions and key recommendations: EPTB epidemiology and risk factors differ from those of PTB, and the proportion of EPTB has increased from 2005 through 2012. Further study is needed to identify causes of the proportional increase in EPTB.

PC-704-04 Extra-pulmonary tuberculosis: case notification trend and treatment outcomes in Southern Nigeria, 2009–2013

C Ogbudebe,¹ J Chukwu,¹ C Nwafor,¹ A Meka,¹ N Ekeke,¹ N Madichie,¹ D Oshi,¹ J Ikebodu¹ ¹German Leprosy and TB Relief Association, Enugu, Nigeria. e-mail: dadasky22@yahoo.com

Background: According to the WHO, Nigeria currently ranks third among the 22 TB burden countries globally and first in Africa.¹ This is sequel to a 2012 national TB prevalence survey which returned incidence and prevalence rates of 338 and 322 cases per 100 000 respectively. With a projected population of 170 million, this means that the country can be saddled with over half a million new cases of TB annually. The situation is further complicated by a generalised HIV epidemic currently

running at a median prevalence of 3.4%.² It is estimated that extra pulmonary (EP) TB accounts for 15%-36% of all cases of TB.^{3,4} Studies in some sub-saharan African countries have reported rates ranging from 25%-44% among childhood EPTB cases.⁵ **Objective:** To determine the proportion and trend of EPTB among notified TB cases as well as the treatment outcomes in the national TB programme (NTP).

Methods: A retrospective cohort study of EPTB patients enrolled under the NTP from 1 January 2009 to 31 December 2013 was conducted in 14 states in Southern Nigeria. Data were extracted from TB registers. National census figures were used as denominators to calculate rates. Outcomes were categorised as favourable (cure and treatment completed) and unfavourable (died, loss to follow-up, failure or transfer out).

Results: Of the 126 806 TB patients (all forms) registered during the 5-year period, 10 395 (8.2%) had EPTB. This translates to an average annual notification rate of 4.1 per 100 000 population (IQR 3.2–5.8). The median age was 35 years (IQR 27–54), female were 6,341 (61%) and children (<15 years) were 1,247 (12%). HIV test was documented for 8,960 (86.2%) patients, 2,331 (26%) were HIV positive. CPT and ART uptake were 94.7% and 51.9% respectively. Overall, there was significantly more children <15 years ($P = 0.002$), females ($P = 0.03$) and HIV positive patients ($P = 0.01$) with EPTB compared with PTB patients. Average treatment success rate was 74%, while loss to follow-up rate was 16% compared to treatment success rate of 84% and loss to follow-up rate of 9% among PTB patients. HIV co-infection was associated with unfavourable treatment outcomes (RR 1.4, CI 1.1–1.9, $P < 0.02$). Among them, those who received ART had better outcomes ($P = 0.04$). **Conclusion:** Although overall proportion of EPTB cases shows a rising trend, especially among children, there is need for the NTP to pay greater attention to diagnosis and case-holding of patients with EPTB.

PC-705-04 Epidemiology of urogenital tuberculosis in Siberia

E Kulchavenya¹ ¹Novosibirsk Research TB Institute, Medical University, Novosibirsk, Russian Federation. e-mail: ku_ekaterina@mail.ru

Background and challenges to implementation: Urogenital tuberculosis (UGTB) is the second most common form of TB in countries with severe epidemic situation and the third most common form in regions with low incidence of TB.

Intervention or response: Estimates of incidence and spectrum of extrapulmonary tuberculosis (EPTB) in Siberia have been made on the basis of the data available in the official reporting forms. Also 131 history cases of UGTB patients, who were revealed in Novosibirsk (large industrial center of Siberia) in 2009 – 2011 years, were analyzed retrospectively.

Results and lessons learnt: In 1999 the incidence rate of TB as whole in Siberia was 116 per 100 000 inhabitants; in 2011 it increased up to 124. Every year in Siberia there

are about 1000 new revealed EPTB patients. Within the last decade the spectrum of EPTB has changed significantly. TB of the central nervous system almost doubled from 4.9% to 8.7%. Bone and joints TB increased from 20.3% to 34.5. The proportion of UGTB decreased from 42.9% to 31.7%, as well as peripheral lymph nodes TB from 16.7% in 1999 to 11.2% in 2011. Among 131 patients with UGTB in 88 (67.2%) the isolated kidney TB was diagnosed, in 33 (25.2%) – male genital TB; 10 (7.6%) men had generalized UGTB. We found the change in gender distribution from male : female of 1:2 in 1999 to 1:1.2 in 2011. Among all cohort of UGTB asymptomatic course was in 12.2%, among kidney TB - in 15.9%. Every third patient complained of flank pain and dysuria (accordingly 35.2% and 39.8%), 17% presented toxicity symptoms, 9.1% - renal colic, 7.9% - gross-hematuria. MBT in urine was found in 31.8% in isolated kidney TB as whole. The onset of TB orchio-epididymitis was in 35.7% of patients, hemospermia was in 7.1%, dysuria - in 35.7%. Most common complaints for prostate TB were perineal pain (31.6%), dysuria (also 31.6%), hemospermia (26.3%). MBT in prostate secretion / ejaculate was revealed in this group in 10.5%.

Conclusions and key recommendations: UGTB remains an important problem. All urogenital tract infections should be suspected on UGTB in patients living in the region with high incidence rate, who had contact with TB infection, who has recurrent course of the disease, resistant to standard therapy.

PC-706-04 Optimization of therapy for prostate tuberculosis

E Kulchavenya,¹ A Osadchiy¹ ¹Novosibirsk Research TB Institute, Medical University, Novosibirsk, Russian Federation. e-mail: ku_ekaterina@mail.ru

Background: In its 2012 global report on tuberculosis, WHO estimates that 3-7% (range 2.1-5.2%) of new cases and 20% (range 13–26%) of previously treated cases have multidrug-resistant (MDR) tuberculosis (defined as tuberculosis caused by *M. tuberculosis* isolates that are resistant to rifampicin and isoniazid). In many countries in Eastern Europe and central Asia, 9–32% of new patients and more than 50% of previously treated patients have MDR-TB. One of the reasons for treatment failure is non-optimal therapy. The therapy of prostate tuberculosis (PTB) is very difficult as a few antibacterial agents are able to distribute to the prostatic tissue and achieve sufficient concentrations at the site of infection.

Design/Methods: Efficiency of optimized scheme for the therapy of prostate tuberculosis (PTB) was estimated in 53 pts in the age of 24 - 69 (on average 32.1 ± 7.2). Infiltrative PTB was diagnosed in 24, cavernous - in 29. *M. tuberculosis* was found in 21 pts (39.6%): in 6 by culture and in 15 – by PCR; histological verification was in 8 (15.1%), in 29 patients (54.7%) diagnosis was established by X-ray. First group (25 pts) was treated with a standard scheme of chemotherapy: in intensive phase 4 anti-TB drugs daily (isoniazid + pyrazinamid +

rifampicin per os and streptomycin i.m.). In phase continuation the therapy includes only isoniazid and rifampicin – in intermittent regime (3 times a week). Second group (28 pts) alongside with standard chemotherapy received ofloxacin during intensive phase, and isoniazid was given as intravenous infusion. The phase continuation was in both groups identical. The efficiency was estimated in 2 and 8 months. The criteria of the efficiency were: resolution of pain, dysuria, pyospermia, negative results of bacteriology.

Results: Patients in the first group had faster positive dynamic concerning pain, dysuria, pyospermia and negative growths on *M. tuberculosis* as well as PCR in ejaculate; in 8 months best results of optimized therapy were as well. In 1st group 77.8% of pts had good results; moderate results had 6 patients (22.2%), while in the control group, who received standard therapy good results showed 11 patients (44.0%) only, moderate results – 13 patients (52.0%), one patient (4.0%) had poor result after completion full course of standard therapy.

Conclusion: Optimization of the standard therapy of prostate TB by additional administration of ofloxacin improved treatment results in 33.8%: patients in the group with optimized therapy.

PC-707-04 Comparison of outcomes of extra-pulmonary and pulmonary tuberculosis among HIV patients in an HIV clinic in Uganda

D Nalwanga,¹ S Okware,¹ P Kizito,¹ A Von Braun,^{1,2} C Wiltshire,¹ B Castelnuevo¹ ¹Infectious Diseases Institute, Kampala, Uganda; ²University of Zurich, Zurich, Switzerland. e-mail: dnalwanga@idi.co.ug

Background: The prevalence of extra-pulmonary tuberculosis (EPTB) among patients with human immunodeficiency virus (HIV) is increasing while that of pulmonary tuberculosis (PTB) is declining. Patients with EPTB are often very sick and in resource limited settings diagnosis is difficult, therefore treatment is presumptive. We hypothesize that this may lead to poor treatment outcomes in those with EPTB compared to those with PTB. We set out to compare treatment outcomes of patients treated for EPTB and PTB in an urban HIV outpatient clinic.

Design/Methods: The study was carried out at the Infectious Diseases Institute. All HIV positive patients treated for tuberculosis (TB) between 1st January 2012 and 31st December 2014 who had a documented World Health Organization (WHO) TB treatment outcome were included in the analysis. Patients' clinical and demographic data were extracted from an electronic database. Comparisons were made between baseline characteristics and treatment outcomes (death, favorable outcome which was defined as patients who were cured or completed treatment as defined by WHO, and unfavorable outcomes including transfer out, loss to follow up and treatment failure) of patients with PTB and EPTB. χ^2 test was used to measure the association between TB type and each of the variables.

Results: Of 417 patients with TB, 164(39%) had EPTB with the majority having abdominal TB (60%) and TB adenitis (20%). The patient gender, age and anti-retroviral treatment (ART) status were similar at TB diagnosis. Patients with EPTB had significantly lower baseline CD4, median (IQR) 130 (55-266) compared to PTB 193(58-343) $P = 0.03$. There was no significant difference in treatment outcomes between patients with EPTB and PTB (77% vs. 70% for favorable outcomes, 11% vs. 12% for death, 12% vs. 18% for unfavorable; $P = 0.22$). More patients with EPTB gained weight and had a rise in CD4 count following TB treatment ($P = 0.007$ and $P = 0.002$ respectively). The median CD4 count gain was higher in those with EPTB (99.9, IQR: 29-177) compared to those with PTB (60, IQR: -11-135).

Conclusion: TB treatment outcomes in HIV patients with EPTB and PTB are similar. Presumptive treatment of EPTB is therefore justified in these patients to reduce delays associated with confirming a diagnosis of EPTB.

02. Drug development: something old, something new

PC-708-04 Laboratory and non-clinical evaluation of pulmonary drug delivery in TB

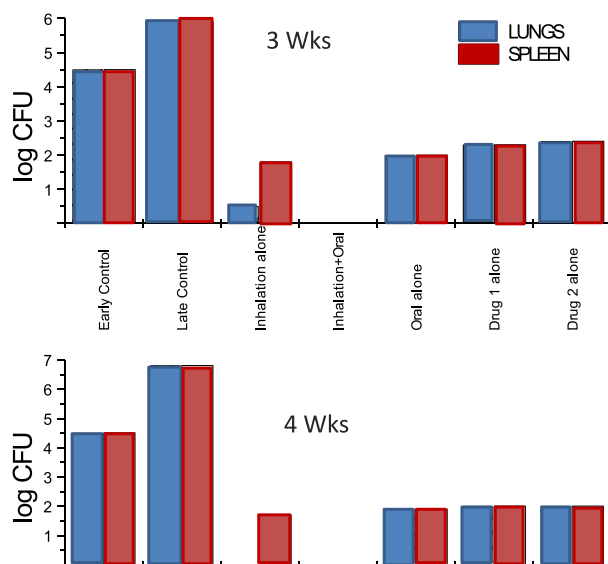
S Pandya,^{1,2} A Gupta,¹ R Ranjan,^{1,2} M Sachan,¹ A Srivastava,^{1,2} A Misra¹ ¹CSIR-Central Drug Research Institute, Lucknow, ²Academy of Scientific & Innovative Research (AcSIR), New Delhi, India. e-mail: amit.cdri@gmail.com

Background: Particles capable of targeting lung and airway macrophages when administered as a dry powder inhalation (DPI) have successfully completed pre-clinical development. We demonstrate that micro-doses of anti-TB drugs delivered in inhalable particles are safe, efficacious and capable of recruiting innate, potentially bactericidal macrophage responses in pre-clinical models.

Design/Methods: Studies were designed in accordance with the Indian Drugs and Cosmetics Act. Particles were prepared by spray-drying and subjected to Pharmaceutical Quality/CMC (Chemistry, Manufacturing and Controls). Animal studies were conducted with permission from the Institutional Animal Ethics Committee. Pharmacokinetics and biodistribution, especially to lung tissue and lung/airway macrophages was established in rodents and non-human primates at three logarithmic dose levels. Acute, sub-acute and 90-day repeated dose toxicity studies were carried out in rodents and macaques. Efficacy was investigated in mice and guinea pigs infected with *M. tuberculosis* H37Rv through a low-dose aerosol.

Results: Particles containing 50% by weight of equal amounts of isoniazid and rifabutin were amenable to deep lung delivery as a DPI. Inhaled particles were avidly taken up by airway and lung macrophages and established high drug concentrations in the lungs. They also evoked nitric oxide, oxidative free radicals, T-helper 1

cytokines and pro-apoptotic gene expression. Infected macrophages underwent apoptosis and displayed signs of intensive Golgi activity suggestive of microautophagy upon taking up the particles. Once-daily inhalations elicited no observable toxicity in macaques at doses up to 100 mg/day. Mice/guinea pigs treated for four weeks with once-a-day inhalations completely cleared bacteria from their lungs, but not spleens. Combining inhalations of 100 µg/day with oral administration of 5 mg/Kg of isoniazid and rifabutin each for four weeks cleared the lungs and spleens, and did not allow recrudescence of infection up till four weeks after cessation of treatment. **Conclusion:** Radical cure of pulmonary tuberculosis can be achieved within four weeks if inhaled particles are combined with half the standard oral dose of first-line anti-TB drugs. Data for an Investigational New Drug Application for clinical studies on safety and efficacy of a formulation that has potential to significantly reduce duration of drug-sensitive TB is now in place and a clinical testing plan needs to be evolved.



PC-709-04 Can vitamin C augment sputum conversion in TB patients while on anti-tuberculosis treatment?

L Gujral,¹ S Mugudalabetta,¹

R K Ramalingapuram Muthusloahy¹ ¹Damien Foundation India Trust, New Delhi, India. e-mail: lgujral@gmail.com

Background: TB control programmes have been successfully implemented with short term treatment regimens. The duration of treatment is still long. Treatment adherence remains as a challenge. This study aims at exploring the efficacy of Vitamin C in augmenting sputum conversion in TB patients while on Anti Tuberculosis Treatment (ATT). A common mechanism of cell death by bactericidal antibiotics involves the generation of highly reactive hydroxyl radicals via the Fenton reaction. Vitamin C, a compound known to drive

the Fenton reaction, sterilizes cultures of drug-susceptible and drug-resistant *Mycobacterium tuberculosis*.

Design/Methods: Non Randomized controlled trial study design was used. New Sputum Positive (NSP) TB patients registered during June 2013 to December 2014 from two Designated Microscopy Centres supported by Damien foundation India Trust were included. NSP TB patients from Centre-A were allocated to study group while those from Centre-B to control group. Study group received two grams of Vitamin C daily along with ATT and the controls had only ATT. Sputum microscopy for Acid Fast Bacillus (AFB) was done at the time of diagnosis, end of intensive phase, end of 2 months of continuous phase and end of treatment

Results: Study group had 43 NSP TB patients and control group had 56. Sputum AFB level of 2+ and 3+ was observed in 53.4% of study group and 51.7% of control group. Sputum conversion at 60 days was observed in 82.6% in study group with AFB level of 2+ and 3+ while it was 66.6% in control group. The overall sputum conversion at 60 days in study group was 88.4% and it was 75.9% in control ($P = 0.059$, Fisher exact = 0.089).

Conclusion: There is indication that Vitamin C has beneficial effect when administered with ATT. It seems to augment sputum conversion and hence bacterial killing. However a detailed study is required with adequate sample size and confounding factors need to be considered.

PC-710-04 Identification of optimal dose and dosing regimen of clofazimine for the treatment of MDR-TB based on pharmacokinetic modeling

G Subramanian,¹ G Sunkara,² D Mcneeley,² D Hughes³

¹Novartis, Hyderabad, India; ²Novartis, East Hanover, NJ, USA; ³Novartis, Basel, Switzerland. e-mail: subramanian.ganesan@novartis.com

Background: Currently, clofazimine is classified as a WHO Group 5 (unproven efficacy), second-line drug recommended for the treatment of MDR-TB. Clofazimine is absorbed relatively slowly and it is strongly lipophilic and accumulates mainly in fatty tissue and in macrophages of the reticuloendothelial system. Steady-state concentrations can take around 110 days to be reached. Therefore, in order to reach early steady-state a loading dose is essential to reach the target plasma concentrations in humans during the initial months of TB treatment. Clofazimine has not demonstrated early bactericidal activity in a recent phase 2a study. The objective of this research work was to determine the optimal dose and dosing regimen of clofazimine based on its pharmacokinetic properties to achieve the target concentration expected to achieve anti-mycobacterial activity.

Methods: A population pharmacokinetic model for clofazimine was developed by pooling the data from two clinical studies of clofazimine after single and multiple dosing in healthy (200 mg dose once a day) and leprosy patients (50 or 100 mg once a day),

respectively. Plasma concentration data from these two studies were analyzed by non-linear mixed effect modelling with first order conditional estimation method with interaction. The population estimates in combination with in vitro MIC₉₉ data (1.18 µg/ml) in drug resistant clinical MDR-TB isolates and in vivo data from mouse efficacy model, several simulations were performed to identify the dose and dose regimen that reach target concentration of 1.18 µg/ml in earliest treatment duration (~ 6 weeks) and sustain it for 18 weeks of the intensive phase of TB treatment.

Results: The clofazimine plasma concentration time data were best described by a two-compartment model with first order absorption. Inter-individual variability component was included in all parameters. Several clinical scenarios with different dose and dosing durations were simulated during the initial assessment. The time to reach the target concentration of 1.18 µg/ml and the duration for which the plasma concentrations are the selection of dose and dosing regimen. The loading dose of 200 mg once daily administration of clofazimine for 18 weeks followed by once daily administration of 100 mg of clofazimine till 24 weeks can provide target plasma concentration in approximately 6 weeks. This dose is planned in the clinical study planned in pivotal study.

PC-711-04 A comparison of the effectiveness of a six- vs. eight-month anti-tuberculosis regimen for pulmonary tuberculosis under programme conditions

K Ukwaja,¹ S Oshi,² I Alobu,³ D Oshi² ¹Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, ²Centre for Development and Reproductive Health, Enugu, Enugu State, ³National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, Nigeria. e-mail: ukwajakingsley@yahoo.co.uk

Background: The WHO recently changed the guidelines of first-line treatment of tuberculosis (TB) from an 8-month regimen containing rifampicin for two the first two months only (2RHZE/6EH) to a 6-month rifampicin containing regimen (2RHZE/4RH). However, the impact of the shorter anti-tuberculosis regimen (2RHZE/4RH) on treatment outcomes in Nigeria has not been assessed. Local evidence conducted under routine conditions in high TB burden settings to support the current WHO-recommended changes in anti-tuberculosis treatment policy is crucial but lacking. The aim of this study was to compare the epidemiological characteristics and treatment outcomes of TB patients treated with (2RHZE/6EH) and those who received the 6-month regimen (2RHZE/4RH) under programme conditions.

Design/Methods: This was a retrospective cohort study of newly diagnosed, smear-positive TB patients treated in two large hospitals in Ebonyi State, Southeastern Nigeria, between 1 January 2011 and 31 December 2012. The diagnosis and treatment of TB in Nigeria uses standard WHO/NTP methods. Standard treatment outcome categories according to the WHO/NTP guidelines (cured, treatment completed, died, treatment failure, loss to follow-up [default] and transferred out) were used

Results: A total of 928 newly-diagnosed, smear-positive TB patients were treated with daily ethambutol, isoniazid, rifampicin, and pyrazinamide for two months followed by ethambutol and isoniazid for six months (2RHZE/6EH), or the same intensive phase as the first regimen followed by four months of daily rifampicin and isoniazid (2RHZE/4RH). The proportion of successful outcomes was 381/490 (77.8%) with 2RHZE/6EH and 373/438 (85.2%) with 2RHZE/4RH ($P = 0.004$). The proportion of loss-to-follow-up was significantly higher in patients who received 2RHZE/6EH (14.3% vs. 5.5%; $P < 0.001$). Treatment failure was not significantly higher in patients who received 2RHZE/6EH (2.9% vs. 1.6%; $P = 0.15$). After adjusting for confounders, older age (adjusted odds ratio (aOR) 1.7), 2RHZE/6EH treatment (aOR 1.6), and male gender (aOR 1.5) independently predicted unsuccessful outcomes in HIV-negative TB patients.

Conclusion: Newly-diagnosed TB patients on 2RHZE/4RH have a higher treatment success rate compared to those treated with 2RHZE/6EH under programme conditions in a low-resource, high-burden setting. Current WHO recommendations should be maintained.

PC-712-04 Therapeutic drug monitoring of isoniazid and rifampicin

L Moreno Exebio,¹ L Lecca,² G R Davies³ ¹National Institutes of Health, Peru, Lima, ²Partners in Health, Peru, Lima, Peru; ³University of Liverpool, Liverpool, UK. e-mail: lemoreno70@hotmail.com

Background and challenges to implementation: Peru has made considerable progress on prevention and control of tuberculosis (TBC); the rate of mortality in 1990 was 198.6 per 100 000 inhabitants, for 2012 it was reported 105.2 cases per 100 000 inhabitants. Lima, capital of Peru, concentrates 54% of total TB cases, 82% of MDR-TB and 89% of extensively drug-resistant tuberculosis (XDR-TB). Historical analysis show that best way countries struggle TBC is the implementation of national programs of control, with national coverage using appropriate technologies and including during current activities methods of monitoring and permanent evaluation.

Intervention or response: We monitored plasma levels of rifampicin (RFP) and isoniazid (INH) and correlate concentrations with clinical evolution of 204 naïve patients (older than 18 years old) from National Tuberculosis Program from Ministry of Health, Peru. Patients were from south and north area of Lima. Dosages in plasma were done by liquid chromatography method (HPLC), for rifampicin an own method was developed; for isoniazid we used a validated HPLC method from literature. Dosages were done at Day 5 (First Phase) and at Month 2 (Second Phase) of treatment. Two samples of blood (5 ml) were collected each time (2 and 4 hours after drug intake). During 6 months, patients were monitored for adverse drug reactions, abandoned or failure of treatment. At the end of 6 months of treatment, we reviewed charts to see if the patients cured or not.

Results and lessons learnt: Median concentration (2.3 µg/ml) for INH were below recommended values for daily administration (3-6 µg/l) and below (8.2 µg/ml) from recommended values for twice a week schedule (9-18 µg/ml). Median concentration for RFP 34.4 µg/ml (First phase) and 41.4 µg/ml (Second phase) exceeded recommended ranges (8-24 µg/ml); however, concentrations above 40.6 µg/ml were related with success outcomes at 6 months ($P < 0.05$). A delay of absorption of RFP was detected, concentration of rifampicin were significantly higher at 4 hours in comparison than 2 hours, either phase of treatment. Moreover, concentrations of INH and RFP at 2 hours were significantly higher during second phase than first phase of treatment.

Conclusions and key recommendations: This study demonstrated its utility to dose RFP and INH in plasma and determine which cases constitute a risk for treatment failure.

PC-713-04 Plasma concentration of first-line anti-tuberculosis drugs in relation to minimal inhibitory concentrations: a prospective observational study

K Niward,¹ L Davies-Forsman,² J Bruchfeld,² J Paues,¹ E Eliasson,³ J Werngren,⁴ U Simonsson,⁵ T Schön⁶

¹Department of Infectious Diseases, Linköping University Hospital, Linköping, ²Unit of Infectious Diseases, Institute of Clinical Medicine, Karolinska Institutet and Department of Infectious Diseases, Karolinska University Hospital, Stockholm, ³Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital, Stockholm, ⁴The Public Health Agency of Sweden, Stockholm, ⁵Department of Pharmacology, Uppsala University, Uppsala, ⁶Department of Clinical Microbiology and Infectious Diseases, Kalmar, Sweden. e-mail: tschon@hotmail.com

Background: Individualized treatment against tuberculosis (TB) based on therapeutic drug monitoring could enhance the efficacy of current treatment. So far, few studies have related plasma concentrations to the minimal inhibitory concentrations (MICs) of *M. tuberculosis*. Our objective was to investigate the distribution of plasma drug concentrations of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), in relation to the MICs.

Methods: Adult patients ($n=33$) receiving first line anti-TB treatment were included. Plasma samples were obtained after an overnight fast, at 0, 2, 4 and 6 hours after drug intake (week 2) and at 0 and 2h during week 4 and 12. The drug concentrations were determined by mass spectrometry and the MICs by serial dilutions in BACTEC 960 MGIT. Sputum samples were obtained at day 0 and 2, as well as week 1, 2, 4 and 8. Sputum culture conversion as well as time to culture positivity (TTP) were recorded.

Results: The median age was 34 years, 67 % (22/33) were females and 58% were originating from sub-saharan Africa. Most patients had pulmonary TB (73%), of whom 94% had attained sputum culture conversion by week 8. The MIC levels for INH and RIF were low, ranging from 0.032-0.064 mg/l and 0.032-

0.125 mg/l. The median peak plasma concentrations for INH, RIF, PZA and EMB evaluated as the highest concentration at 2, 4 or 6h after drug intake at two weeks of treatment were 5.3, 10.0, 39.3 and 2.5 mg/l, respectively. Low plasma levels of RIF (<8mg/l) was found in more than one third of the patients (13/33; 39 %), whereas 6% had low levels of INH (<2mg/l). Importantly though, most of the patients with low RIF concentrations (83%), had high ratios between peak concentrations and individual MICs (>10). Low plasma drug concentrations of RIF were observed for the only two out of the 17 sputum culture positive patients who exhibited an increasing bacterial load during the first two weeks of treatment, as well as the only patient who did not sputum culture convert by week 8.

Conclusion: In this study, where drugs were taken after an overnight fast, low drug concentrations of RIF were observed in 39% of the patients. Interestingly, the ratio of drug concentrations of RIF and INH in relation to the MICs, was high even in patients with low plasma drug concentrations. The findings highlight the potential importance of MIC determination in order to enable individualized treatment of TB through therapeutic drug monitoring.

PC-714-04 The role of wild-type distributions and epidemiological cut-offs in determining breakpoints for susceptibility testing against *M. tuberculosis*

T Schön^{1,2} ¹Department of Clinical Microbiology and Infectious Diseases, Kalmar County Hospital, Kalmar, ²Department of Medical Microbiology, Linköping University, Linköping University, Linköping, Sweden. e-mail: tschon@hotmail.com

Background: The current drug susceptibility breakpoints (BPs) for *Mycobacterium tuberculosis* are well established for some of the first line drugs but less so for the second line drugs. Along with increasing drug resistance, it is important that BPs are systematically reviewed and revised. In this project, the aim is to define the susceptible population of *M. tuberculosis* (i.e. the wild-type (WT) distribution) for currently used drugs which is one of the cornerstones for setting accurate BPs together with pharmacokinetics/pharmacodynamics and clinical outcome data.

Methods: We have investigated the minimal inhibitory concentration (MIC)-distributions of consecutive WT and resistant isolates of *M. tuberculosis* ($n=225$) from a mixed population of patients from all continents for more than 20 first- and second line drugs, primarily by using solid Middlebrook 7H10 medium (7H10) but also BACTEC MGIT 960. Additionally, resistance genes have been sequenced (*inhA*, *katG*, *gyrA*, *rpoB* and *embB*). From the literature, MIC-data for the major first- and second line drugs were extracted.

Results: For ethambutol, the current BP (5mg/L for 7H10) splits the upper end of the WT distribution which leads to poor reproducibility within and between laboratories. Additionally, up to 40% of isolates at

4mg/l have resistance mutations in *embB*. For important second line drugs such as fluoroquinolones, current BPs classify up to 26% of isolates with resistance mutations in *gyrA* as susceptible which have implications for treatment and the definition of extensively drug resistant TB. The currently used breakpoint for rifabutin (RIB; 0.5mg/L for 7H10) is substantially higher than the epidemiological cut-off (ECOFF), i.e. the highest MIC within the wild-type distribution (0.064mg/l). Among 73 rifampicin resistant isolates with mutations in *rpoB*, 26% of the isolates were susceptible to RIB at 0.5mg/L although there are no clinical data to support that such isolates could be treated by RIB. MIC distributions from the literature search were recently published at the EUCAST home page such as 1151 MIC-values from 12 laboratories for levofloxacin which could be used for defining the ECOFF.

Conclusion: In this project, we defined the susceptible population of *M. tuberculosis* for the majority of the drugs currently used. Such data are important for defining susceptibility breakpoints, for epidemiologic surveillance and to resolve issues where there are discrepancies between phenotypical and mutational resistance analyses.

PC-715-04 Spectinamides: a new class of semisynthetic protein synthesis inhibitors against tuberculosis that overcome native drug efflux

R E Lee,¹ B Meibohm,² A Lenaerts,³ E C Boettger,⁴ M M Butler,⁵ T L Bowlin⁵ ¹St. Jude Children's Research Hospital, Memphis, TN, ²University of Tennessee, Memphis, TN, ³Colorado State University, Ft. Collins, CO, USA; ⁴University of Zurich, Zurich, Switzerland; ⁵Microbiotix, Inc., Worcester, MA, USA. Fax: (+1) 970 491 5125. e-mail: lenaerts@colostate.edu

There is an urgent need for new tuberculosis (TB) drugs with a novel mechanism of action which are effective against multidrug and extensively drug resistant TB, that are safe, and do not interact with HIV/AIDS medications. The spectinamides, a new class of semisynthetic analogs of the natural product spectinomycin, have been modified to overcome efflux in *Mycobacterium tuberculosis*, thereby improving their activity dramatically. The spectinamides are protein synthesis inhibitors which bind to a distinct region of the 30S ribosome without showing cross resistance to other aminoglycoside anti-tubercular agents. Studies demonstrated no appreciable cytotoxicity and no in vitro activity against eukaryotic cytosolic or mitochondrial ribosomal translation. This reduces the potential for side effects, such as ototoxicity and myeloid suppression, which are liabilities commonly associated with other protein synthesis inhibitors. Spectinamides are highly soluble, with low protein binding, are not subject to hepatic metabolism and are largely excreted unchanged in the urine. The many compounds in the series show robust in vivo activity in acute and chronic mouse TB infection models when administered by injection and inhalation. The lead compounds 1599 and 1810 demonstrate a promising therapeutic profile in

mice as a single agent and combined with current and new TB drugs. Combinations with rifampin and pyrazinamide showed additive to synergistic efficacy in chronic Balb/c and C3HeB/FeJ mouse models suggesting that the spectinamides may be good combination partner agents. Current preclinical work ongoing includes: dose fractionation studies in mice, GLP PK and rat toxicity, neuromuscular blockade and nephrotoxicity safety testing, manufacture optimization, and further combination efficacy trials in mice. The current development plan is to develop a spectinamide combination regimen with current and pipeline TB drugs suitable for treatment of MDR tuberculosis without the noted ototoxicity liability associated with aminoglycosides, which will be replaced with the spectinamides in these regimens.

PC-716-04 Comparing the efficacy of drug regimens for patients with drug-sensitive pulmonary tuberculosis – an aggregate data meta-analysis of phase II studies

L Bonnett,¹ G R Davies¹ ¹University of Liverpool, Liverpool, UK. e-mail: L.J.Bonnett@liv.ac.uk

Background: First-line therapy for tuberculosis (TB) has remained unchanged for forty years. Most clinical drug development programs begin with a short monotherapy study using quantitative sputum bacteriology in a small number of patients. Such studies of early bactericidal activity (EBA) are then extended into Phase IIB studies with longer treatment periods, using combinations of drugs and larger numbers of patients. More commonly, Phase IIB studies are based around culture conversion at fixed time-points, usually two months. A complete understanding of the performance of TB treatment regimens in early phase clinical trials is crucial to understanding their usefulness in predicting Phase III trial results. We undertook a systematic review of Phase II trials to determine the overall ranking of efficacy of drugs and combinations.

Design/Methods: Phase II studies evaluating key drugs in first-line treatment regimens for drug sensitive individuals with pulmonary TB were included. Outcomes of interest were EBA over 2, 7 and 14 days, and the proportion of patients with negative culture results at 8 weeks. Pooled estimates were obtained via the generalised inverse variance method.

Results: 131 relevant studies were identified presenting data on 33,537 patients and 66 drug combinations. EBA over 2 days was considered in 24 studies (32 drug combinations). EBA over 7 and 14 days were less frequently reported (6 and 8 studies respectively). The proportion of patients culture negative by 8 weeks was reported in 107 studies (46 combinations). Only 10 distinct regimens were considered across multiple studies and phase II endpoints. All 10 were represented by EBA 0-2, 8 in EBA 0-7, and 7 in EBA 0-14. However, data for 2 month culture conversion was available for only 3 regimens. While rankings across EBA endpoints were fairly consistent, it was not possible to compare these to 2 month culture conversion results.

Conclusion: This is the first review to systematically appraise the performance of single drugs and combination regimens in Phase II trials of treatment of pulmonary TB. While the results partly reflect the history, development and differing goals of such trials, the narrowness of this evidence base is concerning. Likewise, while rankings of the efficacy of treatment were reasonably consistent on different Phase IIA endpoints, the existing dataset is too small to provide convincing support to the effectiveness of the current typical drug development pathway.

03. Treatment outcomes and ethics: bedaquiline

PC-717-04 The ethics of risk-benefit analysis of new tuberculosis drugs

D Silva,¹ R Upshur,² A Dawson³ ¹Hannover Medical School, Hannover, Germany; ²University of Toronto, Toronto, ON, Canada; ³University of Birmingham, Birmingham, UK. e-mail: diego.silva@utoronto.ca

Background: Since 2012, two new antitubercular drugs have been approved for use to treat M/XDR-TB, namely bedaquiline and delamanid; however, both have serious side effects (e.g., unaccounted deaths in the treatment arm of the bedaquiline study). Given the current uncertainty surrounding TB, patients and communities are required to balance the risks and benefits of new treatments with incomplete or suboptimal information, which requires normative judgments as to what is worth risking and for how much. However, the very use of the words 'risk' and 'benefit' should give pause: how do we understand these terms, and from whose perspective?

Design/Methods: A philosophical analysis using Jonathan Wolff's framework for evaluating risk and benefit from an ethics viewpoint.

Results: What constitutes a risk or benefit related to taking bedaquiline or delamanid may depend on, among other things, whose risk and benefit is taken into account and the context in which that risk evaluation is made. Whether to take risks with new antitubercular drugs will depend not only on whether one is the patient, the healthcare worker, or member of the community, but will also depend on the interpretation of the moral landscape that led to contracting TB and the very need for suboptimal pharmaceuticals in the first place.

Conclusion: Building on Jonathan Wolff's distinction between an individual's perception of risk vs. the perception of the imposition of risk, we argue that the balancing of risks and benefits, both from the perspective of individuals with TB and their communities, requires a careful understanding of the social and political context in which the risk of new TB drugs are introduced. How supported or unsupported a TB patient feels may affect not only psychologically, but also morally, how patients and the public do, and ought to, balance the risks associated with new TB drugs and the disease itself.

PC-718-04 Treatment interruption and directly observed treatment of multidrug-resistant tuberculosis patients in China

X Wei,¹ J Yin,¹ G Zou,² Z Zhang,² J D Walley,³ J Harwell,¹ Q Sun,⁴ H T Li⁵ ¹Chinese University of Hong Kong, Hong Kong; ²COMDIS-HSD China Research Consortium, Nuffield Centre for International Health and Development, University of Leeds, Shenzhen, China; ³Nuffield Centre for International Health and Development, University of Leeds, Leeds, UK; ⁴Center for Health Management and Policy, Shandong University, Jinan; ⁵Center for TB Control, Shandong Provincial Chest Hospital, Jinan, China. Fax: (+86) 755 2225 0390. e-mail: zgy1021@hotmail.com

Background and challenges to implementation: China has nearly one fifth of global multidrug-resistant tuberculosis (MDR-TB) cases, and follows the 24-month World Health Organization (WHO) standardised regimens. The paper aims to assess treatment interruption among MDR-TB patients and its association with the provision of directly observed treatment (DOT).

Intervention or response: We reviewed clinical charts and conducted a questionnaire survey among all confirmed MDR-TB patients who had been treated for at least 6 months from 1 January 2009 to 30 April 2012 in Shandong Province. Treatment interruption was defined as missing a dose for at least 1 day but for <8 consecutive weeks; the subset 'severe interruption' was defined as missing doses for 2–8 consecutive weeks.

Results and lessons learnt: Of 110 patients, 75 (68%) interrupted treatment; 19 (17%) reported severe interruption, with a median duration of 30 days. Of the 110 patients, 26 (24%) received injections from family members and 55 (50%) received DOT, 7 (13%) from village doctors and 48 (87%) from family members. Patients who underwent DOT with a family member had less severe interruptions (OR 0.25, 95%CI 0.05–0.98) than those who were given DOT by a village doctor or who did not undergo DOT.

Conclusions and key recommendations: Family members may act as treatment supporters for MDR-TB patients to reduce treatment interruptions, but require orientation on their role.

PC-719-04 Compassionate use of bedaquiline: interim outcomes from the Armenian National Tuberculosis Control Office

C Hewison,¹ J Faqirzai,² A Hayrapetyan,³ N Khachatryan,² S Qayyum,¹ F Varaine¹ ¹Médecins Sans Frontières (MSF), Paris, France; ²MSF, Yerevan; ³National Tuberculosis Control Office, Yerevan, Armenia. e-mail: cathy.hewison@paris.msf.org

Background: In 2013, confronted by the growing challenge of drug resistant TB, the National Tuberculosis Control Office of Armenia, supported by Médecins Sans Frontières (MSF), introduced bedaquiline (Bdq) containing treatment through compassionate use for extensively drug resistant (XDR-TB) or MDRTB patients with additional resistance to fluoroquinolones (MDR+FQ) or injectables. We present results after two years.

Design/Methods: Eligible patients were enrolled to receive 6 months of Bdq added to a background regimen according to WHO recommendations. Two WHO Group 5 drugs (imipenem and linezolid) previously not used in Armenia were included in the regimen when needed. Monitoring included monthly sputum smear, culture, biochemical tests and ECG monitoring. Culture conversion was defined as 2 consecutive negative culture results one month apart for culture positive patients at start of treatment.

Results: Between April 2013 and March 2015, 60 patients with a mean age of 42 years (range: 18-68) initiated a Bdq containing regimen; 88% (53/60) were male; 41.6% (25/60) had XDR-TB and 50% (30/60) had MDR+Fx. Three cases were HIV positive (5%). All 60 patients also received linezolid and 43/60 (71.6%) received imipenem-cilastatin. Of the 38 patients enrolled before July 2014, 30 were culture positive at start of treatment. Culture conversion was achieved in 53.3% (16/30) at 2 months and 80% (24/30) at 6 months. Serious adverse events were reported in 4 patients, 1 attributed to Bdq QT effects without clinical consequences for the patient who completed Bdq treatment. Fifty five percent (21/38) had an increase in QTcF from baseline with a mean increase of 37.4 milliseconds (ms) (range: 4-96 ms), 86% (18/21) of whom were taking clofazimine concomitantly. Results at 14 months of treatment were assessed for the 28 patients who started treatment before February 2014: 20(71%) culture negative, 1 (4%) died, 1 (4%) lost to follow up, 6 failures (21%). Amongst the failures, 3 never converted and subsequently died and 3 reverted after initial conversion and are still under treatment.

Conclusion: These preliminary outcomes of a Bdq containing regimen show good tolerability and early treatment response. However reversion rates highlight the need for further studies on the optimum length of Bdq treatment and the importance of considering prolongation of Bdq beyond 24 weeks on a case by case basis for patients with otherwise weak regimens.

PC-720-04 Is bedaquiline as effective as fluoroquinolones in the treatment of MDR tuberculosis? A microbiological appraisal through a case-control study

L Guglielmetti,^{1,2} D Le Dû,^{3,4} N Veziris,^{1,2,5} E Caumes,⁵ Y Yazdanpanah,⁶ J Robert,^{1,2,5} M Jachym,³ for the MDR-TB Management Group of the French National Reference Center for Mycobacteria and the Physicians of the French MDR-TB Cohort⁵ ¹Institut National de la Santé et Recherche Médicale, U1135, Team E13 (Bacteriology), Paris, ²Sorbonne Universités, UPMC Univ Paris 06, CR7, Team E13 (Bacteriology), Paris, ³Centre Hospitalier de Bligny, Briis-sous-Forges, ⁴APHP, Centre Hospitalier Raymond Poincaré, Garches, ⁵APHP, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, Paris, ⁶APHP, Hôpital Bichat Claude Bernard, Paris, France. e-mail: lorenzo.guglielmetti@gmail.com

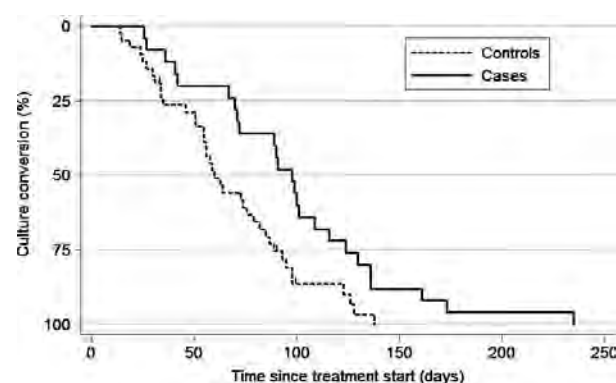
Background: Bedaquiline (Bdq) is a new drug approved to treat multidrug-resistant tuberculosis (MDR-TB,

resistant to isoniazid and rifampicin). Because of the paucity of drugs available for MDR-TB treatment, interventional studies aimed at evaluating the activity of Bdq are difficult. Therefore, we designed a retrospective study to compare the microbiological efficacy of Bdq- and fluoroquinolones (Fq)-containing regimens, as Fq are a mainstay of the treatment of MDR-TB.

Design/Methods: A nested case-control study was performed within the cohort of MDR-TB cases hospitalized from 2006 to 2014 in a single referral TB center in France. Case-patients were defined as those treated with Bdq without Fq, or with Fq when isolates were moxifloxacin (Mfx)-resistant. Control-patients were those treated with Fq but without Bdq, and harboring ofloxacin (Ofx)-susceptible isolates. All patients had positive sputum cultures at treatment start, and received at least one second-line injectable drug and linezolid. Time to culture conversion was measured from treatment start to the first of two consecutive negative examinations. Kaplan-Meier curves were estimated. Mantel-Cox test was used to compare time to culture conversion between cases and controls. A Cox proportional hazards model was used to assess the association between time to culture conversion and explanatory variables.

Results: A total of 25 cases and 42 controls were eligible among a cohort of 172 MDR-TB patients. The culture conversion rate at 3 months was higher in controls (74%) than in (44%) cases, while no statistical difference was found at 6 months (93% vs. 96%, respectively). The time to culture conversion was significantly shorter for controls (60 days, IQR 35-89) than for cases (98 days, IQR 70-124; $P < 0.01$) (Figure). Characteristics associated with slower time to culture conversion were presence of lung cavities (Hazard Ratio (HR) 0.15, 95% Confidence Interval (CI) 0.07-0.31), sputum-smear positivity at treatment start (HR: 0.21, 0.05-0.99), and male sex (HR: 0.31, 0.16-0.61).

Conclusion: Patients treated with Bdq and those treated with Fq reached a similar 6-month culture conversion rate, although Fq-treated patients had a faster time to culture conversion. Cavitory, smear-positive pulmonary TB, together with male sex, was associated with slower time to culture conversion.



Kaplan-Meier analysis of time to culture conversion of cases (solid line) and controls (dashed line). Dots indicate censoring.

PC-721-04 Reasons for not participating in a tuberculosis clinical trial, Lima, Peru 2014

C C Contreras,¹ C Morán,¹ M Lindeborg,² F Garcia,¹ M Milstein,³ L Lecca,¹ C Mitnick³ ¹Socios En Salud Sucursal Perú, Lima, Peru; ²Harvard College, Boston, MA, ³Harvard Medical School, Boston, MA, USA. e-mail: ccontreras_ses@pih.org

Background: Clinical trials are essential to optimize TB treatments and to minimize safety concerns from medication use. Social and personal factors, such as stigma, barriers to access, and lack of patient education, can impede trial participation. This study seeks to better understand the underlying reasons for non-participation in a TB clinical trial in Lima, Peru.

Design/Methods: Data were collected from adults (≥ 18 years old) with newly diagnosed, drug-susceptible, pulmonary TB in metropolitan Lima who were invited to participate in a clinical trial between September 2013 and February 2015. Participants chose not to partake at three main times: 1) refusing a screening invitation at the health center, 2) not signing the informed consent form (ICF), and 3) screen failure after enrollment.

Results: 542 potential candidates were invited to screening, of which 392 accepted the invitation to go to the study site and 150 (27.7%) did not because: 66 (44.0%) prefer health center treatment/have different insurance; 33 (22.0%) lack of time; 26 (17.3%) family influence, 7 (4.7%) lack of desire to be in a trial; 6 (4.0%) site decision; 5 (3.3%) drug susceptibility test not available; and 7 (4.7%) other reasons. Of the 392 who accepted the invitation, 345 signed the ICF and 47 (12.0%) did not because: 10 (21.3%) want immediate treatment; have negative feelings about sputum (4, [8.5%]) and blood collection (3, [6.4%]); 3 (6.4%) dislike study-specific requirements; 3 (6.4%) family influence; 2 (4.3%) lack of desire to be in a trial; 13 (27.7%) pre-screening criteria not met; and 9 (19.1%) site decision. Finally, of the 345 who signed the ICF, 165 (47.8%) did not pass screening and get randomized to study drug because: 146 (88.4%) met at least one exclusion criterion, 4 (2.4%) family influence; 3 (1.8%) prefer health center treatment/have different insurance; 1 (0.6%) dislike of home visits; 4 (2.4%) study suspension/enrollment already closed; 1 (0.6%) drug susceptibility test not available; 1 (0.6%) loss-to-follow-up; 5 (3.0%) other.

Conclusion: It is important to distinguish between personal reasons (lack of time, negative view of trials or study-specific protocol) and social reasons (family influence, proximity to health center vs. study site) that TB patients choose not to participate in TB trials. To improve study participation, researchers should aim to strengthen patient/family education and address social gaps impeding access to health services.

PC-722-04 Bedaquiline-containing treatment regimens for multidrug-resistant tuberculosis

S Borisov,¹ T Ivanushkina,¹ D Ivanova,¹ N Litvinova,¹ A Filippov¹ ¹Moscow Research and Clinical Center for TB Control, Moscow, Russian Federation. Fax: (+7) 499 785 2082. e-mail: sebarsik@gmail.com

Background: The second-line drugs optionally combined with the WHO's "fifth group" drugs (especially linezolid) are effective in MDR-TB patients. In some cases, the adequate chemotherapy (min 4 drugs) is unrealizable due to the extended drug-resistance (XDR) and/or treatment intolerance. The new drug – bedaquiline (Bdq) – is essential, but it is not yet thoroughly tested in regimens with traditional TB-drugs and new anti-mycobacterial agents.

Design/Methods: The prospective unblinded non-randomized one-centered study include 54 pulmonary TB pts, 18-73 y.o., 68.5% male; 20,4% (11 pts) new and 79,8% (43 pts) retreated. MDR was identified in 29.6% (16 pts) and XDR – in 70.4% (38 pts). Lung cavities detected in 87.0% (47 pts), bilateral lesions – in 40.7% (22 pts). Bdq was included in regimens in all patients, the next one was, if possible, linezolid (96.3% – 52 pts), cycloserine/terizidone (81.5% – 44 pts), fluoroquinolones (70.4% – 38 pts), capreomycin (46.8% – 25 pts), prothionamide (29.6% – 16 pts), PAS (27.8% – 15 pts), pyrazinamide (18.7% – 10 pts), ethambutol (13.0% – 7 pts). If the regimen didn't include at least four drugs, we add macrolides (38.9% – 21 pts), meronem (9.5% – 5 pts), amox/clav (1 pt), isoniazid in high doses (1 pt). The evaluation performed after 24 weeks of Bdq administration and all patients will be followed up to 24 months.

Results: The treatment with Bdq was completed in 87.0% (47 pts), in 4 pts (7.4%) treatment was interrupted (but they weren't lost to follow-up) and in 3 pts (5.%) Bdq was excluded due to the serious adverse events. The evident involution of symptoms were obtained in 85.1% (40/47 pts), the X-ray improvement – in 80.5% (38/47 pts). The sputum smear conversion total score (on liquid media): 87.2% (41/47 pts) with Med=4 wks (IQR 2.0-11.5). The time of conversion was prolonged in pts with large cavities: 8 vs. 2 wks, $P = 0.001$ (log-rank test) and bilateral involvement (4 vs. 2 wks, $P = 0.05$). The SAE III-IV were obtained in 11 pts (20,4%), include hepatitis in 3, hypereosinophilia (19% and more) – in 3, QTc prolongation up to 520 ms – in 2 (without arrhythmia), obstinate vomiting – in 2, anemia ($Hb < 69$ g/l) – in 1 pt. SAE III-IV were attributed to Bdq in 4 pts and only 3 stopped the treatment with Bdq.

Conclusion: The regimens, based on Bdq, second-line TB-drugs and the "fifth group" drugs are well-tolerated and high effective in XDR-TB. We need obtain data to argue the prolongation of Bdq course.

PC-723-04 Bedaquiline: new capabilities to treat MDR-TB patients

I Vasilyeva,¹ A. Samoilova,¹ T. Bagdasaryan,¹ V Testov,¹ A. Tikhonov,¹ L Chernousova¹ ¹Central TB Research Institute, Moscow, Russian Federation. Fax: (+7) 499 785 9108. e-mail: vasil39@list.ru

Background: Study treatment efficacy of MDR-TB patients under chemotherapy regimen with bedaquiline. **Design/Methods:** 54 MDR/XDR-TB culture positive patients treated in CTRI during 2010 – 2014 participated in the study. DR to 1st and 2nd line drugs was confirmed for all patients with culture method on liquid media in the certified high quality laboratory. Patients were divided into two groups according to DR patterns: 1st group – 23 MDR-TB patients without additional DR to fluoroquinolones, 2nd group – 31 MDR-TB patients with additional DR to fluoroquinolones (including 21 XDR-TB patients). Kanamycin or amikacin or capreomycin, pyrazinamide, protionamide or aminosalicylic acid, cycloserine or terizidone, levofloxacin in the dose of 1.0 were included in the chemotherapy regimen of all patients during first 6 months of treatment with further transfer to moxifloxacin. Bedaquiline was appointed to all patients during first 6 months of treatment according to the following treatment plan: 400 mg daily during 2 weeks, then 400 mg 3 times per week. Intensive phase of treatment continued till getting two-four negative cultures but not less than eight months. Treatment at a continuation phase lacked injection drug. Culture negativation was an indicator of TB patients' treatment efficacy. Treatment efficacy of TB patients included into the study also was assessed according to WHO definitions (2013) in 24 months after treatment initiation and full treatment course finalization.

Results: 39.1% (9 of 23) of patients in the 1st group and 19.4% (6 of 31) of patients in the 2nd group had culture negativation in 2 months of treatment, 73.9% (17 of 23) and 61.3% (19 of 31) – in four months, 87% (20 of 23) и 90.3 (28 of 31) – in six months correspondingly, $P > 0.05$. Full recovery was observed among all patients included into the study.

Conclusion: 88.9% of MDR-TB patients regardless additional DR as a result of inclusion of bedaquiline in a chemotherapy regimen had culture negativation by six months of treatment. Observations made in 24 months of treatment initiation and after full treatment course finalization demonstrated 100% recovery of MDR-TB patients including XDR-TB patients and gave hope to patients, who used to be considered hopeless.

PC-724-04 Geographical differences in baseline drug resistance patterns and their impact on treatment outcomes in a single-arm bedaquiline phase II trial (C209)

A Pym,¹ A Diacon,² F Conradie,³ S Tang,⁴ M Haxaire-Theeuwes,⁵ N Lounis,⁵ B Van Baelen,⁵ B Dannemann⁶ ¹Medical Research Council and Kwazulu Research Institute for TB and HIV (K-RITH), Durban, ²Division of Medical Physiology and the Department of Science and Technology/National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research and Medical Research Council Centre for Tuberculosis Research, Cape Town, ³Clinical HIV Research Unit, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ⁴Tuberculosis Department, Beijing Chest Hospital, Capital Medical University, Beijing, China; ⁵Janssen Infectious Diseases BVBA, Beerse, Belgium; ⁷Janssen Research & Development LLC, Titusville, NJ, USA. Fax: (+27) 31 203 4702. e-mail: alexanderpym@hotmail.com

Background: Global variations in the distribution of drug resistance patterns could potentially influence regional treatment outcomes for multi-drug resistant tuberculosis (MDR-TB). C209 (NCT00910871) was a Phase II, open-label, single-arm trial of bedaquiline (BDQ) as part of an individualized MDR-TB treatment regimen in patients (pts) most of whom had received prior MDR-TB treatment.

Design/Methods: 233 pts ≥ 18 yrs from 11 countries with confirmed sputum-smear positive pulmonary MDR-TB (either newly diagnosed or previously treated), including pre-extensively (pre-XDR) or extensively (XDR) drug-resistant TB received BDQ for 24 wks (400mg qd for 2 wks, 200mg tiw for 22 wks) with an individualized background regimen (BR), followed by BR only for up to 120 weeks (final assessment). Baseline resistance patterns by region (defined as China, other Asian countries, Eastern Europe, South America, South Africa) and their impact on treatment response (sustained culture conversion at 120 wks) were assessed in the modified intent-to-treat population ($n = 205$) excluding 28 pts with drug-susceptible TB or negative MGIT cultures at baseline.

Results: Baseline rates of second-line drug resistance (Table) were highest in China: 73% fluoroquinolone resistance, 32% aminoglycoside resistance and 27% ethionamide resistance. Eastern Europe had the highest rate of aminoglycoside resistance (44%). Baseline rates of pre-XDR-TB and XDR-TB were higher in China (48% and 28%, respectively) than in other Asian countries (37% and 26%) and in Non-Asians (14% and 17%). Surprisingly higher rates of baseline resistance patterns in these regions did not lead to lower conversion rates at 120 wks (M=F): China (86%), other Asian countries (77%), Eastern Europe (76%), South Africa (60%) and South America (62%).

Conclusions: Addition of BDQ to an MDR-TB regimen resulted in high conversion rates at 120 wks in a population who had mostly received previous second-line drugs. There were wide regional differences in baseline drug resistance, with the highest rates of

fluoroquinolone resistance and XDR-TB in China, and highest rate of aminoglycoside resistance in Eastern Europe. Regional differences in the distribution of baseline drug resistance patterns did not result in poorer treatment outcome in regions with more extensive drug resistance patterns.

Table. Second-line drug resistance at baseline; mITT, 7H11 agar proportion method*

Drug resistance	Asia (other) <i>n</i> = 26 <i>n</i> (%)	China <i>n</i> = 41 <i>n</i> (%)	Eastern Europe <i>n</i> = 34 <i>n</i> (%)	South America <i>n</i> = 10 <i>n</i> (%)	South Africa <i>n</i> = 63 <i>n</i> (%)
Ethionamide	4 (17)	11 (27)	8 (24)	0 (0)	6 (10)
Capreomycin	2 (8)	7 (17)	8 (24)	3 (30)	5 (9)
Kanamycin	7 (29)	13 (32)	15 (44)	3 (30)	8 (14)
Streptomycin	19 (79)	37 (90)	34 (100)	8 (80)	36 (62)
Ofloxacin	14 (58)	30 (73)	13 (38)	1 (10)	7 (12)
Pyrazinamide †	18 (72)	30 (73)	30 (88)	9 (90)	48 (76)

*Drug susceptibility testing was performed at a central laboratory (Institute of Tropical Medicine, Antwerp, Belgium).

†Pyrazinamide drug susceptibility testing was performed using the MGIT960 PZA kit.

PC-725-04 Encouraging early outcomes for individualized treatment of multidrug-resistant tuberculosis using bedaquiline and linezolid in Khayelitsha

E Mohr,¹ H Cox,² L Wilkinson,¹ G Van Cutsem,^{1,3} V Cox,¹ J Daniels,¹ O Muller,¹ J Hughes¹ ¹Médecins Sans Frontières (MSF), Khayelitsha, ²University of Cape Town, Cape Town, ³MSF, Cape Town, South Africa. e-mail: mohrek27@gmail.com

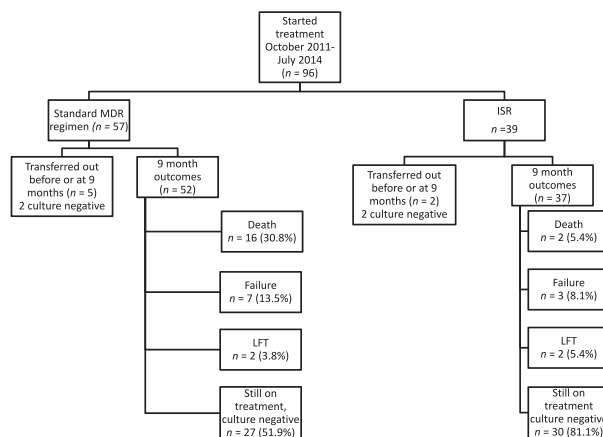
Background and challenges: Current treatment options for multidrug resistant tuberculosis (MDR-TB) with second-line (SL) resistance are limited and yield poor outcomes. We describe early outcomes of patients treated with individualized strengthened treatment regimens (ISRs) containing bedaquiline (BDQ), linezolid (LZD), clofazimine and/or rifabutin, following detection of SL resistance.

Intervention or response: Patients with any SL resistance (ofloxacin, amikacin) who started MDR-TB treatment (January 2009-September 2011) were compared to those starting treatment after ISR availability (October 2011-July 2014). Patients with previous MDR-TB treatment failure were excluded from the analysis. Prior to ISR availability, standardized regimens were adapted with addition of one or more of PAS, clofazimine and capreomycin. LZD and BDQ became available in 2011 and 2013 respectively; implementation of ISRs was slow due to cost and administrative constraints. Patients were offered ISRs if SL resistance was confirmed, whether or not current treatment was failing.

Results: Overall, 176 patients were assessed (72% HIV positive); 80 in the standard cohort and 96 in the ISR cohort. The proportion of previously treated MDR-TB cases was 14% in the ISR and 1% in the standard cohort ($P = 0.003$). Thirty nine (41%) patients in the ISR cohort received ISR; 20 (51%) received LZD and BDQ, 18 (46%) received LZD only and 1 (3%) received rifabutin.

Mortality at 9 months was 20% and 31% ($P = 0.2$) and treatment failure was 11% and 21%, in the ISR and standard cohorts respectively ($P = 0.08$). More patients in the ISR cohort were culture negative and on treatment at 9 months (64% vs. 40%, $P = 0.002$). Among the 37 patients given an ISR (excluding 2 transferred out), 2 (5%) had died and 30 (81%) had negative cultures at 9 months (Figure 1). Median time to initiation of an ISR following standard MDR treatment initiation was 1.9 months (IQR 1.1-3.5).

Conclusion: Interim outcomes among patients starting ISRs containing BDQ and LZD are encouraging, showing increased culture conversion and a trend towards lower mortality and treatment failure. A significant impact on mortality might be delayed due to slow implementation of ISRs and short follow-up time. As more patients are eligible and access ISRs, continued analyses of outcomes are required.



04. New approaches to health systems, care and management for drug-resistant TB

PC-726-04 Occluding cavities with endobronchial valves for the treatment of multidrug-resistant tuberculosis: early clinical experience

Z Wang,¹ H An,¹ L Liu,¹ T Wang¹ ¹309th Hospital of Chinese People's Liberation Army, Beijing, China. e-mail: wzy2004177@sina.com

Background: Multi-drug resistant tuberculosis (MDR-TB) is a serious clinical problem in many parts of the world i.e., 650 000 patients according to WHO (2010). Because the development of new anti-TB drugs has not kept pace with drug resistance, and also patient poor treatment compliance, alternative approaches are needed.

Design/Methods: We investigated whether placement of endobronchial valves (EBV, Zephyr®, Pulmonx, Redwood City, CA, USA) to induce selective atelectasis in lobes that have TB cavities may be effective in improving

the treatment of MDR-TB. Zephyr EBV are one-way valves that allow air and secretions to exit a lobe, but prevent air from entering, inducing a lobar collapse or atelectasis and an anaerobic environment. This minimally invasive form of treatment, carried out via bronchoscopy, is usually indicated for reducing hyperinflation in COPD patients with severe emphysema.

Results: We present here our first 3 cases (Chinese, 1M, 2F) with MDR-TB that were treated with EBV valves. They had previously received optimal TB treatments for an average of 9.0 ± 4.7 y (range: 3-16 y) but remained multi-drug resistant. EBV implants to collapse TB cavities was considered. Age at EBV treatment was 29.7 ± 5.1 y. On average, 3.4 valves were implanted (range: 1-5) per patient in 1 to 4 sequential sessions. In total, 4 cavities were treated i.e., 2 in one patient and 1 in the others. Full cavity collapses (100%) were achieved in two instances and a partial collapse (i.e., 87% and 58%) for the other cavities. TB status improved and all patients became smear negative after EBV treatments. The average follow-up period at the time of abstract submission was 9.7 ± 4.6 mo (range: 5-16 mo).

Conclusion: The early experiences reported here indicate a promising potential for EBV implantation in the management of multi-drug resistant lung tuberculosis. Prior to the implantation of EBV in these patients, anti-tuberculosis drugs failed to limit the number of lesions and the development of cavities, but these conditions were reversed post EBV implantation. There also was conversion to smear negative sputum, thus potentially limiting contamination risks. These results suggest that lobar exclusion could be effective in the successful control of tuberculosis and that sequential treatments with several valves may be required. Longer follow-up periods and additional cases will be available by the time of the conference.

PC-727-04 Decentralized MDR-TB service model increased access to case finding in the Amhara and Oromia regions of Ethiopia

Y Molla,^{1,2} M Aseresa Melese,^{1,2} I Jemal Abdulahi,^{2,3} D Habte,¹ Y Haile,⁴ D J Dare,¹ Y Anteneh Kassie,¹ P G Suarez² ¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, Ethiopia; ²Management Sciences for Health, Center for Health Services, Arlington, VA, USA; ³Oromia Regional Health Bureau, Addis Ababa, ⁴USA Agency for International Development (USAID), Addis Ababa, Ethiopia. e-mail: ymolla@msh.org

Background and challenges to implementation: The prevalence of MDR-TB in Ethiopia among re-treated cases was 17.6% and that of new patients was 2.3%, with over 3000 patients estimated to have MDR-TB in 2013. However, the number of treatment centers was only two in 2011 for a country of 90 million population, with huge geographic barriers to access. To address this challenge, the country developed more treatment initiating centers, and for daily dose of directly observed treatment of stabilized patients decentralized to health centers.

Intervention or response: In 2012, the FMOH began working to decentralize MDR-TB services with support from the USAID-funded Help Ethiopia Address the Low TB Performance (HEAL TB) project. First, we renovated, equipped three MDR TB centers, and also provided technical support to sites already renovated by other partners. The partners also trained health workers throughout the regions to identify presumptive MDR-TB cases and refer sputum samples for culture. The sample transport was strengthened for presumptive MDR-TB cases to Regional Reference Laboratories and we assisted with placement of 40 GeneXpert machines in the two regions. The project also supported targeted clinical mentoring, organized special clinic days, provided continuing medical education system for the health workers, and instituted a mortality audit.

Results and lessons learnt: Between January 2012 and December 2014, these interventions helped expand MDR-TB treatment service: treatment initiating centers (TIC) increased from 2 to 17; testing for presumptive MDR-TB from 662 to 12,369; and patients ever enrolled from 56 to 548 (Table). More than 300 health facilities are providing monthly follow up to patients who began treatment in the TICs, but were discharged after culture conversion. Six-month culture negativity rate improved from 41% to 69%. The cure and treatment success rate for the first cohort of 36 patients were 61.1% and 74.9% respectively. The proportion of death, failure of treatment and lost to follow up for the first cohort were 11.1%, 2.8% and 11.1% respectively.

Conclusions and key recommendations: Decentralizing MDR-TB services to secondary and primary care levels improved access to services, and improved treatment outcomes. Designated clinic appointment days for follow up, continuing medical education for health workers, and death audits were critical in improving the quality of care.

PC-728-04 Drug use review program in Uzbekistan: pathway to improved rational use of anti-tuberculosis medicines

M Tillyashaykhov,¹ I V Liverko,¹ V Belotserkovets,¹ M Kavtaradze,² A Salakaia² ¹Republican Specialized Scientific and Practical Medical Center of Phthisiology and Pulmonology, Ministry of Health, Tashkent, Uzbekistan; ²Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, Management Sciences for Health (MSH), Arlington, VA, USA. Fax: (+995) 322 232 490. e-mail: kavtaradze.maya@gmail.com

Background: When a comprehensive indicator-based assessment of Uzbekistan's tuberculosis (TB) pharmaceutical system was conducted in 2014, findings revealed gaps in the rational use of anti-TB medicines: only 60.4% of prescriptions for intensive phase and 70.6% of continuation phase for multidrug-resistant (MDR)-TB patients were in accordance to the national standard treatment guidelines. To respond to this problem, the National TB Program (NTP) of Uzbekistan decided to implement a drug use review (DUR) program—a quality

assurance intervention that identifies and remedies problems related to drug use.

Intervention: In February 2015, with the technical assistance of the US Agency for International Development (USAID)-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, the NTP piloted DUR at 3 TB facilities of Tashkent City. The objectives of the review were to identify gaps in the rational use of second line anti-TB medicines through criteria-based review including prescribing of medicines, monitoring of treatment and management of side effects. The methodology included data collection according to preset criteria through review of treatment cards and patient interviews followed by analyses of collected data.

Results: Justification criteria for prescribing drug-resistant TB treatment regimen were met 100%. On average, 67% of baseline tests were conducted for patients before start of treatment. The average percentage of patients receiving the appropriate dose of all anti-TB medicines was observed in 94% cases. During the intensive phase of treatment, the treatment regimen was changed at least once in 38% cases; of these cases, only 58% were justified by a doctor in the treatment card. During the continuation phase, the regimen was changed at least once only in 17% of cases, of which only 40% was justified in the treatment card. Average percentage of side effects most reported by patients during the interviews was 57% each for vestibular disorders and arthralgia; the average percentage of records for these side effects in the treatment cards was 22% and 11%, respectively.

Conclusion: Based on the DUR results, an improvement plan was developed and disseminated to appropriate treatment facilities staff. The DUR is scheduled to be repeated in six months after the improvement interventions are in place. The DUR program will also be expanded to other TB facilities, making the process systematic.

PC-729-04 Systematic expansion of drug-resistant tuberculosis services reduced treatment initiation delay by five fold in Jharkhand, India

V Ghule,¹ A Sreenivas,¹ P Parmar,¹ R Dayal,² R Pathak,¹ S Saruk,³ A Mitra² ¹World Health Organization Country Office for India, New Delhi, ²Government of Jharkhand, Ranchi, ³Government of Maharashtra, Washim, India. e-mail: ghulev@rntcp.org

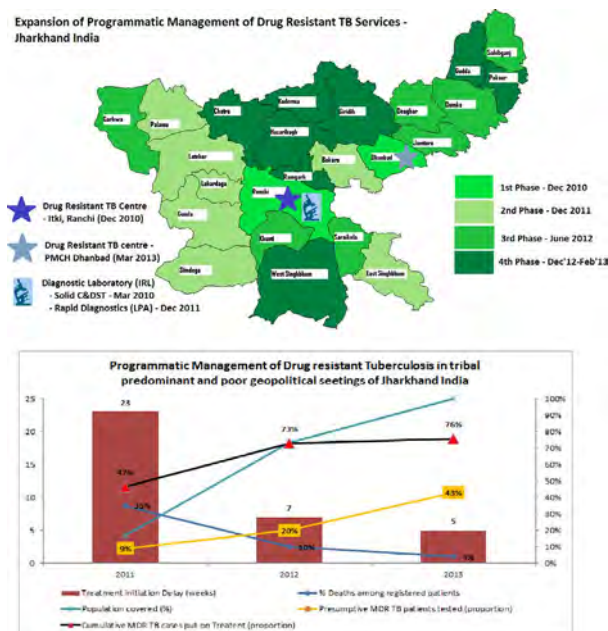
Background and challenges to implementation: Multi drug resistant tuberculosis (MDR-TB) is a major challenge for India's Revised National TB Control Program (RNTCP). New TB patients are treated free under program with first line drugs. Non responders are screened by culture and drug sensitivity testing (C&DST) in quality assured laboratory. TB patients with known resistance to first line drugs (isoniazid and rifampicin) are known as MDR-TB patients. Programmatic Management of drug resistant tuberculosis (PMDT) - a systematic approach to address MDR-TB care was launched by Government of India in 2007. Establishment of quality

assured laboratory and treatment initiation centres - drug resistant TB (DR-TB) centres as per guidelines; early diagnosis and treatment initiation within a week of diagnosis were challenges in resource poor settings of Jharkhand state. We sought to assess program performance and impact of systematic service delivery on MDR-TB care in the state.

Intervention or response: Jharkhand is predominantly a tribal province of eastern India with poor geopolitical settings and difficult hilly terrain. With establishment of one certified laboratory and one DR-TB centre, phase wise implementation of PMDT was launched in 2010 to cover 34.4 million population of 24 districts. (Table 1) One more diagnostic technology and DR-TB centre was established to improve access to MDR-TB care. PMDT services were launched after technical assessment and approval by Govt. of India. Systematic record review of treatment register (417 patients) and performance reports (2011 to 2013) was conducted to assess performance trend of MDR-TB care.

Results and lessons learnt: Systematic roll out of PMDT services resulted in 100% access to care (additional 34% screening and 29% treatment initiation), reduction in treatment initiation delay (by 18 weeks) and decreased death proportions (by 31%) of MDR-TB patients in Jharkhand India. (Figure 1)

Conclusions and key recommendations: Systematic roll out of PMDT services improves access to MDR-TB care. Decentralised care delivery saves additional lives.



PC-730-04 Need to improve knowledge about management of MDR-TB among medical personnel in India

P Mithra,¹ P Banuru Muralidhara,² B Unnikrishnan,¹ R Thapar,¹ N Kumar¹ ¹Manipal University, Manipal, ²International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 114 605 4430. e-mail: bmprasad@theunion.org

Background: Globally and in India, there is a rise in number of Multiple Drug Resistant (MDR) Tuberculosis patients. Many argue that this increase is also contributed due to irrational use of medicines; mainly antibiotics by private medical practitioners. Following graduation almost 90% of students from medical college adopt private practice. Prior to the graduation, it is therefore necessary to assess their knowledge about management of MDR-TB.

Methods: A cross sectional study was conducted in a medical college from south Indian city of Mangalore. A total of 188 students included; Interns ($n=98$) and Post Graduates [PG] ($n=90$) were interviewed through a semi-structured questionnaire from January to March 2015. They were selected using a convenience sampling method. The collected data was analysed using Statistical Package for Social Sciences [SPSS] version 16.0.

Results: Overall, 61.8% had adequate knowledge about MDR-TB and knowledge was higher among PGs. In total, >80% of them knew correct diagnostic methods. However, only 21% of Interns and 34% of PGs were aware of correct duration of treatment. Management about MDR-TB cases was known only to about 24% of Interns and 13% of PG students.

Conclusion: Knowledge and management of MDR-TB among students – Interns and PGs is limited. There is a great need to have Continued Medical Education on MDR-TB and include Standard Treatment Guidelines into curriculum of medicine.

PC-731-04 Pathways of care for DR-TB in Mumbai slums: case for use of rapid diagnostic tests

E Lobo,¹ A Patil,¹ S Rangan,¹ S Shah,¹ Y Dholakia,¹ N Mistry¹ ¹Foundation for Medical Research, Mumbai, India. Fax: (+91) 222 493 2876. e-mail: fmr@fmrindia.org

Background: The rising threat of drug resistant –TB (DR-TB) in India necessitates early detection of drug resistance and appropriate treatment initiation. In recent times Mumbai has become the epicenter of various forms of DR-TB with about 60% of Mumbai population living in overcrowded slums with poor hygiene, sanitation and ventilation. The objective of this study was to record the duration of first care seeking, diagnosis and subsequent initiation of DR-TB treatment of vulnerable patients from Mumbai slums. Twenty-three DR-TB patients identified by a household level survey of 15 high burden TB wards in Mumbai were interviewed using a semi-structured interview schedule. Median durations of first care-seeking, diagnosis, initiation of DR-TB treatment and total pathway were calculated.

Results: The entire pathway from onset of symptom/s till initiation of DR-TB comprised of 109 days (IQR 52, 277). Delay was more pronounced for first care seeking (20 days, IQR 12, 46), and DR-TB diagnosis (83 days, IQR 14, 200). Treatment initiation however was rapid (0 days, IQR: 0, 1) with most patients initiated on treatment on the same day as diagnosis. The total DR-TB pathway time of patients with first episode of TB disease (179 days, IQR 122.5, 345.5) was found to be more than twice as that of patients with previous episodes of TB (69 days, IQR 41.5, 126).

Conclusion: The unacceptable delay for diagnosis and treatment of DR-TB in Mumbai advocates for stronger implementation of early screening of patients for DR-TB, especially in vulnerable setting through use of rapid gene-based technologies.

PC-732-04 A novel therapeutic vaccine against tuberculosis in the cynomolgus monkey model: preclinical study and clinical trial

M Okada,¹ T Nakajima,² Y Kaneda,³ Y Inoue,¹ K Tomono,³ K Tsuyuguchi,¹ S Shoji,⁴ T Saito⁵ ¹National Hospital Organization Kinki-chuo Chest Medical Center, Osaka, ²Genomidea Co., Osaka, ³Osaka University, Osaka, ⁴National Hospital Organization Tokyo Hospital, Tokyo, ⁵National Hospital Organization Ibaraki-Higashi Hospital, Ibaraki, Japan. Fax: (+81) 722 512 153. e-mail: okm@kch.hosp.go.jp

Background: Multi-drug resistant (MDR), especially extremely drug resistant (XDR), *Mycobacterium tuberculosis* is a big problem in the world. We have developed novel TB therapeutic vaccine (HVJ-E/HSP65 DNA +IL-12 DNA vaccine) to eliminate MDR-TB.

Design/Methods: DNA vaccine (so called HSP65 vaccine) expressing *M. tuberculosis* heat shock protein 65 and IL-12 was delivered by the hemagglutinating virus of Japan (HVJ)-envelope. Human *M. tuberculosis* was intratracheally instilled into cynomolgus monkeys and then the monkeys were treated with the vaccine i.m.

Results: HSP65 vaccine provided remarkable protective efficacy and strong therapeutic efficacy against MDR-TB and XDR-TB in murine models (prolongation of survival time and the decrease in the number of MDR-TB). Furthermore, we extended our studies to a cynomolgus monkey model, which is currently the best animal model of human tuberculosis. HSP65 vaccine provided therapeutic efficacy of prolongation of survival time (100% survival) compared to saline control group (60% survival) of TB infected monkeys. This vaccine augmented the immune responses (IL-2 production and the proliferation of PBL) in TB-infected monkeys. In addition, the IL-2 production from PBL correlated with the survival. Therefore, the preclinical tests were studied in the good laboratory practice (GLP) level. The injection of 100µg of the vaccine /mouse i.m. three times in two weeks was optimal for the production of IFN-γ and IL-2. The GMP-level DNA vaccine was made by constructing the master cell bank. By using this vaccine, safety pharmacology and toxicology tests are studying using monkeys. High dose 5mg DNA vaccine/monkey (kg)

showed little toxicity (body weight, food consumption, hematology, blood chemistry). Furthermore, we have planned to do clinical phase I trial. Targets are human patients with MDR-TB. 8 weeks after 5 times injection of this vaccine, the number of MDR-TB and sputum-culture conversions of MDR-TB are defined as an efficacy (primary efficacy of end point) of the vaccine. Adverse events will be also examined.

Conclusion and recommendations: These data indicate that our novel vaccine might be useful against tuberculosis including XDR-TB and MDR-TB for human therapeutic clinical applications. (Co-workers: A Kumanogoh, A Mikami, T Matsumoto, Y Kita, S Hashimoto, Y Nishida, H Nakatani, S Nishimatsu, Y Kioka, Seiji H, P Saunderson, E V. Tan and D McMurray.)

PC-733-04 Universal access to the MODS assay reducing the incidence of MDR-TB cases in Arequipa, Peru

A Mendoza-Ticona,¹ C Figueroa,¹ M Perea,² V Vargas,¹ D Zavala,¹ A Ortega,² V Alarcon¹ ¹Peruvian National Tuberculosis Program, Lima, ²Regional Tuberculosis Program, Arequipa, Peru. e-mail: mendozalberto@hotmail.com

Background: Arequipa is the second-largest city of Peru, with a TB incidence of 48 cases per 100 000 inhabitants in 2014. In 2008, the Peruvian Government implemented the universal access to the MODS assay for rapid detection of isoniazid and rifampicin resistance from sputum samples. Objective: to evaluate the impact of MODS universal access on MDR-TB incidence in Arequipa

Methods: This is an operational research project. We reviewed NETLAB and RME systems from the National TB Program in Peru, looking for MODS assay production and results from the Arequipa Regional Laboratory and the incident MDR-TB cases reported by Arequipa Region between 2008 and 2014. We reported the number of cases and the proportion of TB patient that were MDR-TB per year. The trends were evaluated by χ^2 for trends.

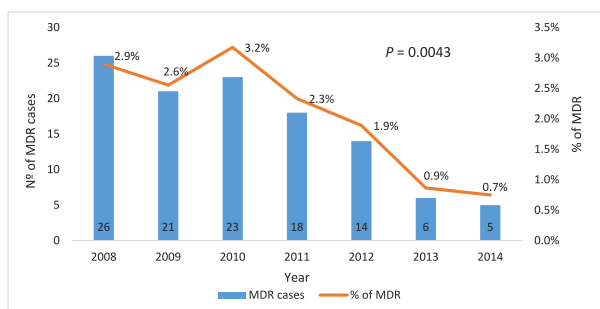


Figure. Incidence and proportion of MDR-TB cases in Arequipa region, Peru 2008 – 2014

Results: There was a significant reduction of notified MDR-TB cases in Arequipa Region ($P=0.0043$) after the implementation of universal access of the MODS assay, between 2008 and 2014, with lowest number being in 2014, with 5 cases (Figure).

Conclusion: MODS assay implementation as a universal access method was a successful public health intervention supported by the Government of Peru. MODS is currently available in six Regional Public Health Laboratories in Peru and is being rolled out in another seven regions.

PC-734-04 Modeling scenarios to determine the optimal MDR-TB treatment regimens in India

L Smith,¹ P Yadav,^{1,2} N Arinaminpathy,³ R Anupindi,² B Balogh¹ ¹William Davidson Institute, Ann Arbor, MI, ²University of Michigan, Ann Arbor, MI, USA; ³Imperial College London, London, UK. e-mail: lisacsmi@umich.edu

Background and challenges to implementation: In many countries there is considerable variation in the multidrug resistant tuberculosis (MDR-TB) regimens used for treatment. In a given setting, the optimal MDR-TB regimen requires consideration for recommended first line drugs, drug resistance, and regimen success. In addition to accurate transmission modeling, a model to help determine optimal MDR-TB regimens needs to incorporate important facets of the market and production economics for different product markets (e.g., drug price, price-volume relationships). However data scarcity makes this exercise challenging and requires thoughtful consideration for specific scenarios of drug resistance.

Intervention or response: The authors built a mathematical model that optimizes regimen choice as shaped by a variety of factors, including: the transmission implications of non-adherence (for example as driven by adverse events); the profile of resistance in a population; the way in which procurement cost scales with the numbers of different drugs being procured; and the programmatic costs of treating drug resistance (whether incurred or averted). Our model examines the optimal MDR-TB treatment regimen in India under several different epidemiological and market scenarios. The objective for the model is to minimize the cost per QALY gained over a ten-year period, under different choices for how a given budget is apportioned between different treatment regimens.

Results and lessons learnt: This model highlights the trade-off that while extensive regimen variation may further fragment what are considered small-demand drug markets, a certain degree of tailoring treatment regimens aids in better adherence and individual treatment outcomes, thus potentially reducing opportunities for onward transmission. This decision space has become increasingly important to consider with the inclusion of increasing numbers of drugs, and combinations thereof.

Conclusions and key recommendations: The model will provide National Tuberculosis Treatment Programmes with decision support when considering modifications to existing MDR-TB drug regimens. This model may inform regimen design particularly in light of new product introduction and improved access and use of drug susceptibility testing. Procurement groups at the country level may also use the described modeling approach to inform purchasing decisions through an understanding of both the market and public health impact.

05. Collaborative services for TB and diabetes

PC-735-04 Body mass index and risk of tuberculosis: analysis from two prospective cohorts

H Fu,¹ H-H Lin¹ ¹National Taiwan University, Taipei City, Taiwan. e-mail: b97801047@ntu.edu.tw

Background: Previous studies suggested that people with higher-than-normal level of body mass index (BMI) had a lower risk of tuberculosis compared with those with normal BMI. Few of these studies controlled for important confounding factors including tobacco smoking and alcohol use.

Design/Methods: We conducted two cohort studies in Taiwan to investigate the association between different levels of BMI and risk of incident tuberculosis. The first cohort used adult participants from two rounds of National Health Interview Surveys (NHIS) ($n = 30\,486$). The second cohort consisted of general population from community-based health screening service ($n = 116\,893$). Baseline information on BMI and other covariates was collected through structured questionnaires. The incidence of tuberculosis was ascertained from the National Tuberculosis Registry (NHIS cohort) and the national health insurance database (screening cohort). Cox proportional regression was used to estimate the adjusted hazard ratio (aHR) and 95% confidence intervals for different levels of BMI.

Results: After a median follow-up of seven years, 85 and 388 cases of active tuberculosis developed in the NHIS and screening cohorts respectively. Compared with normal BMI, underweight was associated with increased risk of tuberculosis, and overweight and obesity were associated with decreased risk of tuberculosis (Table). The analyses were adjusted for age, sex, smoking, alcohol use, diabetes, and education level.

Conclusion: Our studies confirmed the findings from previous studies that high-than-normal level of BMI was associated with decreased risk of tuberculosis. The implication of global epidemic of obesity on tuberculosis epidemiology, especially in the lower and middle income countries should be further investigated.

Table. Association between BMI and risk of incident tuberculosis

NHIS cohort (n=30,486)			Screening cohort (n=116,893)		
BMI (kg/m ²)	aHR	95%CI	BMI (kg/m ²)	aHR	95%CI
<18.5	1.45	0.70-3.01	<18.5	2.85	1.96-4.16
18.5 - 22.9	1.00	ref	18.5 - 24.9	1.00	ref
23.0 - 24.9	0.40	0.23-0.71			
25.0 - 29.9	0.29	0.16-0.53	25.0 - 29.9	0.39	0.30-0.50
≥ 30	0.41	0.13-1.31	≥ 30	0.17	0.08-0.36

PC-737-04 Screening of tuberculosis patients for diabetes in public-private partnership projects in India

S Mugudalabetta,¹ L Gujral,¹ S K Muthusamy,¹ R Begum¹

¹Damien Foundation India Trust, Chennai, India. Fax: (+91) 44 2836 0496. e-mail: admin@damienfoundation.in

Background and challenges to implementation: Diabetes is emerging as a major threat to progress made in tuberculosis control. Screening of all TB patients for diabetes and ensuring strict blood glucose control is important to improve the treatment outcomes. Revised National Tuberculosis Control Program has issued guidelines for screening and management of diabetes among TB patients. The aim of the study is to share the experience in screening of TB patients for diabetes in projects managed under public private partnership.

Intervention or response: Damien Foundation India Trust organized training for all the staff involved in TB control program in Salem (Tamil Nadu), Nellore (Andhra Pradesh) and South West Delhi. In 2014, after a brief training all the TB patients registered in third and fourth quarter were screened for diabetes using glucometer. At the time of registration, all the TB patients were enquired about history of diabetes. TB patients who were not aware of their diabetic status underwent random blood glucose test. Patients with random glucose value more than 110 mg/dl were screened with fasting blood glucose. If fasting blood glucose was more than 126 mg/dl, patients were considered as suffering from diabetes.

Results and lessons learnt: During the third and fourth quarter 2014, 1533 TB cases were registered for treatment. Among them 139 were found to be already suffering from diabetes. Out of 1394 patients who didn't know their diabetic status, 1347 (97%) underwent random blood glucose test. It was found that 380 patients had random blood glucose level >110 mg/dl, among them 322 were screened with fasting blood glucose. This screening initiative was helpful in diagnosing 37 new diabetic cases among TB patients. Overall 11.5% of TB patients were found to be suffering from diabetes. Most of the patients who already knew their diabetic status were found to be taking treatment from private sector, therefore coordination with them remains as a major challenge.

Conclusions and key recommendations: Screening of tuberculosis patients for diabetes is feasible. Future research should focus on coordination with private sector to improve management of diabetes.

PC-738-04 Study of TB-diabetes collaborative activities under the Revised National TB Control Programme, Maharashtra, India

B Pawar,¹ S Bharaswadkar,² O Bera,³ S Kamble¹ ¹State TB Office, Pune, ²World Health Organization South East Asia Office, New Delhi, ³International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: bhagawanpawar.gbvb@gmail.com

Background: Revised National TB Control Programme (RNTCP) is implementing National strategic plan (NSP) for universal access of TB care. Management of comorbidities is a part of NSP. RNTCP has developed framework for TB- Diabetes collaborative activities in collaboration with National Programme for Prevention and control of cancer, Diabetes, cardiovascular diseases and stroke (NPCDCS). This study was undertaken with the following objectives: To assess completeness of TB-Diabetes collaborative activities in Central India; and to assess outcome of NSP patients with respect to diabetic status to ascertain impact of diabetes and treatment of diabetes on TB treatment outcome.

Intervention: Record Review of TB patients registered in 5 districts of Maharashtra in India in year 2013. Records like Treatment card, TB register and reports like quarterly report of TB- Diabetes collaborative activities were reviewed for the year 2013. Data entry and analysis were performed in Excel.

Results: 7145 TB patients were registered in 5 districts in year 2013. 1% (98) patients were known diabetic patients. 59% (4082) TB patients were screened for diabetes. 19% (784) TB patients had random blood sugar more than 110mg/dl. 64% of 784 TB patients underwent fasting blood sugar. 136 (27%) of the patients were diagnosed as diabetic. Total 231 Diabetic patients were diagnosed in TB patients. 206 (89%) of the patients reached diabetic care. Review of treatment outcome of New smear positive TB patients who are diabetic found that conversion rate and success rate of New smear positive TB patients who are diabetic is similar to the success rate of new smear positive TB patients who are not diabetic i.e. 88% each.

Conclusions and key recommendations: TB Diabetes collaborative activities have been taken up well under programme. This initiative may be expanded in entire country. Coverage may be strengthened by improving supervision. Establishment of district coordination committee for monitoring of activities may be considered for the same. Good comparable outcome in between diabetic NSP patients and non-Diabetic NSP patients draws attention importance of complete treatment of both TB and diabetes. Moreover it underlines significance of early and prompt diagnosis of diabetes in TB patients.

PC-739-04 Performance of laboratory glycated haemoglobin (HbA1c) as a screening test for diabetes mellitus in pulmonary tuberculosis

S Imaculata,¹ N Nathalia,^{1,2} S Mcallister,³ R Koesoemadinata,¹ R Ruslami,¹ B Alisjahbana,^{1,2} P Hill,³ R Van Crevel⁴ ¹Universitas Padjadjaran, Bandung, ²Universitas Padjadjaran/ Hasan Sadikin General Hospital, Bandung, Indonesia; ³Otago University, Dunedin, New Zealand; ⁴Radboud University Nijmegen Medical Center, Nijmegen, Netherlands. e-mail: sofia.imaculata@gmail.com

Background: Screening for diabetes mellitus (DM) in pulmonary tuberculosis (PTB) patients is an increasing concern due to the rise of DM and PTB co-existence. Fasting plasma glucose (FPG) and two hours post-prandial plasma glucose, while commonly used, are less practical for screening. Glycated haemoglobin (HbA1c) should be considered as an alternative but its performance can be influenced by abnormal haemoglobin (Hb) level. This study examined the anaemic status and performance of HbA1c in PTB patients.

Design/Methods: Screening for DM among PTB patients, as part of TANDEM program (www.tandem-fp7.eu), was performed in Bandung from December 2013 to April 2015. Routine haematological examination, random capillary glucose (RCG) using AccuChek, laboratory HbA1c using high-performance liquid chromatography analyzer (NGSP standardized), and point-of-care (POC) HbA1c using HemoCue HbA1c analyzer were conducted. DM was considered if RCG was ≥ 11.1 mmol/l and/or HbA1c $\geq 6.5\%$, which was confirmed by a FPG and/or second HbA1c measurement. Sensitivity and specificity of laboratory HbA1c were calculated separately.

Results: From 349 PTB patients screened for DM, 319 cases with complete data were included in this analysis. Mean age was 41.1 (SD 14.3) years and 54.2% were male. HIV co-infection and kidney disease were found in 7 (2.2%) and 10 (3.1%) patients, respectively. Anaemia was found in 181 (56.7%) patients. Between those with and without anaemia, there was no significant difference in age (mean 40.5 vs. 41.8 years, $P = 0.405$), sex (male 50.3% vs. 59.4%, $P = 0.104$), ethnicity (Sundanese 90.6% vs. 83.3%, $P = 0.097$), and HIV co-infection (3.3% vs. 0.7%, $P = 0.118$). DM was confirmed in 26 (14.4%) patients with anaemia and 36 (26.1%) patients without anaemia. Sensitivity of laboratory HbA1c in both anaemia and non-anaemia group was 100.0%, whereas specificity was higher in the non-anaemia group (98.1% vs. 100%). Positive predictive value (PPV) and negative predictive value (NPV) of laboratory HbA1c in the anaemia group were 89.6% and 100%, respectively. In the non-anaemia group, PPV and NPV of laboratory HbA1c were both 100%.

Conclusion: Regardless of the anaemia status of PTB patients, laboratory HbA1c could be used as screening test for DM. HbA1c provides high sensitivity and is a practical tool as it does not need to be measured in a fasting condition and the blood sample does not need to be processed within two hours.

PC-740-04 Age, body mass index and family history of DM as predictors of DM for TB patients

L Prasiddha,¹ T Pakasi,¹ I S Widyahening¹ ¹Faculty of Medicine Universitas Indonesia, Dki Jakarta, Indonesia.
e-mail: lorens.prasiddha@gmail.com

Background: Tuberculosis (TB) and diabetes mellitus (DM) are diseases commonly found as comorbidities. TB patients are known to be prone to DM. DM may cause further complications in TB and therefore, to prevent further complications, early screening of DM is required for TB patients. One of several methods of screening is the utilization of predictors of DM. This study aimed to develop age, body mass index, and family history of DM as predictors of DM among TB patients.

Design/Methods: This is a cross-sectional study among TB patients registered in primary health facilities and Diabetes Center of Ternate, one of DM endemic areas in Indonesia. All subjects were assessed for DM based on Indonesian National Consensus of Diabetes Mellitus. We took note of every subject's age and family history of DM. Height and weight of subjects were measured using the proper examination tool. The height and weight data were used to calculate the subject's body mass index. Data of subject's age, family history of DM, and body mass index were analyzed as individual and combination predictors of DM among TB patients.

Results: Among 55 subjects of TB patients, 31 subjects (56.4%) were diagnosed with DM whereas 24 subjects (43.6%) were excluded from diagnosis of DM. TB patients aged over 44 years higher risk ($P < 0.001$, RR = 3.8) over TB patients aged below 44 years to develop DM. TB patients with body mass index $< 18.5 \text{ kg/m}^2$ years had higher risk ($P = 0.004$, RR = 3.2) over TB patients with body mass index $\geq 18.5 \text{ kg/m}^2$ to develop DM. TB patients with positive family history of DM had higher risk ($P = 0.035$, RR = 1.9) over TB patients with negative family history of DM to develop DM. TB patients aged over 44 years having body mass index $\geq 18.5 \text{ kg/m}^2$ had higher risk to develop DM ($P = 0.038$, RR = 2.0). TB patients aged having body mass index $\geq 18.5 \text{ kg/m}^2$ with positive family history of DM had higher risk to develop DM ($P = 0.049$, RR = 1.8). Age and family history of DM did not have significant relationship as predictors ($P = 0.277$).

Conclusion: This study concludes that age, body mass index, and family history of DM were available as predictors of DM for TB patients. Combination of age and body mass index and also body mass index and family history of DM were highly suggested as combination predictors of DM for TB patients. TB patients aged over 44 years, body mass index $< 18.5 \text{ kg/m}^2$, or positive family history of DM are more susceptible to DM and therefore should always be screened for DM.

PC-741-04 Avances de la estrategia nacional de atención integrada de la comorbilidad tuberculosis-diabetes mellitus en México

Y Dávila,¹ M A Garcia,¹ M Castellanos¹ ¹Ministerio de Salud, México City, Mexico. e-mail: gpejazz@gmail.com

Background and challenges to implementation: La Tuberculosis (TB) y la Diabetes Mellitus (DM) representan dos problemas de salud pública, cada uno constituye un desafío para su abordaje y control. En México, 21% de los casos de TB están asociados a la DM. De 2000 al 2013 se registró incremento de 208%. Durante el 2014 se identificaron 4,269 casos nuevos con TBTF y DM. Desde el año 2010 el Programa Nacional de Tuberculosis y el Programa Nacional del Adulto y Anciano han colaborado para impulsar estrategias que coadyuven en el control de la comorbilidad TB-DM. En 2011 la OMS y la Unión Internacional contra la Tuberculosis y Enfermedades Respiratorias reconocieron la necesidad de guías internacionales sobre el manejo conjunto de la TB y la DM. Asimismo puntualizó que el establecimiento de mecanismos de colaboración entre los programas nacionales de TB y DM es fundamental para el seguimiento y control de ambas patologías.

Intervention or response: •Implementación de la propuesta mexicana para la Estrategia Nacional de atención integrada TB-DM. •Desde 2014 se incluyó el indicador de desempeño en la evaluación nacional del programa de TB. Detección de DM en pacientes con TBTF de 20 años y más de edad, aplicable para todas las instituciones del Ministerio de Salud. •Se emitieron recomendaciones de atención integrada para garantizar el seguimiento y control glicémico en las personas con TB-DM. Realizar glicemia capilar de manera semanal, glicemia central de manera mensual y hemoglobina glicosilada de manera trimestral. •Se elaboraron algoritmos de atención integrada para la detección, monitoreo y control de las personas con TB-DM.

Results and lessons learnt: - Mejora en la cobertura del indicador de desempeño: La detección de DM en personas con TB fue de 83.1% para el tercer trimestre de 2014 en todo el país, el año previo la actividad alcanzó el 72.7%. -Aumento en el éxito terapéutico de la cohorte de tratamiento primario TB-DM de enero a junio 2014: 87.9%. El resultado de la cohorte anterior fue de: 86.2%. -Fortalecimiento de la atención integrada de la comorbilidad TB-DM.

Conclusions and key recommendations: México ha avanzado en la recomendación internacional de integración de servicios para personas con TB y DM al ofertar el tamizaje bidireccional e impulsar algoritmos de atención integrada de la comorbilidad. La atención integrada de la comorbilidad TB-DM favorece la detección oportuna de ambos padecimientos, así como la adherencia terapéutica y la curación.

PC-742-04 Life after TB: a systematic review of imaging defined post-TB lung disease

J Meghji,¹ H Simpson,² K Mortimer,³ S B Squire³

¹University of Liverpool, Liverpool, ²London School of Hygiene & Tropical Medicine, London, ³Liverpool School of Tropical Medicine, Liverpool, UK. e-mail: jamilah.meghji@gmail.com

Background: Pulmonary and pleural TB cause changes in lung structure and function that persist after treatment completion. The pattern and prevalence of structural damage, its relation to airway physiology, and the associated morbidity are poorly defined. A systematic review was conducted to identify studies describing the prevalence of imaging defined (CT/CXR) post-TB lung disease.

Design/Methods: A protocol driven literature search was used to identify studies of pulmonary or pleural TB using CXR or CT imaging. 2 reviewers selected English language studies in which consecutive patients were imaged after completion of TB treatment, and the prevalence of abnormal imaging or severity of residual disease were reported. Studies of children and those with non-HIV immunosuppression were excluded. Additional articles were found using reference and citation reviews. Data were extracted and study quality was assessed.

Results: Of the 4495 articles identified, 35 were selected. These were published between 1973-2014 with data for 4273 patients, and included 6 CT studies. Imaging was performed at treatment completion in 19/26 studies of pulmonary TB sequelae. The prevalence of cavitation was higher in studies of multi-drug resistant (MDR) disease (51.5-69.7% vs. 7.4-55.0%). The prevalence of fibrosis (70.0-92.6%), bronchiectasis (35.0-85.2%), and emphysema / bullae (15.4-45.0%) was high on CT studies. Residual pleural thickening >10mm was seen in 19.6-46.0% of patients on treatment completion in 9 studies of pleural disease. Only 2 studies from sub-Saharan Africa (sSA) were found, both of which were from South Africa. Disaggregated data were available for 96 HIV-infected people. Only 1 study included serial imaging. 3 studies described the relationship between imaging findings and spirometry, and 2 described the relationship with morbidity: impairment of functional capacity and symptom burden were greater in those with abnormal imaging.

Conclusion: A high burden of structural lung damage persists after TB disease, for which CT is more sensitive than CXR. The high prevalence of damage after MDR disease is a concern for areas with high rates of drug resistance. There is a paucity of data from sSA and in HIV-infected patients. Phenotyping of post-TB lung disease along multiple respiratory parameters is needed to optimise patient management. Further investigation of the evolution of lung disease over time, its associated morbidity, and its impact on patients' lives is needed.

06. TB surveillance from Swaziland to Japan

PC-743-04 District-level performance monitoring improved the accuracy of TB program reporting in Ethiopia

D Habte,¹ N Demmelash,¹ G Negussie,²

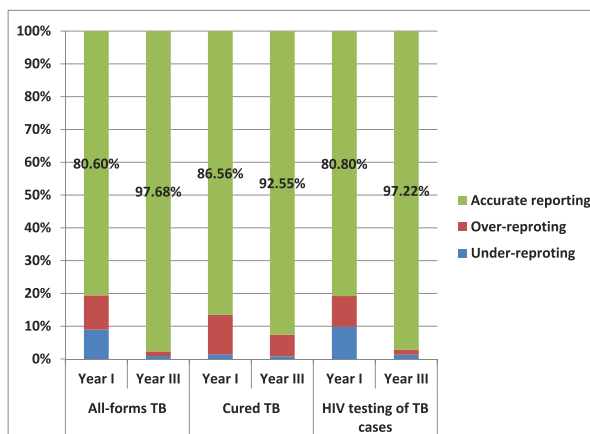
I Jemal Abdulahi,³ D J Dare,¹ M Aseresa Melese,¹

Y Haile,⁴ P G Suarez⁵ ¹Management Sciences for Health-Help Ethiopia Address the Low TB Performance (HEAL TB) project, Addis Ababa, ²Amhara Regional Health Bureau, Bahar Dar, ³Oromia Regional Health Bureau, Addis Ababa, ⁴United States Agency for International Development (USAID), Addis Ababa, Ethiopia; ⁵Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: dhabte@msh.org

Background and challenges to implementation: Health programs are highly dependent on data for planning, implementation, monitoring and evaluation purposes. The USAID-funded Help Ethiopia Address the Low TB Performance (HEAL TB) has been supporting the Amhara and Oromia Regions of Ethiopia in TB program including data quality.

Intervention or response: HEAL TB project implemented a standard of care performance monitoring tool to track the performance of health facilities in relation to TB program implementation as well as the accuracy of selected TB program indicators. District TB focal persons visited health facilities in their jurisdiction on quarterly basis to validate the accuracy of the TB program report submitted by the health facilities against the re-count made on the records kept at the health facilities. The district TB focal persons provided feedback on data quality issues based on the consistency check and decided on improvement plan whenever there is a problem of data quality. We present the trend of data quality on 3 selected indicators in health facilities in 10 zones of Amhara and Oromia from 2011-2014.

Figure Percentage improvement in the accuracy of reporting of selected TB program indicators in Ethiopia, 2011-2014



Results and lessons learnt: In the 10 zones, 691 health facilities have been supported with a comprehensive package of TB program support. Over 85% of the health

facilities were mentored each quarter by the district TB focal person where data quality check was also conducted. The accuracy of reports (reported and re-counted) in the health facilities improved significantly over the three years: 80.6% (95%CI: 77.5-83.4%) to 97.7% (95%CI: 96.3-98.6%) for all forms of TB; 86.6% (95%CI: 83.8-88.9%) to 92.6% (90.4-94.3%) for TB cure rate; and 80.8% (95%CI: 77.7-83.5%) to 97.2% (95%CI: 95.8-98.2%) for HIV testing among TB patients ($P < 0.05$).

Conclusions and key recommendations: The use of routine standard of care performance monitoring and onsite feedback significantly improved the quality of data and reports at health facility levels. The data quality improvement is also attributed to a strong program.

PC-744-04 Surveillance system evaluation of the integrated disease surveillance project (IDSP) in Shimla district, Himachal Pradesh, India

O K Bharti¹ ¹State Health and Family Welfare Training Centre Parimahal, Shimla, India. e-mail: bhartiomesh@yahoo.com

Background: The major objective of IDSP is to recognize early warning signals of impending outbreak and help initiate an early response in a timely manner. A project to study the disease surveillance project in reference to tuberculosis was undertaken to know the causes of increase in the incidence of tuberculosis

Design/Methods: A protocol for evaluation was prepared and shared with all the stakeholders to get their involvement. We mailed self administered questionnaires to various health functionaries and also had informal discussions with various stakeholders in the district. We also assessed the level of integration as well as sensitivity of IDSP with respect to TB as component of Revised national tuberculosis programme, RNTCP. We entered the data in Excel software and calculated various indicators as proportions using Epi Info.

Results: The prevalence of TB in the district is 257/Lakh population and is higher than the state prevalence of 210/lakh population. 208 of 275 health workers in place responded to the questionnaire with a response rate of 78%. IDSP reported 249 cases of cough more than 3 weeks out of that only 131 were sputum positive, while those reported by RNTCP for similar period was 2333 chest symptomatic screened and 263 cases were confirmed, and the difference was significant. ($\chi^2 = 297$; Df = 1, $P = 0.00$). This translates into sensitivity of 10% of suspect cases and 50% of confirmed cases. Positive predictive value is only 20% at MPW level and only 57% reports are timely. 52 out of total 90 posts of lab technicians (58%) are vacant in the district, even 7 DMCs are without lab technicians. Mean population served by a single lab is 69203 $\pm$ 162458. Vacancy of MPW is related to the cure rate of TB that is as the vacancy increases cure rate decreases and is inversely correlated ($r = 0.99$). This is due to the fact that MPWs are also DOTS providers. Only 33% of the health workers are able to visit their villages in a week. 59% of them said that

people try to hide the disease even from them due to prevalent stigma in the community.

Conclusion: There was mismatch between cases reported by IDSP and those reported by official channels of the Revised National Tuberculosis Programme (RNTCP). To fill all the vacancies and to have more involvement of private sector and medical colleges is the key to have a sensitive IDSP and better RNTCP. Need to have less area for monitoring and some mobile allowance for MPWs to SMS data to higher authorities.

PC-745-04 Accelerating TB notification among private providers using ICT based applications in Delhi, India

D Kundu,¹ K Chopra,² A Khanna,³ T J Padmini,³ B Neeti³

¹World Health Organization Country Office for India, Delhi,

²New Delhi Tuberculosis Centre, Delhi, ³Directorate of Health Services, Delhi, India. e-mail: debashishkundu@yahoo.com

Background: In India almost half of all patients with Tuberculosis (TB) seek care in the private sector as the first point of care. The National Program is unable to support TB patients and facilitate effective treatment as there is no information on TB and M/XDR-TB diagnosis and treatment in private sector. To improve this situation, Government of India declared TB a notifiable disease for establishing TB surveillance system, to extend supportive mechanism for TB treatment adherence and standardised practices in the private sector. But, TB notification from the private sector is a challenge and still a lot needs to be done to accelerate TB notification.

Intervention or response: Delhi State TB Control Programme has taken special initiatives for accelerating notification of TB cases from the private sector in 2014 by constituting a state level TB notification committee, collaborating with the interface agencies like Delhi Medical Association (DMA) for placing TB notification advertisements periodically in their news bulletin and Initiative for Promoting Affordable Quality TB Tests (IPAQT) to facilitate notification from the IPAQT partner laboratories. A most important initiative was direct 'one to one' sensitization of private providers (PP) by state level TB notification teams for providing options on notification modalities using ICT based applications - Nikshay (Case-Based Web Online application) and convenient web-login or mobile apps for the purpose of direct notification of TB cases in Nikshay TB notification portal [Table]. A total of 102 PP's were sensitised on TB notification modalities, of which 40 PP's were also given live on-line demonstration using web-login. Eight private laboratories were sensitised in Nikshay and direct web-login process.

Results and lessons learnt: 83% (85/102) of PP's post sensitisation started to notify TB cases in Nikshay and total of 2837 TB cases were notified by the private sector. 38% (15/40) of PP's directly notified 110 TB cases using web-login access and 100% (70/70) PP's notified 2727 TB cases in Nikshay using active support from the field staff, including of IPAQT.

toms, diagnosis delay, and time of death during the treatment were summarised. The χ^2 test for categorical data was applied to compare proportions.

Results: In 2013, the proportion of pulmonary TB (PTB) patients with bacteriologically positive results was higher (89.9% vs. 77.5%, $P = 0.00$), but that of patients with cavitory lesions on CXR was lower (29.1% vs. 35.0%, $P = 0.00$) among those aged ≥ 65 years than among those aged 15–64 years. Among all the symptomatic PTB patients, the proportion of those with non-respiratory symptoms only was higher (26.5% vs. 18.0%, $P = 0.00$) in those aged ≥ 65 years, increasing with age from 21.6% in those aged 65–75 years to 30.3% in those aged ≥ 85 years. The proportion of TB patients with patient delay (duration between onset of symptoms and the first consultation visit) of ≥ 2 months was lower (14.2% vs. 25.6%, $P = 0.00$), whereas that with doctor delay (duration between the first consultation visit and TB diagnosis) of ≥ 1 month was slightly higher (23.0% vs. 20.3%, $P = 0.00$) among the patients aged ≥ 65 years than among those aged 15–64 years. Among the TB patients aged ≥ 65 years who were notified in 2012, 32.2% died within 1 year after the initiation of TB treatment.

Conclusion: The elderly tended to have a lower frequency of respiratory symptoms, to have a late TB diagnosis after the first consultation visit, and to die at the early stage of TB treatment compared with the patients in the other age groups. Health-care workers and those in other sectors, including the welfare service, need to be aware of the characteristics of the elderly at the time of TB diagnosis and throughout the treatment course, not only in Japan but also in countries that experience age progression among TB patients.

PC-748-04 Use of the national electronic database to map TB patients with transfer out outcomes in Kenya

J Kiarie,¹ D Mibei¹ ¹Ministry of Health, Nairobi, Kenya.
e-mail: jckiarie@gmail.com

Background: Tuberculosis being a disease of public health concern has further been complicated by the emergence of MDRTB. There has been lots of effort globally to fight the disease and Kenya has made much progress in this. TB patients in Kenya are managed according to WHO guidelines. While the TB program recommends follow up, it's hard to control movement of patients within the country and across borders. Patients who move to another district permanently to continue with treatment are allocated a transfer out outcome. Therefore, proper referral for these patients by the facility of origin is vital to control default rate, treatment interruption, disease transmission and risk to MDRTB. Transfer out outcome is inevitable since patients move due to various reasons during their treatment period which impacts negatively on TB treatment success rate. Among adverse TB treatment outcomes, Transfer outs are low hanging fruits since a follow up can be done at the facility of origin to improve treatment success rate

hence the need to assess whether transfer out TB patients arrive at their destination facilities

Design/Methods: This study was done to determine the proportion of smear positive patients with a transfer out outcome who could be matched in the national database, determine the treatment outcomes among patients who recorded a transfer out outcome and establish gaps in documentation of data for patients who were transferred out. A cross sectional descriptive study was done using secondary data from the national electronic database to match patients with a transfer out outcome using Names, Age, Type of TB, Smear results at month 0, HIV status and date of treatment initiation variables

Results: From 366 smear positive patients registered in quarter 1 2013, most cases with transfer out outcomes were from the prison sector, 10% under nutrition cases, 10% HIV- and 13% those not initiated on ARVs. 27% of the total of cases was found with 76% of them having a cured treatment outcome. Key gaps identified included documentation of names and patient type classification. After incorporating the mapping results the National treatment success rate increased by approximately 2%.

Conclusion: There is need to strengthen the patient referral system, capacity building to health care workers and standardize documentation procedures to improve TB treatment outcomes in Kenya

PC-749-04 Swaziland active surveillance and patient safety monitoring for patients on ARVs and TB drugs

K Kunene,¹ N Shongwe² ¹SIAPS, Management Sciences for Health, Mbabane, ²Ministry of Health, Mbabane, Swaziland.
Fax: (+268) 2404 2787. e-mail: kkunene@msh.org

Background: Swaziland remains one of the countries with the highest dual human immunodeficiency virus (HIV) and tuberculosis (TB) burden globally. The HIV incidence rate is 26% and there are around 1382 per 100 000 incident TB cases annually. Exacerbating this challenge is the TB-HIV co-infection rate that remains high at around 80% and 66% of the co-infected patients are receiving treatment for both. The continuous introduction of new essential medicines necessitates the concurrent monitoring of adverse effects and safety of the patients on antiretrovirals (ARVs) and TB medicines. As such, the Ministry of Health (MOH), supported by the USAID-funded Systems for Improved Access to Pharmaceuticals and Services program (SIAPS) implemented an active pharmacovigilance and patient safety monitoring system for patients on ARVs and TB medicines.

Design/Methods: SIAPS supported the MOH to develop the protocol and tools to operate the Sentinel Site-based Active Surveillance System for Antiretroviral and Anti-TB (SSASSA) electronic system. The cohort event monitoring was introduced at 5 pilot hospitals in June 2013. Clinicians enrol (and follow up) treatment naïve HIV patients and TB patients starting a new regimen. Relevant patient information is captured onto the system by data clerks. Data is collected monthly and analysed

centrally using the electronic data collection and analysis tool. Supportive supervisory visits are conducted every month. Data is disseminated quarterly through a newsletter.

Results: A total of 2001 patients have been enrolled from June 2013 to March 2015 (67% females and 33% males) and there have been 936 adverse events (ADRs) reported. Peripheral neuropathy (15%) and rash (10%) are the most common, with kidney failure, ototoxicity and death being the most severe. ADRs accounted for 2% of 956 regimen switches. The causality assessment showed that 90% of the reported ADRs were probably or possibly caused by the medicines using the WHO and Naranjo causality assessment methods.

Conclusion: The active surveillance system is systematically documenting and quantifying the incidence rate of adverse events associated with ARVs, 1st and 2nd line anti-TB medicines. In addition, the active surveillance system is generating local data to provide better estimates of risk-benefit profiles and help prevent and minimized such risks at sentinel sites. The MOH is in the process of expanding the active surveillance system to four more regional hospitals.

PC-750-04 Evaluation of the tuberculosis surveillance system in Shamva District, Zimbabwe, 2014

R Makurumidze,¹ N Gombe,¹ D Bangure,¹ M Tshimanga,¹ T Magure² ¹University of Zimbabwe, Harare, ²National AIDS Council of Zimbabwe, Harare, Zimbabwe. e-mail: ricmanie2000@yahoo.com

Background: A review of tuberculosis (TB) surveillance data for 2013 in Shamva District showed shortcomings. An average of 10 health facilities out of 15 was reporting TB data on time. There was incomplete and incorrect filling of TB surveillance tools. We therefore evaluated the tuberculosis surveillance system in the district.

Design/Methods: A descriptive cross – sectional study was carried out using Centre for Disease Control Guidelines on Evaluation of a Public Health Surveillance System. Study participants were healthcare workers and key informants. Data was collected using questionnaires from healthcare workers and interview guide from key informants. Quantitative data was analyzed using Epi-Info. Permission to carry out the study was sought from the relevant authorities. All ethical considerations were duly observed.

Results: 41 healthcare workers were interviewed. Females constituted (70.3%) and males 29.3%. Median age was 39 years (Q1:33; Q3:45) and median length of service was 6 years (Q1:4; Q3:9). The majority of the healthcare workers were primary care nurses (43.9%). Only 22 % were trained in TB disease surveillance. Knowledge levels on TB symptoms and signs were above 90% and for objectives of the surveillance system was between 60 - 90%. Lack of transport; lack of stationery; delay in compilation; negative attitude and motivation were mentioned as reasons for reporting delays. Thirty three (80.5%) mentioned that the TB data collected is

used in any way at their health facility. Only 19.5% had access to TB screening flow chart. 85% of the healthcare workers were willing to complete TB notification forms. The median time for sample to reach the lab was 1 day; a result to reach health facility was 3 days and monthly report to reach district was 8 days. There was integration of HIV-TB activities in the district. Majority of health facilities did not have computers, internet access, faxes and landlines. Shortage of various TB surveillance tools was reported.

Conclusion: Knowledge levels were poor on the objectives of the surveillance system. The TB surveillance system was not simple, stable and timely but was useful, flexible, and acceptable. Mentoring, training and capacity building of healthcare workers in TB surveillance and provision of surveillance tools will improve the system performance.

07. Tuberculosis: from the bench to the grave

PC-751-04 Recurrence rate of tuberculosis and mortality among smear-positive patients in Viet Nam

G Fox,¹ N Nguyen,² T A Nguyen,¹ T L Phan,¹ B H Nguyen,² N A Le,¹ W Britton,³ G Marks¹ ¹Woolcock Institute of Medical Research, Sydney, NSW, Australia; ²National Lung Hospital, Hanoi, Viet Nam; ³Centenary Institute of Cancer Medicine and Cell Biology, Sydney, NSW, Australia. Fax: (+61) 2 9114 0010. e-mail: foxsimile@gmail.com

Background: The recurrence rate of tuberculosis (TB) is an important indicator of the effectiveness of a TB control program. Throughout Vietnam, 7.1% of all notified TB patients treated by the National TB Program (NTP) are reported to develop recurrent TB. This may underestimate the true recurrence rate, as it excludes patients lost to follow-up. We aimed to determine the TB recurrence rate and mortality among patients with smear positive TB treated by the Viet Nam National Tuberculosis Program (NTP) in the first 24 months or more of follow-up.

Design/Methods: This prospective cohort study, with nested case-control study, was conducted in 70 districts selected at random from eight provinces in Viet Nam, with the probability of district selection in proportion to the total population. Patients with smear positive pulmonary tuberculosis, enrolled in a cluster-randomized controlled trial of household contact investigation, were re-traced for between two and four years after treatment initiation and recurrent episodes of TB and mortality were documented. In addition, all patients with incident TB, and a random sample of healthy contacts, completed a more detailed questionnaire.

Results: 11 200 patients with smear positive TB were enrolled between 1st September 2010 and July 31st 2013. Of 9331 index patients enrolled, 8480 (90.9%) were re-traced and 851 (9.1%) were lost to follow-up. Median follow-up for patients was 34 months (inter-

quartile range 28 – 40 months). Among 7327 patients who completed treatment, 510 (7.0%, 95%CI 6.4 – 7.5%) developed recurrent TB during follow-up. Of these, 66 individuals died as a result of TB. Among re-traced patients, 895 (10.6%, 95%CI 9.9-11.2%) died during the follow-up period, including patients died with recurrent TB. The age and gender Standardized Mortality Ratio for all patients compared to their household contacts was 5.

Conclusion: The recurrence rate of TB among smear positive patients was similar to official estimates. Further research is required to identify factors associated with recurrence and mortality, in order to strengthen TB control in Viet Nam.

PC-752-04 Deaths due to tuberculosis in Natal, Rio Grande do Norte, Brazil, 2008-2014

A Queiroz,¹ M C C Garcia,¹ L H Arroyo,¹ A Belchior,¹ J Crispim,¹ M Touse,¹ M Popolin,¹ R Arcencio,¹ ¹Ribeirão Preto School of Nursing, University of São Paulo, Ribeirão Preto, SP, Brazil. e-mail: aninha_arego@hotmail.com

Background: Despite the advances in prevention and treatment people are still dying due to tuberculosis (TB) around the world, mainly in 22 High-TB Burden countries. The World Health Organization has just approved the ambitious goal of reducing 95% of TB deaths by 2015. It is necessary to know why and where these people die due to TB, in Brazil. Thus, this study aimed to characterize the clinical and epidemiological profile of patients who died due to TB and to identify the areas where these events occurred more frequently.

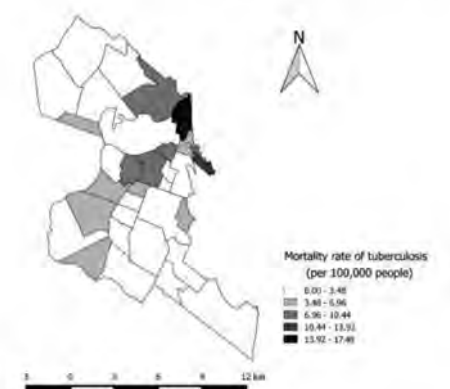
Design/Methods: Descriptive and ecological research developed in Natal - Rio Grande do Norte Brazil, which has a population of 817 590 inhabitants (2010), and it is considered a priority city for TB control with an incidence of 46.6 per 100 000 inhabitants. It was possible to include all cases of TB death occurred during the period 2008-2014 obtained through the Mortality Information System (MIS), whose primary and associated causes were pulmonary and/or extrapulmonary TB with or without bacteriological confirmation. Descriptive statistics was applied with calculating measures of central tendency for continuous and categorical variables, absolute and relative frequency counts. TB mortality rates were estimated by neighborhood. Chorochromatic maps were developed by using the free software Quantum GIS (QGIS) 2.6.1 in order to identify sites with the higher occurrence of deaths.

Results: 235 cases of TB death were identified. 169 (71.9%) were male, with a median age of 51 years; 125 (53.1%) were race/brown color. Concerning the clinical form, 196 (83.4%) were pulmonary ones, and it was possible to note that 203 cases (86.3%) died at the hospital. HIV/AIDS appeared as the principal cause of death in 48 cases (58.5%). Regarding the mortality rate, 16 neighborhoods showed higher coefficients than the municipality (4.17 deaths/100 000 inhabitants per year). The highest coefficient was in the neighborhood of Santos Reis (17.42 deaths/100 000 inhabitants per year),

and the lowest in Ponta Negra (1.18 deaths/100 000 inhabitants per year) (Figure 1).

Conclusion: The study revealed that deaths occurred mostly in males, with working ages and pulmonary TB. In addition, there was a heterogeneous distribution of deaths in space, appearing more susceptible or vulnerable areas to the event than others, which suggests those places prioritization in terms of disease control measures.

Figure 1- Spatial distribution of mortality due to tuberculosis in Natal, Rio Grande do Norte, Brazil (2008-2014).



PC-753-04 Excess mortality of tuberculosis patients in Shanghai, China: a 10-year follow-up study

W Wang,¹ Q Zhao,¹ B Xu¹ ¹Fudan University, Shanghai, China. Fax: (+86) 215 423 7811. e-mail: wwwb@fudan.edu.cn

Background: China has the second highest tuberculosis (TB) burden worldwide, and the premature mortality of TB patients makes this a critical issue.

Methods: The study cohort was drawn from residents in 4 of 19 districts in Shanghai City. All subjects in the cohort were registered with TB between January 1, 2004 and December 31, 2008. Baseline data were collected at the most recent TB diagnosis, and patient mortality was assessed between March and May of 2014.

Results: Overall, the cohort had a standardized mortality ratio (SMR) for all-cause deaths of 5.2 (95%CI: 4.8-5.6). Males had a higher SMR than the females (6.1 vs 3.0). Patients with hemo-disseminated pulmonary disease had an SMR of 18.5, and those with secondary pulmonary disease had an SMR of 5.3. Patients living with other comorbidities also had high SMRs, especially those with chronic obstructive pulmonary disease (22.6) and cancer (30.1). The 1-, 5- and 10-year cumulative case fatality rates were 7.48%, 17.20%, and 21.23%, respectively. With adjustment for age and sex, all-cause hazard ratios (HRs) were significantly greater previously treated patients (HR = 1.26, $P = 0.005$) and smear-test positive patients (HR = 1.55, $P < 0.001$); the risk to TB-caused deaths were also significantly greater for previously treated patients (HR = 1.88, $P = 0.003$) and smear positive patients (HR = 3.16, $P < 0.001$).

Conclusion: Numerous groups of TB patients from Shanghai have increased risk of mortality. Identification

and more vigilant post-treatment follow-up of these high-risk patients may help to reduce mortality.

PC-754-04 Analysis of factors associated with overdiagnosis of tuberculosis

Z Laushkina¹ ¹Novosibirsk Research TB Institute, Novosibirsk, Russian Federation. Fax: (+7) 383 203 8675. e-mail: zlaosh@list.ru

Background: Differential diagnosis of pulmonary TB is still difficult. We found the tendency to overdiagnosis of pulmonary TB in TB hospital.

Design/Methods: Noncomparative retrospective study, subject of interest were medical records of 230 most difficult cases, in which previously established diagnosis of pulmonary TB was rejected. The chances for establishment of true diagnosis and influencing factors were estimated. Odds ratios (OR) and nominal 95% confidence intervals were presented.

Results: Males 81 %, mean age 48.3 ± 16.5 yrs. Diseases, most often initially misdiagnosed as tuberculosis, were pneumonia (46 %), lung cancer (24 %), and sarcoidosis (15 %). Clinico-radiological signs in these cases were more characteristic for TB, than for other pulmonary diseases. 49 % of patients were previously treated of an assumed pneumonia before hospitalization in TB hospital, 36 % of patients up to making a hospital diagnosis received TB treatment. All patients have been hospitalized with wrong diagnosis "pulmonary TB", a principal cause – misinterpretation of chest radiogram. In 5 % of all cases a few acid-fast bacilli were found in sputum by luminescent microscopy. Factors found to be associated with false-positive diagnosis of TB are: old age (OR 0.57, $P = 0.01$), detection of AFB in sputum (OR 0.5, $P = 0.037$), pulmonary dissemination (OR 0.57, $P = 0.045$), inconspicuous disease onset (OR 0.54, $P = 0.009$), nonspecific inflammatory findings detected by flexible bronchoscopy (OR 0.46, $P = 0.000$).

Conclusion: Several reasons for long delays were found, but the main reason were the error of radiologist and false-positive detection of AFB. Due to high incidence of tuberculosis in our country there is a tendency to overdiagnosis tuberculosis. Application of contemporary methodologies of diagnostic tests interpretation, use of rapid TB diagnostic is highly needed.

PC-755-04 Feasibility of a streamlined Single-sAMPLE (SIMPLE) TB diagnosis and treatment initiation strategy in Uganda

P Shete,^{1,2} E Ochom,³ P Howlett,⁴ P Haguma,³ L Chaisson,¹ A Katamba,⁵ D Moore,⁴ A Cattamanchi^{1,2}
¹San Francisco General Hospital, San Francisco, CA,
²University of California, San Francisco, San Francisco, CA, USA;
³Infectious Diseases Research Collaboration, Kampala, Uganda;
⁴London School of Tropical Medicine & Hygiene, London, UK;
⁵Makerere University College of Health Sciences, Kampala, Uganda. Fax: (+1) 415 206 1551. e-mail: pbshete@gmail.com

Background: In high burden countries, many patients with tuberculosis (TB) who present to community health

centers are lost to follow-up before TB can be diagnosed or treated, leading to ongoing transmission. A primary reason is that the standard approach of collecting sputum specimens over multiple days for microscopic examination is not only insensitive but also inconvenient and costly for patients. We report on the feasibility of a patient-centered, Single-sAMPLE (SIMPLE) TB diagnosis strategy.

Design/Methods: The SIMPLE TB strategy includes: 1) Single-sample LED fluorescence microscopy (analysis and reporting of smear results from the initial specimen within two hours); 2) Daily transport of smear-negative sputum samples to GeneXpert® MTB/RIF (Xpert) testing sites; 3) SMS-based reporting of Xpert test results to patients and health centers; and 4) Routine feedback of TB evaluation metrics to health center staff. In a single-arm interventional pilot study, we evaluated the feasibility of the first two components at 4 community health centers in Uganda. Using data from TB laboratory and treatment registers, we evaluated process measures that reflect implementation of the two intervention components and TB case detection.

Results: Of 145 consecutive patients referred for TB testing, 87 (60%) were female and their median age was 39 years (IQR 28-49). Two smears from the initial spot specimen were analyzed and reported on the same-day for 125/145 (86%) of patients. Overall, 11 (9%) were smear-positive and all results from smear-positive patients were obtained on the same day as presentation. Sputum was transported to an Xpert testing site for 65 patients (3 smear-positive, 55 smear-negative and 7 smear not done). All samples were transported on the same day as the initial health center visit. Xpert results were positive in 7 (11%) patients including 4/55 (7%) smear negative patients. Follow up of patient treatment initiation is currently underway.

Conclusion: The SIMPLE TB strategy enables same-day diagnosis of TB cases by facilitating access to and utilization of novel diagnostics such as Xpert, even when not available at the point-of-care. By strengthening health systems and reducing the cost and burden of TB diagnostic evaluation for patients, the SIMPLE TB strategy has strong potential to ensure that more people with TB presenting to community health centers are diagnosed and treated.

PC-756-04 Tuberculosis mortality in Puerto Rico, 2009–2013

D Thomas,^{1,2} T Chorba,² M Bermudez,¹ S Mase,² O Joglar,^{1,2} A Khan,² B Rivera-Garcia¹ ¹Puerto Rico Department of Health, San Juan, Puerto Rico, ²U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: wii6@cdc.gov

Background and challenges to implementation: Puerto Rico (PR) is a U.S. territory in the Caribbean with a history of significant tuberculosis (TB) burden prior to the development and effective use of chemotherapeutic agents in the 1950's. Greater than 90% of the foreign-born population in PR originates from a high burden TB country, Dominican Republic. PR ranks among the top

ten states and territories for persons living with HIV (PLHIV) and the territory has an HIV associated mortality rate four times the national average. However, the reported rate of active TB is only two-thirds the U.S. rate, 2 cases per 100 000 suggesting that there is under-reporting.

Intervention or response: To assess the extent of under-reporting, we evaluated PR specific TB mortality data compared to those of the USA, during 2010–2013 as mortality is associated with delays in diagnosis. TB mortality was defined as cases reported as dead at diagnosis or during TB treatment through the national Report of Verified Case of Tuberculosis.

Results and lessons learnt: TB mortality occurred in 61 of 294 TB cases (21%) in PR compared with 4259 of 52 654 (8%) in the USA. The majority of deaths had pulmonary TB (84% in both groups) and occurred in men (80% in PR, 67% in U.S.). In PR, 92% of TB mortality was among U.S. born (including PR), compared to 53% in the USA. In PR, 3% of TB mortality was among persons born in Dominican Republic. Of persons with a known HIV status, 37% of TB mortality in PR was among PLHIV compared with 14% in the USA.

Conclusions and key recommendations: TB demographics in PR are significantly different as compared with the USA. TB cases in PR are more than twice as likely to die. TB mortality is 1.7 times more likely to occur among U.S.- born in PR compared to the USA. Mortality among foreign born cases is highest for Dominican Republic nationals, however, this represents only 3% of all known TB mortality in PR. Due to PR's high HIV incidence and mortality rates and the high likelihood of co-infection with TB, and we recommend annual TB symptom screening and radiographic evaluation if symptomatic for all PLHIV. Based upon mortality data, PR likely has significantly more tuberculosis disease than previously identified. Outreach to clinicians in Puerto Rico will be important to prevent, detect, and cure TB.

PC-757-04 Mortality amongst TB cases in the UK: an analysis of surveillance data

D Pedrazzoli,¹ R Houben,¹ R White,¹ M Lalor,² L Thomas²

¹London School of Hygiene & Tropical Medicine, London,

²Public Health England, London, UK. e-mail:

debora_pedrazzoli@hotmail.com

Background: The World Health Organization (WHO) estimates that globally the TB mortality rate fell by 45% between 1990 and 2013; therefore progress needs to accelerate to reach the Stop TB Strategy target of a 50% reduction by 2015. Although this target is within reach in half of the WHO Regions, it is unlikely to be met in the European Region where the majority of countries (including the UK (UK)) are classified as having a low TB incidence. Risk factors for death in the UK have not been fully investigated.

Design/Methods: Cases notified to the Public Health England (PHE) Enhanced Tuberculosis Surveillance System with death as reported outcome between 2003 and 2012 were included in the analysis. Vital registration

data were matched to national surveillance data to estimate the underreporting of mortality associated with TB. Univariate and multivariate analyses were performed to describe the characteristics of those who died from TB in the UK, to identify risk factors for having the outcome of death compared to another outcome, and to compare the characteristics of those reported to vital registration systems compared to those only reported to national surveillance.

Results: UK-born patients aged 65 years or over, those with social risk factors, patients with sputum smear positive pulmonary disease and patients with MDR-TB remained at increased risk of death. We found no evidence of any difference across quintiles of deprivation. We also found that 43% of deaths were only reported to vital registration systems but not to national surveillance. Analyses to explore the characteristics of cases notified to PHE vs. cases reported to vital registration systems is currently underway.

Conclusion: Despite an overall decline over time in TB mortality, the number of patients who still die from this disease remains significant, and efforts to control TB and improve diagnosis and treatment outcome in the UK should be sustained. If we wish to achieve a reduction of 95% in TB deaths from 2015 to 2035 more will need to be done. Missing deaths in notification remain worrying; this is a limitation that national TB surveillance aims to address by linking TB and vital registration data on a routine basis in order to ensure notification and reporting of all TB deaths in the UK in future.

PC-758-04 Occupational exposure to indoor congregate settings and tuberculosis mortality

J Wolny,¹ C Jackson,¹ H Stagg,¹ I Abubakar,^{1,2} T Yates^{1,3}

¹University College London, London, ²MRC Clinical Trials Unit (at University College London), London, UK; ³Africa Centre for Health and Population Studies, Ns Somkhele, South Africa. e-mail: t.yates@ucl.ac.uk

Background: In high burden settings, molecular epidemiology suggests that most *Mycobacterium tuberculosis* transmission occurs outside the household. Modelling suggests much transmission occurs in indoor congregate settings with workplaces being important sites of transmission between adults. Data on age-specific TB mortality by occupation for men in England and Wales were recorded in Registrar General's decennial supplements for 1890-2, 1900-2 and 1910-2 (when TB rates may have been even higher than in Southern Africa today). We examined these data to see if there was an association between TB mortality and working in a crowded indoor environment.

Design/Methods: Data on follow up time and deaths from 'phthisis' (TB) were extracted. Occupations were coded as exposed (involving exposure to crowded indoor environments) or unexposed (outdoor occupations or those involving little exposure to indoor congregate settings). We described crude TB mortality rates by exposure status. In regression analysis we assessed the association between occupational exposure to indoor

congregate settings and mortality from TB adjusting for decade, age group and socioeconomic position.

Results: There were 24 366 TB deaths over 15.2 million person-years among men in 'exposed' occupations (160 deaths per 100 000 person-years). There were 28 775 TB deaths over 20.1 million person-years follow up time among men in 'unexposed' occupations (143 deaths per 100 000 person-years). However, most men worked in occupations that we were unable to classify and these men had the highest mortality. These trends persisted in adjusted analysis but were attenuated if occupations with additional risk factors for TB, such as silica exposure, were excluded.

Conclusion: These data are consistent with crowded indoor workplaces being important sites of *M. tuberculosis* transmission. Non-differential misclassification of cause of death and the fact that men may have worked in both exposed and unexposed occupations may have caused us to underestimate the strength of the association. We were unable to adjust for urban or rural residence nor address the possibility that men might have moved into more or less exposed occupations after developing TB disease. The substantial differences between England and Wales a century ago and high burden settings today should caution against generalisation of these findings. Future research should assess whether crowded indoor workplaces remain important sites of *M. tuberculosis* transmission.

08. Trends, transmission and tuberculosis case finding

PC-759-04 Offer incentives and directly observed treatment of tuberculosis in primary health care in a Brazilian city

A Beraldo,¹ N H Orfao,¹ A Wysocki,¹ M E Brunello,¹ R Andrade,¹ L M Scatena,² T C Scatena Villa¹ ¹College of Nursing of Ribeirão Preto – University São Paulo, Ribeirão Preto, SP, ²Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil. e-mail: li_aab@yahoo.com.br

Background: The Directly Observed Treatment is a strategy used in the organization of care for tuberculosis patients, and should be seen not only as the supervision of the dose, but the involvement of health professionals, and community service. Allied granting incentives offer the opportunity to identify other patient's life needs, helping to control the disease.

Aim: To characterize the offer incentives and the directly observed treatment (DOT) for tuberculosis (TB) in primary health care (PHC) services by patients and professionals nursing team perspective in a Brazilian city.

Methods: Descriptive epidemiological study, conducted in Campinas-SP (Brazil) city, priority for TB control, between August 2012 and May 2013. The study population was composed of professionals nursing team of the PHC and TB patients. A questionnaire with 4 questions with dichotomous response (yes or no), related to the offer incentives and DOT for TB patients in the

PHC services was used. These questions were designed based on the "National Manual Recommendations for the TB control". For data analysis was used descriptive technique, frequency distribution, measures of central tendency and variability.

Results: 183 professional nursing team and 165 TB patients were interviewed. The perceptions of TB patients showed that 94 (57.0%) underwent the DOT, 155 (93.9%) reported that the intake was observed by a health professional, averaging receiving TDO 2.2 times a week (SD = 1.6), 136 (82.4%) were given a breakfast kit and 89 (54.0%) were treated by the same health professional (Table). The perceptions of health professionals showed that 178 (97.3%) professionals offered DOT for patients in treatment; with an average of 3.3 observations of intake of DOT in the week; 158 (86.3%) of professionals offered the Breakfast Kit (Table).

Conclusions: There was disagreement between the perceptions of patients and professionals nursing team for the realization of DOT, and the number of intake of observations in the week. For the effective management of the disease, it is essential the partnership between TB patients, health professionals and health service, regarding the implementation of these actions, taking into account the opinion of the patient as to the place and time of observation of dose, aimed at strengthening treatment, decreased disease transmission and consequent reduction in morbidity and mortality.

Table Frequency distribution of the offer incentives and directly observed treatment of the tuberculosis in the primary health care services by patients and professional nursing team perspectives, Campinas-SP, 2013.

Indicators	Categories of responses	Patients		Professionals Nursing Team	
		n	%	n	%
Providing DOT * to tuberculosis patients.	Yes	94	57,0	178	97,3
	No	71	43,0	5	2,7
Observation the Ingestion of Medicines**	Health Professional	155	93,9	172	94,0
	Family	26	15,8	96	52,5
	Nobody	8	4,9	7	3,8
	People in the Community	-	-	2	1,1
Offering Incentives**	Breakfast Kit	136	82,4	158	86,3
	Basic Food Basket	22	13,3	37	20,2
	Transportation vouchers	2	1,2	13	7,1
	No	29	17,6	1	0,6
Care by the same health professional during the DOT *	Yes	89	54,0	-	-
	No	3	1,8	-	-
	Not applicable	73	44,2	-	-

PC-760-04 Temporal trends of drug-resistant tuberculosis in eastern rural China, 2005–2012

Y Hu,¹ L Wu,¹ Q Zhao,¹ W Jiang,¹ B Xu¹ ¹School of Public Health, Fudan University, Shanghai, China. e-mail: bxu@shmu.edu.cn

Background: To analyze the longitudinal trend of drug resistant tuberculosis (TB) in duration of 8 years in eastern rural China.

Design/Methods: The study was carried out in two rural counties of eastern China during 2005–2012. All registered TB patients received bacteriologic-based TB diagnosis. Drug susceptibility test to first-line anti-TB drugs, including isoniazid, rifampin, ethambutol and streptomycin were applied to all mycobacteria tuberculosis isolates. The temporal trend of drug resistant TB during the 8-year study period were simulated and plotted by non-linear regression model using exponential equation. Growth ratio and doubling time of drug resistant TB were calculated using Graphpad Prism 5.

Results: The prevalence of overall drug resistance was 45.3%, and the prevalence of multidrug-resistant TB (MDR-TB) was 13.4% during the study period (10.4% in new patients and 26.0% in previously treated patients), which was higher than national average level. The prevalence of overall drug resistance and MDR-TB among bacterial culture positive TB patients increased from 33.6% and 3.6% in 2005 to 57.3% and 27.3% in 2012. The growth ratio of overall drug resistance was 1.09 (95%CI: 1.058–1.126), and the doubling time was 7.54 years. The growth ratio of MDR-TB was 1.25 (95%CI: 1.185–1.323), and the doubling time was 2.730 years. The prevalence of resistant to isoniazid, rifampin and ethambutol exhibited an upward trend, while it was downward in streptomycin. In newly diagnosed TB patients, the growth ratio of overall drug resistance and MDR were 1.20 (95%CI: 1.006–1.172) and 1.23 (95%CI: 1.055–1.187) respectively, whereas they were 1.10 (95%CI: 1.055–1.187) and 1.27 (95%CI: 1.155–1.386) respectively in previously treated patients. The growth ratio of overall drug resistant TB was significantly higher in male than female ($F = 23.640$ $P < 0.0001$). Compared to previously treated patients, the newly diagnosed TB patients had a significantly higher growth ratio of overall drug resistance ($F = 15.750$, $P = 0.002$), but a significantly lower growth ratio of MDR-TB ($F = 26.380$, $P < 0.001$).

Conclusion: The temporal trend of drug resistant TB in eastern rural China suggests that the burden of drug resistant TB would be increasing rapidly, and the prevalence of MDR-TB might be doubled in less than three years. An MDR-TB control program targeting high risk TB patients should be scaled up in the basic TB control unit of China's TB control system.

PC-761-04 Is tuberculosis declining in West Papua? Challenges in disease control

T Pakasi,^{1,2} HA Papendang¹ ¹Universitas Papua, Sorong, ²Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia. Fax: (+62) 021 315 3550. e-mail: tpakasi@yahoo.com

Background: West Papua Province is one among the youngest provinces in Indonesia, situated in Papua Island, small population living in wide area. Recently, the ministry of health published in 2013, a population-based study about health situation (Riskesdas 2013). The report mentioned that the tuberculosis (TB) prevalence in West Papua was similar as the national rate, declined from the same study in 2007 (0.9% to 0.4%). It was quite premature to conclude the declining was true and therefore we studied further the report.

Methods: We reviewed several reports regarding prevalence, case finding, services of TB besides the methodology being implemented in the forming of the data. We limited the search from 2000–2014.

Results and lesson learnt: The Riskesdas 2013 reported 0.4% respondents were TB in West Papua and 3.5% had the main symptom in which 2.7% had bloody coughing. It showed clearly that 3.1% of the respondents might have TB but had never been diagnosed. The Directorate General of Disease Control found the decrease of case finding in West Papua from 621/100 000 population (2012) down to less than 500/100 000 population (2013), compared to the Papua province, the achievement was only half. The estimated population of West Papua was 846 711 people with density of 8.5 people/Km². With a wide area and scattered population, the issue of accessibility and availability of the TB service is very important to overcome. For more information, the positivity rate in West Papua achieved 14.8%, almost 5% higher than the national rate (10.4%). The estimated TB patients might be very high. It could be problems in the laboratory or access to health care, thus only the very needed patients went to seek medical care and increase the chance to become positive TB. The Riskesdas 2013 was a paper-based study and the category of TB was self-reported by the respondents, whether respondents had ever been diagnosed as TB. Sputum test was done whenever problems occurred but did not use in the calculation to correct the prevalence. It was different from another population based-study in 2004, the Household and Health Survey, which used sputum test and culture for correction of the diagnosis.

Conclusion: Decrease prevalence of TB reported in 2013, revealed an accessibility issue to health care rather than the successful of the Program in West Papua. Scattered population and fewer facilities were the main reasons as reviewed in many reports.

PC-762-04 Increased case finding among high-risk groups by mobilizing frontline health workforces in Kathmandu Valley

R S Gopali,¹ G Shrestha,¹ B Lamichhane,² N Ishikawa,³ L Ditiue⁴ ¹Japan-Nepal Health & TB Research Association, Kathmandu, ²National Tuberculosis Centre, Kathmandu, Nepal; ³Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association, Tokyo, Japan; ⁴UNOPS/Stop TB Partnership, Geneva, Switzerland. e-mail: gwala73@hotmail.com

Aim: To detect additional TB case finding in Kathmandu Valley.

Methodology: This cross sectional study was done in Kathmandu valley focusing Garbage collectors, suspects visit in the Private pharmacies and street children's. The trained team of health care providers and volunteers working in the Kathmandu valley conducted intensive community mobilization activities, performing door-to-door visit, refer the suspects found in community to near by microscopy centres or camps for the sputum examination. The intervention target to screen approximately 80 000 from the above mentioned groups and detect the additional cases in the valley in one year. Two sputum samples including one early morning and 1 spot specimen were collected in same day. For chest X-ray and Xpert test suspects were advised to visit hospitals and near by health facilities where the facilities are available. **Results:** Among total (53 717) persons screened in 8 month of period, 9585 (18%) were identify with TB sign and symptoms. 83% (8003) suspects identified in the community and private pharmacy actually visited for the sputum examination. Among total examine 120 people were diagnosed as New Smear Positive (NSP) patients. Nearly two third of diagnosed cases were male and their mean age was 36. The prevalence of active pulmonary tuberculosis in those targeted areas is 2 times higher comparde to other general groups. The intensive ACSM activities and door-to-door visits improve the health seeking behavior of the target groups. Among total diagnosed cases 116 (97%) TB patients enrolled their treatment from the near by DOTS centres. This intervention contributes 10% of the additional TB case finding in the Kathmandu valley.

Conclusion: The Public-Private Mix (PPM) activity in the community support to maintain the motivation level of key stakeholders. Regular mobilization of key stakeholders can contribute to increase additional case finding rate from the hard to reach area and it can be sustain by endorsing similar types of the programme in the regular activity of National Tuberculosis Programme.

PC-763-04 Diagnostic value of clinical features of presumptive TB patients in Bagamoyo, Tanzania: a prospective cohort study

F Mhimbira,^{1,2,3} J Hella,^{1,2,3} M Sasamalo,² K Ibrahim,^{1,2,3} E Mfinanga,² F E Haraka,² L Jugheli,^{1,2,3} K Reither^{1,2,3} ¹University of Basel, Basel, Switzerland; ²Ifakara Health Institute, Bagamoyo, Tanzania; ³Swiss Tropical and Public Health Institute, Basel, Switzerland. e-mail: fmhimbira@gmail.com

Background: The hallmark of tuberculosis (TB) control is early diagnosis and treatment of infectious pulmonary TB patients. Symptom-based screening recommended by World Health Organization, is simple and cost-effective way of identifying presumptive TB patients to be tested for TB. Objective: To determine the diagnostic value of clinical features in a microbiologically and clinically well characterized cohort of presumptive TB patients.

Methods: A prospective study adult presumptive TB patients was done between September 2010 and September 2013. Presumptive TB was defined as having any cough and one or more of any other TB symptom. Participants were followed up for 18 months. At five months of follow-up, participants were classified into seven categories based on clinical assessment, radiological findings, sputum smear microscopy, liquid and solid culture results. Sensitivity and specificity were estimated, using culture-positive TB patients and controls (no symptoms at five months without anti-TB treatment) as reference standard.

Results: A total of 499 adult presumptive TB patients had a median age of 39 years (interquartile range; 30-50 years); 259 (51.9%) were females. The estimated HIV prevalence was 45.7 [95% Confidence Interval: 41.2% to 50.2%]. Of 499 enrolled, 114/499 (22.8%) were culture-positive TB patients and 118/499 (23.6%) were non-TB controls at five months (total, $n = 232$). Among the culture-positive TB patients, 84/114 (73.6%) were smear-positive and culture-positive and 30/114 (26.4%) were smear-negative culture-positive. Chest pain was the commonest reported symptom (75.9%) followed by fever in 162/232 (69.8%) and weight loss in 152/232 (65.5%) patients. Weight loss and fever have high sensitivity of 80.7% and 78.9%, respectively. Specificity was high for haemoptysis 85.6% and fair for fatigue 56.8% (Table). In a multiple logistic regression; male, excessive night sweats, weight loss and fatigue and age were significantly associated with culture-positive TB patients with $P < 0.05$.

Conclusion: Symptom screening performs with a fairly good sensitivity but predominately poor specificity to identify TB patients in resource-poor setting with high HIV prevalence. Symptom screening can contribute to ruling out TB in many cases, but better TB point-of-care diagnostics tools are still urgently needed.

Table Patient classification, clinical features at recruitment and their diagnostic value in presumptive TB patients against liquid and solid culture combined as gold standard

Symptom	Culture-positive PTB <i>n</i> (%)	Non-TB controls <i>n</i> (%)	Sensitivity % (95%CI)	Specificity % (95%CI)
Productive cough	114 (100)	117 (99.2)	100 (96.8–100)	0.8 (0.0–4.6)
Haemoptysis	12 (10.5)	17 (14.4)	10.5 (5.6–17.7)	85.6 (77.9–91.4)
Night sweats	83 (72.8)	60 (50.9)	72.8 (63.7–80.7)	49.2 (39.8–58.5)
Fever	90 (79.0)	72 (61.0)	78.9 (70.3–86.0)	39.0 (30.1–48.4)
Weight loss	92 (80.7)	60 (50.9)	80.7 (72.3–87.5)	49.2 (39.8–58.5)
Chest pain	85 (74.6)	91 (77.1)	74.6 (65.6–82.3)	22.9 (15.7–31.5)
Fatigue	76 (66.7)	51 (43.2)	66.7 (57.2–75.2)	56.8 (47.3–65.9)

PC-764-04 Seasonal drivers of tuberculosis: evidence from 100 years of notifications in Cape Town

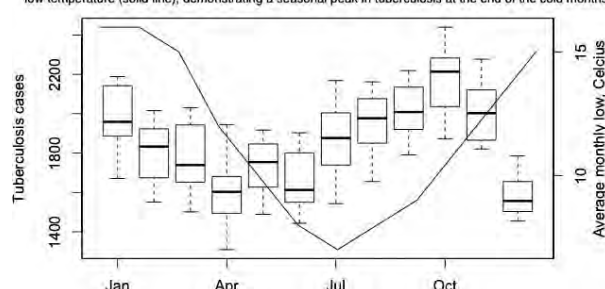
J Andrews,¹ S Hermans,^{2,3} R Wood³ ¹Stanford University, Stanford, CA, USA; ²Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; ³University of Cape Town, Cape Town, South Africa. e-mail: jasonandr@gmail.com

Background: Tuberculosis has been observed to follow a seasonal pattern in many settings; however, the impact of HIV on seasonality and the contribution of seasonal factors influencing reactivation risk vs. variation in transmission risk have not been elucidated. We examined trends in seasonality of tuberculosis before and during the HIV epidemic, and according to age and HIV status. **Design/Methods:** We reviewed data on monthly tuberculosis notifications in Cape Town from 1903 through 2013, exclusive of 1995–2001, which were unavailable. Data from 2003 onward were stratified by HIV status and age. We decomposed time series into seasonal, random, and trend components, and performed time-dependent spectral analysis using wavelets to assess periodicity over time.

Results: In the 20th century, there were intermittent periods in which tuberculosis followed an annual seasonal pattern; however, from 2003 onward, consistent seasonal periodicity was observed, with the highest number of cases occurring in August through November (peak: October), following the coldest months (Figure). Seasonal effects were similar between men and women. Among children under 5 years of age, a second seasonal peak was observed in March and was higher than the October peak; this second peak was not seen in other age groups. Evidence for seasonality was stronger among HIV co-infected tuberculosis cases than in HIV uninfected cases. The amplitude of seasonality was comparable between HIV positive and negative cases, with peak case months recording 47% and 42% times more cases than trough months, respectively.

Conclusion: There is substantial seasonal variation in the burden of tuberculosis in Cape Town in the HIV-era. Stronger seasonal effects were seen in HIV-infected individuals and those in younger age groups, who progress more rapidly to tuberculosis following infection. These findings may support increased transmission in the winter as an important driver of tuberculosis in Cape Town.

Figure 1. Adult cases of tuberculosis by month (2004–2013) in Cape Town (boxplots) and average monthly low temperature (solid line), demonstrating a seasonal peak in tuberculosis at the end of the cold months.



PC-765-04 The importance of household vs. community tuberculosis transmission in Peruvian shantytowns

L Martinez,^{1,2} S Isaacson,² R Gilman,³ M Saito,⁴ L Cabrera,⁵ R Oberhelman,² C Evans^{6,7} ¹University of Georgia School of Public Health, Athens, GA, ²Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, ³Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ⁴Tohoku University Graduate School of Medicine, Sendai, Japan; ⁵Asociación Benéfica Proyectos en Informática, Salud, Medicina y Agricultura (AB PRISMA), Lima, ⁶Universidad Peruana Cayetano Heredia, Lima, Peru; ⁷Imperial College London, London, UK. e-mail: leomarti@uga.edu

Background: Active case finding (ACF) for tuberculosis (TB) has been widely proposed for strengthening TB control. However, it is unclear whether it would be more effective to target ACF in households or community areas. The comparative effectiveness of ACF in community vs. households is likely to depend on relative TB transmission levels in these settings.

Objectives: To compare the prevalence of childhood TB infection in households with and without a known past TB case, calculate the odds of household TB transmission, and assess changes in these data comparing years 1990 vs. 2000.

Methods: Two community-based tuberculin surveys were performed in 1990 and 2000 in Pampas de San Juan de Miraflores, a low-income shantytown in Lima. Tuberculin skin tests were performed in children (0–14 years old) to assess latent TB infection (LTBI) as evidence of transmission. Prevalence of latent TB infection from both surveys were calculated and children with household exposure to a known case of TB disease were identified. We stratified children in both studies by household TB contact and calculated odds ratios of new infection in children with vs. without household TB

exposure. Two-tailed *P* values were calculated using two-sample *t*-tests.

Results: The study sample sizes were 238 in 1990 and 624 in 2000. In children 0-4 years old, overall prevalence of LTBI was significantly higher ($P < 0.0002$) in 1990 (24/149 infected; 16% prevalence [95%CI, 10 – 22]) compared to 2000 (4/188 infected; 2.1% prevalence [95%CI, 0.1 – 4.1]). Similarly, prevalence was significantly higher ($P < 0.0002$) in children 5-14 years old in 1990 (44/238; 19% infected [95%CI, 14 – 23]) vs. 2000 (44/624; 7.1% infected [95%CI, 5.1 – 9.1]). The increased odds of infection in children exposed to a household TB case was 2.4 (95%CI, 1.7 – 3.5) in 1990 and 5.5 (95%CI, 2.7 – 11) in 2000.

Conclusion: In these two community-based studies from the same Peruvian shantytown, we found that the odds of household TB transmission doubled over 10 years while the prevalence of new TB infection decreased significantly. This suggests that household contact investigations may have higher yield in preventing transmission in low TB incidence areas compared to those with high-burden.

PC-766-04 The impact of changes in patterns of migration on TB incidence in the UK

M Muzyamba,¹ D Pedrazzoli,^{1,2} D Zenner,¹ M Lalor,¹ J Davidson,¹ I Abubakar,¹ L Thomas¹ ¹Public Health England, London, ²London School of Hygiene & Tropical Medicine, London, UK. Fax: (+44) 20 8327 6112. e-mail: morris.muzyamba@phe.gov.uk

Background: The incidence of TB in the UK increased by 50% from the mid-1980s to 2011, followed by a small reduction in 2012 and 2013. In contrast, most comparable countries saw a steady decline in incidence over the same time period. The majority of TB cases in the UK are non-UK born, and migration is likely to have a major impact on the changing epidemiology. This study aims to estimate the impact of changes in migration patterns from countries with different levels of TB burden on TB incidence in the UK.

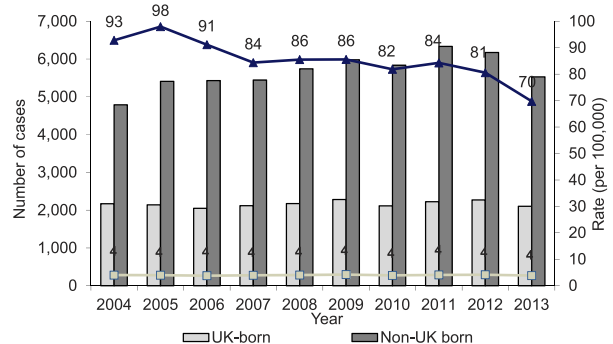
Methods: Data on tuberculosis notifications from the Public Health England Enhanced Tuberculosis Surveillance system from 2004-2013 were analysed. Annual TB rates and TB rates by country of birth were calculated using population estimates provided by the Office of National Statistics and the Labour Force Survey respectively. Data on the annual number of long term migrants to the UK were obtained from Home Office and stratified by the 2012 WHO TB incidence estimates in their country of birth.

Results: From 2004 to 2011 there was an increase in the number of non-UK born TB cases from 4789 to 6,335; from 2011 to 2013 there was a decrease in the number of non-UK born TB cases, to 5529 in 2013. In contrast, the number and rate of TB cases in the UK-born population has remained stable over this period, with just over 2000 cases a year, a rate of 4 per 100 000 (Figure). Over the past 10 years, there has been a steady decrease in the number of long-term migrants to the UK from very high (>250 per 100 000) incidence countries [from 67 917 to

21 406]]. There was an increase in the number of long-term migrants from high incidence countries (151-250 per 100 000) until 2009 (from 143 987 to 200 944), followed by a drop in the number of migrants from these countries to 102 837 in 2013.

Conclusions: The changes in TB incidence in the UK over the past decade are due to changes in the numbers of non-UK born TB cases only. Over the same time period, the numbers of TB cases in the UK born population has remained stable, but has not seen the reduction observed in most other comparable countries. Changes in the pattern of migration to the UK over the past decade, particularly an initial increase, and more recent decrease in the number of migrants from high TB incidence countries, is likely to have had an important impact on TB in the UK. However, additional factors, including transmission within the UK and changes to TB control activities are may also have played a role.

Figure Tuberculosis case reports and rates by place of birth, UK, 2004-2013



09. Public-private strategies to End TB: the case of India

PC-767-04 AYUSH providers' involvement in TB prevention and care under PPP in India

B Entoor Ramachandran,¹ S Chadha,¹ S Waikar²

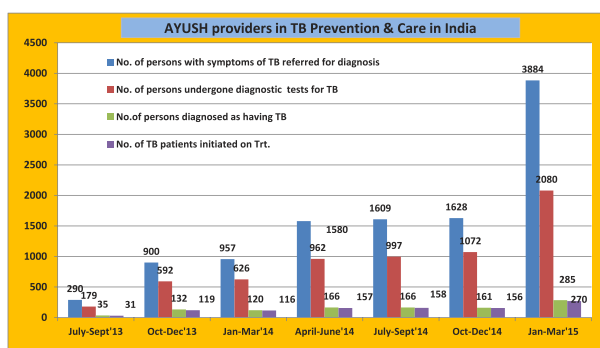
¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ²Population Services International, Delhi, India. Fax: (+91) 1 14605 4430. e-mail: ebabu@theunion.org

Background: AYUSH is an acronym that is used to refer to the non-allopathic medical systems in India. It includes the Indian medical system of Ayurveda, Yoga, Unani, Siddha, and also Homeopathy. (AYUSH mean "life" in Sanskrit). India, Every year, around 30,000 persons are graduated from 494 AYUSH medical colleges as per (2012-2013) Central Council of Indian Medicine, Department of AYUSH, Ministry of Health and Family Welfare, India. In community, AYUSH practitioners are first point of care for any health problems. Provides the bulk of health care, particularly for the poor and their presence in Vulnerable and Marginalised areas or locations and this hold true for TB symptomatics as well.

Intervention: “Axshya” (TB Free) is a Global Funded round 9 TB project launched in India in 2010, it is covering 300 districts across 21 states in the country. The objective of Project Axshya is to expand the reach and visibility of Revised National Tuberculosis Control Programme (RNTCP) of India. Considering the role of AYUSH in TB prevention and care, project Axshya trained and engaged AYUSH practitioners into TB care in 60 Districts in 10 states in India. Axshya intervention focused on following components. Recognition by the Government authorities (National TB Programme, and District Tuberculosis Office [DTO]), Capacity building, Regular coordination with District TB staff, Providing Incentives and Motivation.

Results: Totally 3165 AYUSH practitioners have been sensitized during the period April 2013 to March 2015. AYUSH practitioners were expected to offer following three TB services with support of financial incentives: 1) referral of persons with symptoms of TB, 2) sputum collection and transportation, and 3) provision of DOT to TB patients. Out of trained, 40% of AYUSH practitioners were engaged by providing at least one of the TB service. During the reporting period 10848 persons with symptoms of TB have been referred for diagnosis. Out of the referred, 6508 (60%) persons have undergone diagnostic tests. 1065 (16%) persons were diagnosed as having TB and 95% (1007) of them have been initiated on treatment.

Conclusion: India's National Tuberculosis control programme is aiming towards Universal Access to TB Care. In this context, every provider from different discipline pays a role in identification and serving persons with TB. Ongoing Axshya intervention is a small effort like a drop in bucket towards “Mainstreaming AYUSH with RNTCP to support END strategy”.



PC-768-04 Why are private practitioners not willing to be part of the tuberculosis control programme in India?

P Banuru Muralidhara,¹ S Pattanshetty,² P Mithra²

¹International Union Against Tuberculosis and Lung Diseases, South-East Asia Office, New Delhi, ²Kasturba Medical College, Manipal University, Manipal, India. Fax: (+91) 114 605 4430. e-mail: bmprasad@theunion.org

Background: Engaging private practitioners is the key strategy in reaching the missing 3 million tuberculosis patients and much of this is coming from India. Although, tuberculosis control programme has developed and implemented strategies to engage private sector; results are not encouraging. A study was conducted to answer why private practitioners were not willing to be part of programme?

Design: A cross sectional qualitative survey was conducted among 116 private practitioners (General (GP) and Specialists (SP)) in Udupi district of Karnataka, India from September 2008 to October 2009. The investigator visited each practitioner in their respective clinics and administered pretested questionnaire tool after taking the consent. The data was analysed under patient related, practice related and regimen related indicators as expressed by practitioners.

Results: The sample constituted 41 GPs and 75 SPs and 33% of them did not refer any presumptive TB persons. Only 2% of practitioners cited patient related issues (“Patients don’t believe in government drugs”) for not referring to programme. Nearly 56% of them informed practice related (“We lose patients, why to refer to DOTS? We can also think better ways to treat”) and 36% to regimen related (“Patients are comfortable with the treatment regimen which I am giving”). 90% of the referrals made by practitioners were in view of ability-to-pay by patients (“We refer only poor patients as they get free drugs”). A total of 53 private practitioners responded as not referring presumptive TB persons for programme or DOTS; of which 36% were related to regimen (“Side effects are more with DOTS regimen as it is not adjusted per Kg body weight”) and practice (“Every physician in private sector has his own method of treating tuberculosis, no clear guidelines. CME programme would be better”). Other responses of which 19% were related to patients (“Confidentiality issues are not maintained well as health worker visits patients home”) and 9% programme related (“DOTS programme is for masses not for individual patients, we private practitioners deal with individual patients”).

Conclusion: The results draw our attention to practice related issues as key concern for private practitioners not willing to be part of the programme. Practice related objectives derive the choice of regimen and ability-to-pay by patient. A regulation policy on use of antibiotics by private practitioners and policy on CME is the need of hour.

PC-769-04 Have I notified a TB patient today? Study of TB notification by private sectors after the introduction of Nikshya in India

S Satapathy,¹ B Thapa,¹ S Chadha¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. e-mail: Sachi.Satapathy@theunion.org

Background: Tuberculosis (TB) is a notifiable disease in India since 2012. The private sectors cater to almost 50% of TB patients however the notification is minimal. To strengthen the TB case notification from private sectors, National TB Programme has initiated a web-based notification system-Nikshya in 2013 where the private sectors are registered. The objective of the study was to examine the registration and notification of TB cases from the private sector before (2012) and after the Nikshya (2013).

Design/Methods: This is retrospective study carried to analyse the secondary data on private sector registration and Tb case notification from NTP reports published in 2014. The variables studied were, registration and TB case notified from private practitioner, hospital and lab. The outcome measures were number and proportionate increase in registration and Tb case notification.

Results: Altogether, private sectors registered in the web based system were 55 513 and 1839 in 2013 and 2012, respectively with an absolute increase of 53 674. Of those registered in 2012, 74% (1360/1839) were private practitioners, 22 % were private hospitals and 4% were private labs while in 2013, 64% were private practitioners, 27% followed by 27% private hospitals and 9% private labs. Similarly, a total of TB case notifications reported were 38 596 and 3106 in 2013 and 2012 respectively with an absolute increase of 35490. Of those notified in 2012, except private practitioners, whose contribution is 91%, private laboratories and private hospitals' contribution is 4% each, while in 2013, share of private hospitals is more (50%), followed by private practitioner (45%) and private Lab (9%). Within the private sector participation the proportionate figure of registered vs. notification, private hospital has shown an increase (0.32 in 2012 & 1.29 in 2013), however, the other private laboratories (1.8 in 2012-0.29 in 2013) and private practitioner (2.0 in 2012 - 0.49 in 2013) have shown a negative trend. Within the states in India, out of 36 states and union territories (UT), notification rate of private sector per 100 000 population 16 of them have register the contribution of < 1.0.

Conclusion: A revised strategy to engage private sector needs to be taken up by the NTB program with a focus on private practitioners and private lab engagement with more priority to 16 states, where the contribution of notification is less than one per cent for lakh population.

PC-770-04 How to better equip private health service providers to fight tuberculosis in India: a study of the PHSP perspective on the challenges

S Satapathy,¹ B Thapa,¹ S Chadha¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. e-mail: Sachi.Satapathy@theunion.org

Background: With more than one million TB cases being missed in India, the increasing role of Private Health Service Providers (PHSP) is considered as a potential strategy to reach out to these missing cases. In spite of government's consistent efforts to enhance participation of PHSP in the country's TB control program, the engagement of PHSP does not show much improvement as expected (current national average of PHSP in 2013-14 data is 3.3 per cent per one lakh population). So, there are assumptions that PHSP's perspective on the challenges of working with communities influence case-finding and case-management. However, there is hardly any information about the PHSP's perspective on the challenges they face in working with communities.

Design/Methods: A cross sectional community-based survey in 30 districts of India for Tuberculosis Knowledge, attitude and practices was conducted in 2013. The PHCP's were identified during a door-to-door survey and interviewed using a semi-structured questionnaire.

Results: Of 195 PHSP interviewed in this study, 36% PHSPs have managed TB patients in their practice. Of these, 11% have diagnosed and initiated the treatment on their own. Among these 57% used allopathic medicine for TB treatment. 35% PHSPs interviewed knew about microscopy centres (MC) and knew diagnosis is for free and of these 23% did not used the diagnostic services from the microscopy centres. Moreover, 14% of the PHSPs, who knew of MC, revealed that they face problem in getting sputum smear examination done. The key challenges faced by the PHSP's were; 1) people hesitate to visit their clinic for treatment 45% 2) non-availability of anti TB drugs 24% with PHSP's 3) No pathology or X ray lab available in their vicinity 20% and 4) people do not reveal their history of TB easily 25% .

Conclusion: If resources are provided and challenges faced are addressed, they can contribute to find missing cases.

PC-771-04 Public health marketing: engaging private providers for public health the pharma way

S Vijayan,¹ R Gandhi,¹ V Oswal,² G Ghatawat,² R Chopra,¹ M Datta,¹ J Thakker,¹ S Pandey¹ ¹PATH, Mumbai, ²Mumbai Mission for TB Control, Mumbai, India. Fax: (+91) 114 605 4430. e-mail: shibuvij@gmail.com

Background and challenges to implementation: Effective engagement of private providers (PP) to appropriately diagnose, treat and notify TB cases has been a challenge in India. Conventional methods like sensitization and training workshops have seen limited success. While such

workshops may guarantee participation, there is limited scope for continued engagement with providers. Through Private Provider Interface (PPIA), the engagement of private providers is designed to strengthen the service delivery for TB through increasing the outreach of the services and achieving higher case notifications of TB

Intervention or response: PPIA engaged with PP including less-than-fully qualified (LTFQ), fully qualified providers, chemists, and laboratories for providing subsidized and quality TB diagnostic and treatment services. PPIA field team consists of experienced officers as medical representatives (detailers) with pharmaceutical marketing experience. The officers visit providers in their clinics and explain about the PPIA services like subsidized diagnostic and free treatment. Doctors are also sensitized on Standards of TB Care in India by sharing an information booklet and detailing aids. Doctors' contribution to the program viz. number of patients referred, number of diagnostic tests conducted etc. is shared. Each field officer is allocated a particular geographical area and given per day target visits. Typically, a field officer visits a particular provider twice a month. Each field officer is responsible for engaging with 100-120 providers monthly with daily visits to 8-10 providers. The health provider is ensured accessibility to subsidized services for patients, awareness about the related services and thus acknowledgement of treating the afflicted community at a subsidized cost.

Results and lessons learnt: PPIA has reached out to 2500 private providers through in-clinic visits in six months of operations. This covers 42% of relevant provider universe in Mumbai. We have been able to engage 1145 providers in the PPIA network which is 19% of the relevant provider universe.

Conclusions: Private provider engagement ensures regular interaction with the private providers. Repeat visits to provider clinics enables to capture provider feedback and improve service delivery. The success and cost effectiveness of this model of marketing public health in similar lines with Pharma industry need to be evaluated before expanding

PC-772-04 TB notification in south India: what do private practitioners anticipate?

A Trivedi,¹ S Burugina Nagaraja,² S Chadha,¹ S Prasad,³ Sury Kanth,⁴ K Sagili¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²Employees' State Insurance Corporation Medical College and Post Graduate Institute of Medical Sciences & Research, Bangalore, ³Eli Lilly and Co., New Delhi, ⁴State TB Cell, Bangalore, India. e-mail: atrivedi@theunion.org

Background and challenges to implementation: The Government of India has made TB notification by private healthcare providers mandatory from May 2012 onwards. The National TB Programme has developed a case based web based online reporting mechanism "Nikshay" to facilitate notification. Objective is to determine the awareness, practice and anticipated enablers related to TB notification by private practitioners.

Intervention or response: A cross-sectional study was conducted among private practitioners of Mysore city in south India. All the private practitioners were mapped and the practitioners were interviewed using semi-structured questionnaire. Systematic stratified sampling was adapted to attain the desired sample size and the practitioners were line-listed for interview.

Results and lessons learnt: There were 1249 private practitioners at Mysore city of which 155 practitioners were interviewed. Majority 142 (92%) of the private practitioners were aware that TB is a notifiable disease; however, 82% of them were not aware of "Nikshay". Only one in six practitioners were registered in "Nikshay", while one in three practitioners notified the disease. The anticipated enablers from the programme were free drugs, training and timely feedback for their referred cases. Nearly 47% of them opined that it should also be backed by legal punitive measures

Conclusions and key recommendations: The programme should develop innovative strategies that provide enablers, address concerns of practitioners while having simple mechanisms for TB notification. The programme should strengthen its inherent capacity to monitor TB notification.

PC-773-04 Public private partnership in HIV and TB: a case study of India

R Deshmukh,¹ A Amar Shah,¹ A Elizabeth,² A Sreenivas,¹ K S Sachdeva³ ¹RNTCP, World Health Organization Country Office for India, New Delhi, ²National AIDS Control Organisation, New Delhi, ³Central TB Division, New Delhi, India. e-mail: deshmukhr@rntcp.org

Background and challenges to implementation: India has second highest burden of TB and HIV in the world. India has one of the largest private sectors and this is often the first point of contact for a significant number of TB and HIV patients. There is felt need for decentralised service delivery with involvement of Private, NGO and corporate sector for strengthening the Services of HIV and TB. Initiative were taken by National AIDS Control Program (NACP) and Revised National TB control Program (RNTCP) in India to involve Private practitioners, private medical colleges and public sector institutions as Public Private Partnership to provide decentralised service delivery for TB & HIV and as per the "END TB strategy" engage all care providers for integrated patient centered care and prevention.

Intervention: To address the challenge of providing decentralised services to in India private sector hospitals were engaged to start Integrated counselling and testing centres and designated microscopic services. Memorandum of understanding was signed with 11 ministries under the government of India and public sector institutions were sensitised for service delivery of RNTCP and NACP. Revised flexible schemes have been initiated to engage the private sector. Standards of TB care in India have been developed and disseminated to private sectors. Sensitisation of professional bodies like Indian Medical Association is ongoing and private medical institutions are involved in program.

Results and lessons learnt: 5086 PPs involved in RNTCP schemes and 1033 PPP ICTCs in Private Sector were initiated for HIV and counselling and testing services. RNTCP DMCs provide quality assured microscopic services as per the scheme. Quality services are provided by specialist trained in TB and HIV. Partnership has shown increase case detection rates, reduce diagnostic delays and cost to the patients.

Conclusions and key recommendations: Private sector involvement leads to quality healthcare delivery as seen in the case of the India. PPP approaches are necessary for early diagnosis, decentralised TB and HIV treatment services, to reduce out of pocket expenses to patients. Training and sensitisation meetings between the public and the private sectors are essential prerequisites for the success of the collaboration. Promoting Standards of TB care and address HIV and TB in integrated manner is essential for patient centred care and prevention as per the END TB Strategy.

PC-774-04 Urban free TB service delivery via engagement with private providers in Mumbai, India

S Vijayan,¹ T Shah,² P Keskar,² A Bamne,² M Khetarpal,² J Salve,² R Chopra,¹ J Thakker¹ ¹PATH, Mumbai, ²Municipal Corporation of Greater Mumbai, Mumbai, India. Fax: (+91) 114 605 4430. e-mail: shibuvij@gmail.com

Background: Private providers (PP) account for 1 million of the 3 million 'missing' TB case notifications globally. An estimated 60% of urban population seeks care from PP. Inaccurate and delayed diagnosis and lack of treatment adherence are key challenges in the private sector. We implemented an urban PP engagement model as "Private Provider Interface Agency" (PPIA), with subsidized TB diagnostic and free anti-TB drug services through vouchers and user-friendly e-health systems for early TB diagnosis and quality care.

Intervention: Objective was to increase: TB case notification from private sector, microbiological detection, number of patients accessing Drug sensitivity testing, treatment adherence, and reduce delay in diagnosis. Thus private provider engagement and provision of patient subsidies as incentives to providers for detecting and treating TB cases as per the Standards of TB Care in India (STCI) was sought. PPs, laboratories and chemists in the intervention area were mapped, and prioritized for engagement. Field officers engaged and provided PP services through a voucher system, provisioning free digital Chest X-rays, subsidized CB-NAAT testing, and free standardized treatment through e-vouchers at chemists. An efficient sputum sample collection and transportation system was established to reduce the delay in diagnosis. Treatment adherence was facilitated by SMSs and adherence calls by contact center coupled with health worker personal contact through '15 days follow-up system' established by the NGO staff for patients on TB treatment, and patient counselling.

Results: In 7 months, PPIA reached out to 2500 PPs comprising 42% of relevant provider universe in

Mumbai, and engaged 1426 providers for TB service delivery. So far, PPs have redeemed ~3500 X-ray vouchers (9500 USD), 1750 CB-NAAT vouchers (36 000 USD) and ~9000 treatment vouchers (55 000 USD). Out of 3328 TB positive cases notified by PPIA, 40% (1326) cases have been confirmed microbiologically. TB notification increased from 1070 to 6849 in 7 months.

Conclusions: This unique TB service delivery platform demonstrated an effective model of PP engagement for quality diagnosis and achieving higher case notification as per STCI in an urban slum. With appropriate model tweaking, this could be replicated in other urban setting. Improving PP quality and achieving scale in PP engagement and patient coverage will further enhance the program.

10. What's app doc? Use of m-health

PC-775-04 Effects of electronic tuberculosis information system on quality of TB data in Afghanistan

G Q Qader,¹ S D Mahmoodi,² H Manochehr,² D Azimi,² M Rashidi,¹ M Seddiq,² P G Suarez³ ¹Challenge TB, Management Sciences for Health, Kabul, ²Ministry of Public Health of Afghanistan, Kabul, Afghanistan; ³Challenge TB, Management Sciences for Health, Arlington, VA, USA. e-mail: gqader@gmail.com

Background: The TB data collection and reporting from health facility till national level were vertical; also, there were higher discrepancy between data reported by national health management information system (HMIS) and TB surveillance data. Also, the timeliness of TB data was only 65%. To address these challenges, NTP with technical and financial assistance from USAID funded TB CARE I project designed and integrated TBIS with national HMIS. The objective of this assessment was to assess the outcomes of the integration of TBIS with national HMIS on the quality of TB data.

Methodology: A team from Challenge TB, NTP and HMIS unit of MOPH reviewed the data reported electronically with that sent to NTP. We used the standard TB surveillance reporting and recording forms and TB electronic reporting system as data collection tool. The ever first electronic reporting system made in 2010 and piloted in few provinces, revised based on assessment results. Later, there was shift in implementation strategies from provincial TB coordinators to NGOs HMIS officers and all trained on it.

Results: Just after the training, 540 (80%) health facilities send their electronic data within the deadlines (timeliness) that is 15% improvements compared to the data accuracy assessment of 2013. Also, the comparison of electronic data with that of hard copies of the reports reached to NTP showed a completeness of 95% and accuracy of 97%. Three (0.4%) health facilities were not reported electronically.

Conclusion: The integrated electronic reporting system with national HMIS improved the discrepancy in TB data between HMIS and NTP surveillance, significantly. Also, it progressed into improved data accuracy, completeness and timeliness and advanced evidence based decision making at NGO, PHO and national levels. Thus, we strongly recommend the maintaining of this system, its scale up and upgrading with new definitions for TB reporting.

PC-776-04 Improving smear-negative case detection using social media (WhatsApp) under the Revised National TB Control Program in Ahmedabad district, Gujarat, India

D Kapadiya,¹ P Dave,² B Vadera,² P Prakash,¹ R Solanki,³ S Yadav,⁴ B Dave⁴ ¹State TB Training and Demonstration Center, Ahmedabad, ²State TB Cell, Gandhinagar, ³BJ Medical College, Ahmedabad, ⁴District Panchayat (Health Branch), Ahmedabad, India. e-mail: gutbhiv@rntcp.org

Background: Smear negative case detection is low in Gujarat with annualized new smear negative case (NSN) notification rate of 11 per lakh population. It is even low in Ahmedabad district with annualized NSN case notification rate of 6 per lac population. Lack of confidence in diagnosing TB based on chest X-ray by medical officers (MO) posted at peripheral health institute (PHI) was perceived to be one of the reasons of low detection of smear negative TB cases. "WHATSAPP" is a social media mobile application used to share Images, Video, Messages etc. and majority of mobile users are familiar with using this application on routine basis. Use of this social media app was explored to improve smear negative case detection by transferring images to referral health centre in Ahmedabad district of Gujarat, India.

Intervention: The study was conducted between April to October 2014 at all community health centers where X-ray facility and trained X-ray technicians were available. One health staff was designated as nodal person at Government X-ray facility who captured and sent images of chest X-ray in coordination with MO-PHI and X-ray technician to District TB Officer through WHATSAPP mobile application. DTO transferred X-ray image from mobile phone to computer through data cable or Bluetooth. Then, Chest X-ray reading was done by TB and Chest specialist available at B.J. Medical College and State TB training and demonstration center (STDC). Results of X-ray chest was informed to respective PHI by message through WHASAPP or telephone call. Quarterly data reported routinely under programme on smear negative TB case notification were reviewed and notification rates before and after intervention was reviewed.

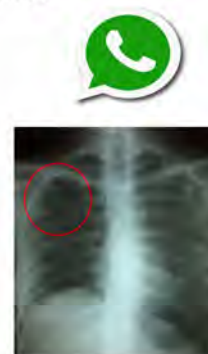
Results: Total 260 chest X-ray images were received during study period and all images were reviewed by TB & Chest specialist and results of chest X-rays were communicated in time to concern health facilities. Before intervention, annualized NSN case notification rate was 8 per lakh population per year and 6 cases per lakh per

year in 4Q13 and 1Q14 respectively. After intervention, annualized NSN case notification rate increased with 15 cases per lakh per year and 14 cases per lakh per year in 2Q14 and 3Q14 respectively.

Conclusions: Due to efforts of using WHATSAPP application (ICT) in X-ray reading, NSN case notification rate is improved under RNTCP. This study highlights the need of ICT and innovation to improve case findings in RNTCP.

Use of ICT in RNTCP

- Use of WHASAPP mobile application in case finding in Ahmedabad (R) district, Gujarat



PC-777-04 The usefulness and feasibility of mobile phone voice based system for notification of tuberculosis by private medical practitioners: a pilot project

B Velayutham,¹ B Thomas,¹ D Nair,¹ K Thiruvengadam,¹ K Thiruvengadam,¹ S Prashant,² S Kittusami,² A Jhunjhunwala,² S Swaminathan¹ ¹National Institute for Research in Tuberculosis, Chennai, ²Indian Institute of Technology Madras, Chennai, India. Fax: (+91) 442 836 2525. e-mail: dinanair73@yahoo.co.in

Background: Tuberculosis (TB) is a notifiable disease and health care providers are required to notify every TB case to local authorities. TB patients in India are diagnosed and managed both in the public and private sector. Various modalities for TB notification is currently being implemented of which Interactive Voice Response System (IVRS) has not been explored. We conducted a pilot study (Mobile interface in TB notification - MITUN) to determine the usefulness and feasibility of mobile phone voice based system for notification of TB cases by private medical practitioners. This technology has a unique Multi-lingual Speech recognition Program for data capture and intelligent analytics tools at the backend for speech to text conversion enabling remote voice based data collection and viewing of real time data on a web portal.

Design/Methods: The study was conducted during September 2013 to October 2014 in three zones of Chennai, an urban setting in South India. Private clinics wherein services are provided by single private medical practitioners were approached. The steps involved in MITUN included: Registration of the practitioners and notification of TB cases by them through mobile phone based voice interactions. Pre and post-intervention

questionnaires were administered to collect information on TB notification practices and feasibility of MITUN after an implementation period of 6 months.

Results: A total of 266 private medical practitioners were approached for the study. Of them, 184 (69%) participated in the study; of whom 11 (6%) practitioners used MITUN for TB notification. There were 138 (73%) of 184 practitioners who were aware of the Govt. Order on mandatory TB notification and 154 (81%) who considered mobile phone as a convenient modality for TB notification. Reasons for not using MITUN include lack of time, referral of patients to government facility, issues related to patient confidentiality and technical problems. Suggestions from private practitioners for making mobile phone based TB notification process user-friendly included reducing call duration, including only crucial questions and using missed call or SMS options.

Conclusion: Mobile phone voice based TB notification system has to be simple and user friendly for effective use. Lack of knowledge, perceived problems, logistical and practical issues preclude scale-up of notification of TB by private practitioners.

PC-778-04 Short message services and interactive voice response system: gateways to quality care and TB treatment adherence in Andhra Pradesh, India

S Achanta,¹ J Jaju,¹ M Parmar,¹ A Sreenivas¹ ¹World Health Organization Country Office for India, New Delhi, India. e-mail: achantas@rntcp.org

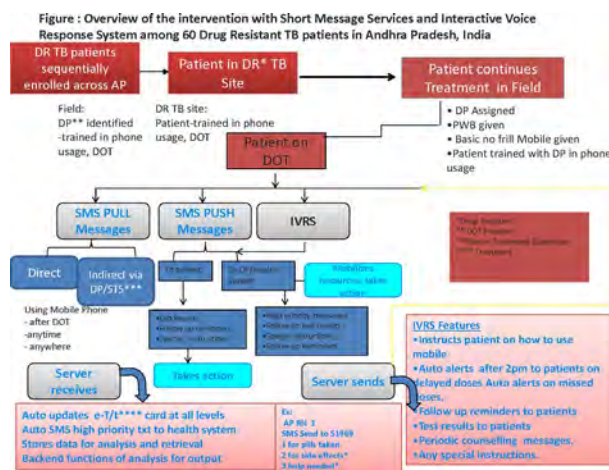
Background: One important challenge in Programmatic Management of Drug Resistant TB (PMDT) in India as it expands is monitoring treatment adherence. There is no formal counselling system and need of behavioural change in TB patients or promoting patient participation in treatment adherence is not systematically addressed. Programme depends on skills of DOT providers (DP), largely community health volunteers with limited ability and informal training to recognize side effects and counsel. Comprehensive and real time information from the point of event where DOT occurs could improve quality of care to patients. TB control measures would be ideal if situated at sub-district or district level, programme supervisors or managers could know if a patient in a far-off village has taken his daily medicine today and if he requires any assistance. Patient must get direct and easy access to health system to register his experience and seek help

Intervention: Andhra Pradesh uses a web based programme 'e-SMARTS' for monitoring PMDT. The technical platform of e-SMARTS was used to create 1) An SMS gateway for drug resistant TB patients to report daily pill consumption, side effects or need for help through simple SMS templates- 'outgoing feature' 2) An interactive voice response system (IVRS) service to inform patients about their test results, send follow up reminders, auto alerts on missed/delayed doses and periodic counselling messages -'incoming feature'. The DP and patient are trained in sending daily SMS. Patient

is encouraged to use the SMS reporting and is helped by DP. The Senior Treatment Supervisor (STS) of the programme monitors a population of 2.5 lakhs with android phones and electronic treatment cards of all drug resistant TB patients in his area. When the patient sends SMS, the treatment cards get automatically updated on real time basis. Daily log auto generated from the server enables comprehensive monitoring of patients missing pills, having side effects and requiring help. STS can then mobilize resources effectively to address these problems promptly

Results: Some encouraging results are seen from the intervention. Since January 2015, 60 MDR-TB patients reported daily DOT through SMS; 5 reported side effects and 2 requested medical help which were promptly attended. Counselling messages were appreciated by all

Conclusions: The SMS/IVRS gateway is a simple, promising tool to effectively monitor DOT and promote treatment adherence. Further large scale deployment is needed to document evidence



PC-779-04 Mobile vs. non mobile user rural health care providers diagnosing TB patients: comparative analysis from a tribal district in India

A Trivedi,¹ S Chadha,¹ S Satapathy¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. e-mail: atrivedi@theunion.org

Background and challenges to implementation: The project funded through Lily Foundation has trained Rural Health Care Providers (RHCPs), "first point of contact" for curative services in many villages' especially in tribal and remote geographic areas in India. A paper based referral mechanism is used to capture the data on referrals made, results of sputum examination and the management of those diagnosed with TB. However RHCP's and Lab Technicians (LTs), often lack information about referred chest symptomatics. The objective is to pilot innovative use of mobile technology to improve referrals and scale up on the basis of results achieved.

Intervention or response: Mobile application developed is being piloted in three blocks of Khunti, a tribal district in Jharkhand, India. This mobile platform is easily customizable- tracks the referred symptomatics, supports RHCPs and creates a central database on real-time basis. Two interoperable applications have been developed. One application is being used by 25 RHCPs and 1 NGO supervisor and other by 3 LTs. 64 trained RHCPs are referring through non-mobile.

Results and lessons learnt: In 21 months of implementation, 762 (74%) symptomatics have been referred by 25 RHCPs' and 264 (26%) by 64 RHCPs'. On an average 32 referrals have been made by each RHCP through mobile and 4 through non-mobile. Smear positive 77 (15% sputum positivity) and 27 (11%) through non-mobile. 86 (71%) TB patients have been diagnosed through mobile and 35 (29%) through non-mobile. 32 patients are cured and 14 completed treatment through mobile. 14 cured and 18 completed treatment through non-mobile. Proportion of referrals reaching DMCs is around 96%-98% from April 2014 onwards. Despite few challenges in implementation like training of RHCPs on use of android phones and maintenance of hand sets, this mobile based management system developed is assisting in follow up of referred chest symptomatics by RHCPs for diagnosis and treatment of Tuberculosis efficiently.

Conclusions and key recommendations: Add on benefits are there in using mobile application. It improves detection, treatment adherence and better outcomes. This platform facilitates compilation and analysis of data. The application is being scaled in other sites. The pilot project has explored possibility of sustainability. Implementing NGO Sankalp Jyoti has received adherence scheme which will help to sustain the intervention after the project ends.

Comparative analysis: mobile vs non-mobile users at tribal district in India: Khunti (May 2013–Jan 2015)

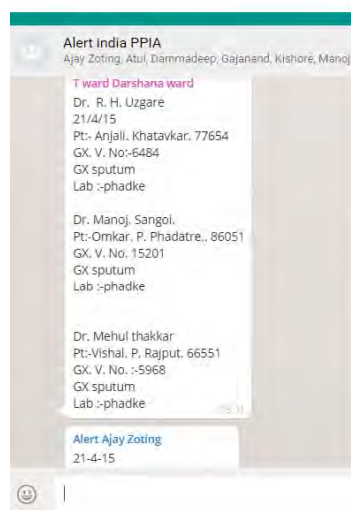
	Mobile Users	Non-mobile users
Number of trained RHCPs referring symptomatics	25	64
Number of referrals by engaged RHCPs	762 (74%)	264 (26%)
Referrals per engaged RHCP	32	4
Referrals reaching DMC	534 (70%)* 96-98% from April 2014 onwards	242 (91%)
Smear positive	77	27
Sputum positivity	15%	11%
Diagnosed TB	86 (71%)	35 (29%)
Cured	32	14
Completed treatment	14	18

PC-780-04 'WhatsApp': could real-time data sharing enable a complementary surveillance system? Future of health information management

S Vijayan,¹ A Karad,² R Gandhi,¹ P Kandasamay,¹ J Thakker,¹ R Chopra,¹ M Datta,¹ V Jondhale¹ ¹PATH, Mumbai, ²World Health Organization Country Office for India, Delhi, India. Fax: (+91) 114 605 4430. e-mail: shibuvij@gmail.com

Background: Real time flow of information is crucial for healthcare programs heavily based on field workers. With increasing penetration of internet and smartphones, the use of 'Whatsapp' which allows seamless flow of messages, photos and geo location makes it a very handy tool. Private Provider Interface Agency (PPIA) has set up virtual communities for sharing information and tracking programme activities via 'WhatsApp'

Figure: Screenshot of the virtual community on Whatsapp for data surveillance



Intervention: PPIA is using 'WhatsApp' for tracking sputum collection and transportation, and for real time flow of information regarding registration of new patients (paper based registration). Sputum agents collect the samples from all PPIA networked health facilities and deliver to nearest laboratory. The PPIA 'WhatsApp' group of sputum agents and supervisors share key information for sample testing process such as referral hospital's, referral physician's name, tests requested, laboratory's name, patient's name, case ID, test voucher details with the NGO central office. Real time information enables NGO staff to follow up with the designated laboratory for test results on the same day. The information shared on this group is accessible to key project staff and data entry operators. This also enables the supervisors to manage and track field activities on a regular basis. The sputum agent can also share a photo of a doubtful sample and ascertain the quality of the sample over a call with the supervisor. 'WhatsApp' group is also used to track the number of new patients registered daily

and the vouchers issued at each level of diagnosis and treatment for suspect group. It provides a platform to share information viz. suspects registered at the health facility, vouchers issued for- Chest X-ray, Gene Xpert test (CBNAAT), first line of treatment drugs, TB positive status and drug resistance status of the patient.

Results: Over 60 program staff are linked via 'WhatsApp' data covering 1000 TB suspects was reported and monitored over 7 months of operation. The real time data are then collated, and analysed via MS Excel. Technical difficulties and flaws during field operations are solved immediately through the experts engaged in the project

Conclusion: This shows that instant messaging applications establish efficient platforms for bidirectional communication and data acquisition from an ongoing program. Advancing this model as a complementary surveillance approach may increase outcome efficiency of a program due to instantaneous data and strong follow up system.

PC-781-04 Optimizing an electronic TB register to increase tuberculosis case notification and treatment success in Uganda and South Sudan

M Mubeezi,¹ N Sewankambo,² E Obuku,² C Nalugwa,¹ J Mogga,³ S Macharia,⁴ H Lasu,³ F Mugabe⁵ ¹Wild Innovations, Kampala, ²Makerere University College of Health Sciences, Kampala, Uganda; ³Ministry of Health, Juba, ⁴Management Sciences for Health, Juba, South Sudan; ⁵Ministry of Health, Kampala, Uganda. e-mail: micah.mubeezi@tbregister.org

Background: Tuberculosis remains a major public health problem particularly in the 22 high burden countries, of which Uganda and South Sudan are part. Despite significant progress in the Directly Observed Treatment Short Course strategy, with a downward trend of the Tuberculosis global burden, recording and reporting has been neglected. Current tools for recording and reporting Tuberculosis notification and treatment outcomes are archaic and paper based particularly in the low and middle income countries. This has resulted in serious delays in reporting, and when reports are submitted in time the quality of such reports is below par with poor estimation of tuberculosis diagnosis and treatment outcomes. Further, the existing reporting framework does not allow for disaggregation of individual patient data to permit more robust analysis for decision making, and better planning for appropriate interventions, at all levels of the National TB Control Programs in Uganda and South Sudan. The advantages of applying an electronic tuberculosis register have been scarcely documented and not rigorously evaluated. As such, decision makers in National Tuberculosis Control Programs in low and middle income countries lack the research evidence to facilitate the uptake of electronic recording and reporting of tuberculosis diagnosis and treatment outcomes.

Intervention: We conducted a study to evaluate the effectiveness of an electronic tuberculosis register over a 24 months' period in 28 health units in Uganda and

South Sudan. We used a mixed-methods operations research study adopting a quasi-experimental design, with two intervention and two control TB management units (between unit comparisons) plus a pre- and post-intervention study period (within unit comparison). **Preliminary results:** Over the study period, the TB management units in the intervention area consistently submitted their quarterly reports within 2 days after the end of each quarter. The cure rates for the bacteriologically confirmed TB cases improved by at least 70% in each of the study sites. The treatment success rates for the newly detected TB cases improved by over 100%. There was no significant increase in the case notification rates. **Conclusion:** Electronic TB recording and reporting significantly improves TB treatment outcomes, accuracy and timeliness in reporting.

PC-782-04 Characteristics associated with mobile phone access among tuberculosis patients in Pune, India

Y Ogale,¹ J Elf,¹ R Lokhande,² S Roy,² V Mave,² A Gupta,¹ J Golub,¹ J Mathad³ ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ²Byramjee Jeejeebhoy Medical College, Pune, India; ³Weill Cornell Medical College, New York, NY, USA. e-mail: yasmin.ogale@gmail.com

Background: Mobile health (mHealth) technology is being considered as a strategy for tuberculosis (TB) treatment adherence. We aimed to describe mobile phone ownership and usage among TB patients in Pune, India to assess the feasibility of a short message service (SMS) mHealth program to improve TB patient care.

Methods: Consenting adults presenting with active TB were administered a brief questionnaire capturing socio-demographics, mobile phone ownership and comfort using SMS messaging. Those with access to a mobile phone were contacted via phone call 4 times over 6 months to understand long-term access to the provided number. Recruitment and enrollment is ongoing; interim analyses are presented.

Results: A total of 73 adults have been enrolled thus far; 53 (73%) were male and the median age was 32 (IQR: 24, 45) years. Fifty (71%) participants had 5 or more years of education, and 45 (64%) were currently employed. Nearly all participants (96%) reported access to a mobile phone, with the majority (78%) personally owning a mobile device and the remaining (22%) borrowing from a family member. Among all participants, 44 (63%) felt uncomfortable sending an SMS message; 32 (46%) felt uncomfortable receiving an SMS message. The majority of participants could be reached by voice call 1 week (86%), 1 month (90%) and 3 months (83%) after initial contact. In multivariate logistic regression, female participants tended to have lower odds of mobile phone ownership (OR 0.4; 95%CI: 0.07, 2.0) while those with more than 5 years of education (OR 6.4; 95%CI: 1.3, 32.6) and those employed (OR 2.3; 95%CI: 0.5, 10.4) tended to have higher odds of ownership. Older age groups (31-50 yrs OR 0.4; 95%CI: 0.08, 1.9 and 51+ yrs OR 0.2; 95%CI:

0.02, 2.3) tended to have lower odds of comfort using SMS messages, while those with more than 5 years of education (OR 39.9; 95%CI: 4.3, 370.8), those who were employed (OR 4.5; 95%CI: 0.8, 25.8), and those who owned a mobile phone (OR 2.5; 95%CI: 0.4, 14.5) had greater odds of comfort.

Conclusion: TB patients in this population had high access to, and ownership of, mobile devices. Heterogeneity in ownership and comfort using SMS highlight potentially vulnerable populations, including women, older individuals, and those of lower sociodemographic status. These trends are expected to reach statistical significance with increasing enrollment. Highlighted groups may require additional interventions or training prior to using SMS programs.

11. Basic science: bugs and drugs

PC-783-04 In vitro anti-mycobacterial activity of selected medicinal plants against *Mycobacterium tuberculosis* and *Mycobacterium bovis* strains

A G Mekala,¹ G Ameni,² M Giday,² A Worku² ¹Haramaya University, College of Health & Medical Sciences, Harar, ²Addis Ababa University, Akilu Lemma Institute of Pathobiology, Addis Ababa, Ethiopia. Fax: (+251) 256 668 081. e-mail: abdgemechu@gmail.com

Background: Tuberculosis (TB) is a global burden with one – third of the world 's population infected with the pathogen *Mycobacterium tuberculosis* complex and annually 1.4 million deaths occur due to the disease. This high incidence of infection and the increased rate of multi-drug resistant and extensively-drug resistant strains of the organism further complicated the problem of TB control and have called for an urgent need to develop new anti-TB drugs from plants. In this study, the in vitro activity of root of *Calpurnia aurea*, seeds of *Ocimum basilicum*, leaves of *Artemisia abyssinica*, *Croton macrostachyus*, and *Eucalyptus camaldulensis* were evaluated against *M.tuberculosis* and *M. bovis* strains.

Methods: Five Ethiopian medicinal plants, root of *Calpurnia aurea*, seeds of *Ocimum basilicum*, leaves of *Artemisia abyssinica*, *Croton macrostachyus*, and *Eucalyptus camaldulensis* used locally for the management of TB. They were investigated for in vitro antimycobacterial activity against *M. tuberculosis* and *M. bovis* strains. 80% methanolic extracts of the plant materials were obtained by maceration. The antimycobacterial activity was determined using 96 wells of microplate with the help of visual Resazurin Microtiter Assay.

Results: The crude 80% methanolic extracts of the root of *C. aurea*, seeds of *O. basilicum*, and leaves of *A. abyssinica*, *C. macrostachyus*, and *E. camaldulensis* had anti-mycobacterial activity with minimum inhibitory concentration (MIC) ranging from 6.25 – 100 µ g/ml. The MIC of 80% methanol extracts in the order mentioned above ranged 25-100 µ g/ml and 12.5-75 µ

g/ml, 25 – 100 µ g/ml and 25 – 50 µ g/ml, 6.25-50 µ g/ml and 12.5-50 µ g/ml, 12.5-100 µ g/ml and 18.25-50 µ g/ml and 6.25-50 µ g/ml and 12.5-50 µ g/ml, respectively for *M. tuberculosis* and *M. bovis* strains.

Conclusion: The results support the local use of these plants in the treatment of TB and it is suggested that these plants may have therapeutic value in the treatment of TB. However, further investigations are needed on isolating chemical constituents responsible for eliciting the observed activity in these plants.

PC-784-04 New horizons for quinolone-class agents

K Drlica,¹ A Mustaev,¹ R Kerns,² X Zhao,¹ J Berger³ ¹Public Health Research Institute, Rutgers University, Newark, NJ, ²College of Pharmacy, University of Iowa, Iowa City, IA, ³Johns Hopkins School of Medicine, Baltimore, MD, USA. e-mail: nicolas.veziris@upmc.fr

Fluoroquinolones are important second-line agents for treatment of tuberculosis. However, resistance is a growing problem that is unlikely to be controlled. As a key part of the quinolone action mechanism, which is understood largely from work with non-tuberculosis bacteria, the compounds trap gyrase on DNA as reversible complexes. X-ray crystallography of these complexes has defined the primary binding mode for the drugs. In that mode, the carboxyl end of the drug forms a water-magnesium ion bridge with amino acids in the GyrA subunit of gyrase. Mutation of these amino acids eliminates the bridge, lowers drug-binding strength, and causes target-based resistance. Fluoroquinolone-like compounds called quinazolinones lack the carboxyl and serve as a way to bypass existing resistance. Efforts are being made to increase the binding strength of quinazolinones. We recently found a second mode of quinolone binding through quinolone-gyrase crosslinking: the C7 end of quinolones rather than the C3 carboxyl interacts with GyrA. One speculation is that the second mode involves a 180 degree inversion of the drug. Surprisingly, adding a phenyl ring to the C7 end removes much of the protective effects of GyrA resistance substitutions, thereby providing a second way to bypass existing target-based resistance. Diones and C7-phenyl derivatives are being modified to improve rapid lethality, limit the mutagenic SOS response, and thereby restrict the emergence of new resistance. Pathways leading to cell death are also being studied to identify targets of small molecule enhancers of lethality (one enhancer targeting DNA recombinational repair increases the lethal action of quinolones with mycobacteria). Two lethal pathways exist, one that involves the accumulation of toxic reactive oxygen species and one that does not. How drug structure and binding to gyrase influences lethal action, which is mechanistically distinct from blocking growth, is not known. Work on action mechanism is leading to new ways to design quinolone-class compounds to bypass existing resistance. Attention on lethal action, which is crucial for slowing the emergence of resistance, is the subject of ongoing work. Involvement of reactive oxygen in drug lethality suggests follow-up work to

determine whether consumption of anti-oxidants interferes with drug lethality.

PC-785-04 Study of herbal bioenhancers extract on various characteristics of isoniazid and rifampicin microspheres

P Pingale,¹ R.P. Ravindra² ¹GES Sir Dr M S Gosavi College of Pharmaceutical Education & Research, Nashik, ²Dharamitra, Wardha, India. Fax: (+91) 253 223 2799. e-mail: prashant.pingale@gmail.com

Background: Bioenhancers are agents when combined with an active drug lead to potentiate the pharmacological effect of the drug but themselves are not having any therapeutic effect. Recent development in bioavailability enhancement of drugs by herbal compounds has produced a new shift in the way of therapeutics. Bioenhancers improve permeability and influence bioavailability of the drug for therapeutic efficacy which may result into decrease in dose ensuring therapeutic availability. The major problems associated with the anti-TB drug therapy include loss of efficacy through bacterial resistance, side effects, and low patient compliance. In the cited research work, we have attempted to solve the above mentioned problems by simultaneous use of both the concepts of microsphere drug delivery (higher bioavailability) and herbal bioenhancers (improved bioavailability).

Methods: Complex coacervation method and modified emulsion method. Materials: Isoniazid and rifampicin as a model drug used in TB therapy. Hydro-alcoholic extracts of *Carum carvi* and *Ocimum sanctum* were used as bioenhancer.

Results: The in-vitro drug release of isoniazid and rifampicin from formulations where bioenhancer extract is used was found to be about 85-90% in 12 hrs. While the same was about 45-50% in case of formulations where bioenhancers were not used. Other parameters like percentage bioadhesion, permeability study using intestinal sac method etc. were also studied.

Conclusion: For microspheres prepared by both complex coacervation and modified emulsion methods, the particle size was uniform and found to be less than 130 micron in size; the particle size may alter on addition of bioenhancer extract to the formulations. The drug encapsulation efficiency was found to be in the range of 43-67% (increased on addition of bioenhancer in the formulations). The percentage bioadhesion of the microsphere where bioenhancers were used found to increase by 20% as compared to basal value (upto 67% from 42%). The in-vitro release study by USP paddle apparatus and the most important results from the in-vitro release study relates to the very significant enhancement in drug release (45 to 90% for microspheres prepared by modified emulsion method and 47 to 90% complex coacervation method), due to presence of bioenhancers alone and in combination.

PC-786-04 Phosphate ABC transporter systems regulate the level of rifampicin resistance in *Mycobacterium tuberculosis*

M Grobbelaar,¹ S Sampson,¹ E Louw,² T Victor,¹ P Van Helden,¹ R M Warren,¹ M De Vos¹ ¹Stellenbosch University, Cape Town, South Africa; ²National Institutes of Health, Bethesda, MD, USA. e-mail: melgrob@sun.ac.za

Background: Evidence demonstrating the differential dynamics in the population structure of *Mycobacterium tuberculosis* within a clinical specimen has been reported recently. It is thus suggested that the phenotype of an entire population reflects the average of the phenotypic characteristic of individual clones within a population. We hypothesise that the resistance phenotype, as measured by the minimum inhibitory concentration (MIC), reflects an average of the MICs of individual clones present in the clinical specimen.

Design/Methods: Single cell colonies from *M. tuberculosis* rifampicin mono-resistant clinical isolates with genetic backgrounds representing the X and Beijing genotypes were purified. Subsequent selection criteria included the presence of the *rpoB* S531L mutation and the differential low and high rifampicin MIC's for each genotype. Genomic DNA was extracted from each single cell culture and sequenced using the Ion Torrent platform. Single nucleotide polymorphisms and InDels were called using the bioinformatic suite, Ion Reporter. All variants were confirmed by PCR and Sanger sequencing.

Results: The level of rifampicin resistance for both the X and Beijing genotype were as follows: the low MIC= 40µg/ml and high MIC >150µg/ml. In the X genotype, 2 unique variants were identified in the high MIC single cell, with 3 variants in the low MIC. Additionally, in the Beijing genotype, 5 unique variants were identified in the high MIC single cells, while 8 variants were identified in the low MIC. The low MIC colony with an X genotype showed a 7bp insertion in phosphate ABC transporter *phoT*, while the low MIC Beijing genotype colony showed a 6251bp deletion spanning the phosphate transporters *pstC2*, *pstS2*, *pstA1*, *pstB*, and *pstS1*.

Conclusion: The insertion in or deletion of ABC transporters may be linked to the low levels of rifampicin resistances within the single cell colonies isolated from two different clinical isolates. We postulate that these natural knockouts demonstrate low rifampicin MICs as they are unable to extrude rifampicin efficiently. Phosphate ABC transporters may be important targets for the development of adjuvant drugs to improve the efficacy of TB treatment.

PC-787-04 Clofazimine: mechanism of resistance within *M. tuberculosis*

H Visser,¹ M De Vos,² R Van Der Merwe,³ T Victor,⁴ P Van Helden,⁵ R M Warren,⁶ L Paul⁷ ¹University of Stellenbosch, Cape Town, South Africa. e-mail: hvisser@sun.ac.za

Background: The observed increase in the global incidence of drug resistant tuberculosis (TB) has renewed

the search for new anti-TB drugs and the repurposing of drugs that are currently used to treat other pathogenic infections including other species of mycobacteria. One such repurposed drug, is clofazimine (CFZ), which is currently used for the treatment of leprosy, caused by *Mycobacterium leprae*. The mechanism of action of CFZ is not clear, but it is hypothesized that CFZ is reduced by a mycobacterial type II NADH oxidoreductase. The reduction of CFZ drives the production of reactive oxygen species which are toxic to the pathogen. The aim of this study was to elucidate the mechanism of CFZ resistance.

Methods: Spontaneous in vitro CFZ resistant mutants were selected. Whole genome sequencing was done to identify SNPs which may cause CFZ resistance.

Results and Discussion: Mutations were identified in the transcriptional regulator Rv0678 and a fatty-acid-AMP ligase (FadD28, Rv2941). Mutations in Rv0678 have previously been shown to play a role in both CFZ resistance and bedaquiline (BDQ) cross-resistance. No link has been found between CFZ resistance and mutations in fadD28. The novel SNP identified in Rv0678 resulted in the replacement of an alanine residue with threonine at codon 84, located in the DNA binding domain. Virtual modeling of the mutated Rv0678 protein showed that the A84T mutation caused a change in hydrophobicity, which may influence binding to DNA. Previous studies showed that mutations in Rv0678 resulted in the upregulation of mmpL5, a putative efflux pump. However, the mechanism whereby CFZ resistance occurs via increased abundance of this efflux pump in the cell wall is not clear and needs further investigation.

Conclusion: Cross-resistance between CFZ and BDQ, caused by mutations in Rv0678, is of concern and may influence the planning of anti-TB drug regimens for the future. The role of the other mutation which causes CFZ resistance is not clear and requires further investigation. Finally, the findings of this study support the role of Rv0678 in CFZ resistance thereby suggesting that this gene could be useful as a diagnostic marker to test for CFZ resistance in clinical isolates.

PC-788-04 Whole genome analysis of IS6110 insertion sites in two closely related *Mycobacterium tuberculosis* Beijing strains with distinct pathogenic phenotypes

K Siame,¹ R M Warren,¹ P Arnab,² A Abdallah,² A Christoffels,³ N Gey Van Pittius,¹ S Sampson¹

¹Biomedical Sciences, DST-NRF Centre of Excellence for Biomedical Tuberculosis Research/SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town, ²Pathogen Genomics Laboratory, BESE Division, King Abdullah University of Science and Technology, Thuwal, ³South African National Bioinformatics Institute, University of the Western Cape, Cape Town, South Africa. e-mail: kksiame@sun.ac.za

Background: A recent molecular epidemiological study showed that *Mycobacterium tuberculosis* Beijing genotype strains, isolated from patients in Cape Town, South

Africa, were either clustered or unique according to IS6110 RFLP. Two isolates reflecting either ongoing transmission (clustered) or the absence of transmission (unique) were shown to have a hyper-virulent or hypo-virulent phenotypes in a murine infection model, respectively. Additionally, the hyper-virulent strain elicited an anti-inflammatory TH2 immune response in the murine model whilst the hypo-virulent strain had a pro-inflammatory TH1 immune response. The genetic mechanism(s) underlying these contrasting phenotypes remain to be elucidated. Objective: This study aimed to use whole genome sequencing to determine whether IS6110 transposition could account for the different virulence phenotypes seen in these Beijing genotype clinical isolates.

Design/Methods: Whole Genome Sequencing of the hypovirulent and hypervirulent strains was performed on an Illumina platform generating 105 bp paired-end reads and on a PacBio platform generating long single end raw reads. De novo assembly was performed using MIRA software to generate a hybrid assembly using Illumina and PacBio raw reads. Gap closure among contigs from the MIRA assembly was done using Platanus genome assembly software; ordering of the assembled genome was done with ABACAS software. The first and last 140 bases of IS6110 in the super-contig were then searched for to reveal the sequence adjacent to the IS6110 location. NCBI BLAST was used to determine the location of the IS6110 element with respect to *M. tuberculosis* H37Rv or CDC1551 reference genomes

Results: The hypo-virulent and hyper-virulent strains shared 22 IS6110 insertion positions and differed only by an IS6110 insertion at position 2,165,961 in the hypervirulent strain. This insertion disrupted the gene ppe34.

Conclusion: Our results showed that ppe34 was uniquely disrupted by an IS6110 element in the hyper-virulent strain. Previous studies have suggested that a domain encoded by ppe34 elicits a TH2 immune response, which is also the case for the hypervirulent strain albeit having the aforementioned domain disrupted. Further investigation will be required to determine whether the IS6110-mediated disruption of ppe34 plays a role in modulating the TH1/TH2 balance, or whether other mechanisms independent of ppe34 involvement are driving this differential host response.

PC-789-04 Global high-throughput analysis of DNA-binding proteins in *Mycobacterium smegmatis*

N Steyn,¹ T Heunis,¹ P Van Helden,¹ R M Warren,¹ M Williams,¹ S Sampson¹ ¹Biomedical Sciences, Stellenbosch University, Cape Town, South Africa. e-mail: nastassja@sun.ac.za

Background: Elucidating changes in the *Mycobacterium tuberculosis* transcriptome in response to stresses encountered within the host environment, including drug treatment, is critical for understanding pathogen adaptation to these adverse conditions. These studies are often

limited to micro-array or ChIP-seq analysis where the transcription factor initiating a transcriptional response is known. A large number of predicted genes in the *M. tuberculosis* genome have unknown functions, and it is therefore plausible to hypothesize that a subset of these proteins are involved in transcriptional regulation. In this study we aim to develop a method that will identify novel DNA binding proteins in *M. tuberculosis*. For the purposes of establishing this method we used the closely related, non-pathogenic and fast growing organism *Mycobacterium smegmatis*.

Design/Methods: *M. smegmatis* was cultured under standard conditions to early log phase and then treated with formaldehyde to crosslink protein-DNA complexes. The complexes were captured onto a solid matrix using an anti-RNA polymerase antibody and an on-matrix tryptic digestion performed. Eluted peptides were analyzed by high resolution LC-MS/MS and DNA binding proteins were identified using the Andromeda search algorithm as part of MaxQuant 1.2.2.5.

Results: Preliminary data obtained using *M. smegmatis* confirmed that our method selectively enriched for proteins known to be bound to DNA. These included the RNA polymerase complex, ribosomal proteins and other RNA associated proteins. In addition, we identified proteins required for energy metabolism. The reproducibility of this method is currently being evaluated.

Conclusion: The identification of proteins that are associated with DNA in *M. tuberculosis* will provide insights into the essential cellular processes of transcription and potentially identify novel proteins involved in the regulation of these processes.

PC-790-04 Expression and purification of *Mycobacterium tuberculosis* Rv1460, a possible SUF system regulator

D Willemse,¹ B Weber,² R M Warren,¹ M Williams¹

¹Biomedical Sciences, Stellenbosch University, Cape Town,

²University of Cape Town, Cape Town, South Africa. Fax: (+27) 219 389 863. e-mail: dwillemse@sun.ac.za

Background: Iron-sulphur clusters (Fe-S) are protein cofactors involved in multiple cellular processes. Clusters are sensitive to oxidation and are therefore synthesised by Fe-S cluster biogenesis systems. *M. tuberculosis* contains only the sulphur mobilization (suf) Fe-S cluster biogenesis system, encoded in an operon (Rv1460-Rv1461-Rv1462-Rv1463-csd-Rv1465-Rv1466) (suf operon) consisting of seven co-transcribed genes. Rv1460 encodes a probable transcriptional regulator that shares homology with the cyanobacterial sufR gene. The Rv1460 encoded protein of *M. tuberculosis* has predicted DNA- and iron-binding domains, but its role in regulating the suf operon and in physiology as a whole is unclear.

Design/Methods: The Rv1460 gene was amplified and cloned into the pET28a expression vector to generate an N-terminal His-tagged fusion protein. The *Escherichia coli* ArcticExpress (DE3) strain transformed with the construct was cultured in LB broth to an OD of ~0.5

(600 nm) at 30°C. Protein expression was induced by the addition of 0.4mM IPTG and incubation at 13°C for 24 hrs. Cell extract from 2.5L of culture was loaded onto a 5ml HiTraP nickel IMAC column in the presence of 20mM imidazole, washed and then eluted with a 20 to 500mM linear imidazole gradient. Fractions containing the fusion protein were pooled, concentrated and applied to a Sephadex S200 gel filtration column. Protein purity was assessed by SDS-PAGE.

Results: SDS-PAGE and western blot analysis revealed that the majority of the Rv1460-fusion protein was present in the insoluble fraction, although sufficient soluble protein was present for purification. Interestingly, the protein was visible as a monomer (~35 000 Da) and a homodimer (~70 000 Da) on a reducing SDS-PAGE gel. The elution profile from the IMAC column showed two major protein peaks eluting within the imidazole gradient, and the second peak was confirmed to contain the Rv1460-fusion protein by SDS-PAGE and western blot analysis. SDS-PAGE analysis revealed that peaks eluting from the S200 gel filtration column corresponding to the size of the monomer and dimer both contained the fusion protein. This is consistent with the finding that cyanobacterial SufR functions as a dimer. The purity of the protein following gel filtration was assessed to be approximately 90%.

Conclusion: Optimised purification of Rv1460 will enable us to characterise its DNA-binding properties and provide insight into its role as a mycobacterial transcriptional regulator.

PC-791-04 Persistence of bacilli during treatment of TB is associated with changes in colony lag phase

D Barr,^{1,2,3} M Kamdolozi,⁴ Y Nishihara,⁴ V Ndhlovu,⁴ J Meghji,¹ M Khonga,⁴ G R Davies,² D Sloan³ ¹Wellcome Trust Liverpool Glasgow Centre for Global Health Research, Liverpool, ²University of Liverpool, Liverpool, ³Liverpool School Tropical Medicine, Liverpool, UK; ⁴College of Medicine, University of Malawi, Blantyre, Malawi. e-mail: david.barr@liv.ac.uk

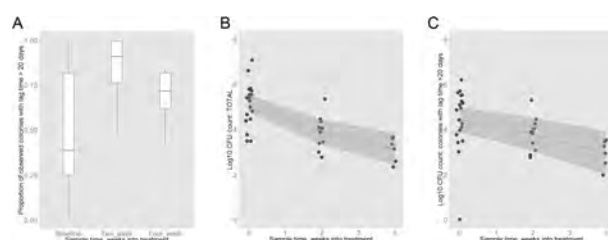
Background: To meet global TB control targets, shorter TB treatment regimens that can still reliably deliver low relapse rates are needed. 'Sterilising cure' without relapse is hypothesised to depend on eradication of drug tolerant sub-populations of *M. tuberculosis* (MTB), made up of slower growing 'persister' bacilli. No well validated biomarker for 'sterilising activity' of anti-tuberculosis drugs exists. Indices derived from serial sputum colony counts and time to detection of growth in liquid culture (TTD) show potential as surrogates, but neither directly measures elimination of sub-populations. Measuring time to colony appearance (lag time) on solid agar might identify slower growing persister sub-populations because they will appear later on the plate.

Design/Methods: Sputum samples from smear ++ or +++ pulmonary TB patients in Blantyre, Malawi were collected from patients at 0, 2 and 4 weeks into standard short course therapy and inoculated without decontamination at serial dilution onto selective 7H11 plates.

Resulting colony growth was digitally imaged. Colony measures were made with OpenCFU software. Lag time and radial growth rate of individual colonies were extracted using custom written R programming scripts to attribute unique identities to individual colonies in serial images.

Results: Measurable colony growth was recorded for 20 patients at baseline, 10 patients at two weeks, & 6 patients at four weeks. 1400 colonies were observed. Mean lag time of observed colonies increased between baseline and two weeks then plateaued. Growth rate was higher for colonies from week 4 samples. A mixed-effects model, accounting for random variation between patients, suggested that colony lag time increased by 6.6 days between baseline and two week samples (fixed effect, $P = 0.01$). While total colony counts per ml sputum showed typical biphasic elimination, counts of colonies with lag time >20 days declined more slowly and linearly (Figure).

Conclusion: Study of individual TB colony growth may identify drug tolerant MTB sub-populations, as shown by differing bacillary elimination profiles when colonies are disaggregated by lag time. This is the first quantitative description of TB colony dynamics, and our findings suggest that colony phenotyping could add value to surrogate markers of efficacy in phase II TB treatment trials, which would be an important step towards shorter regimens.



12. TB diagnostic challenges: molecular and other techniques

PC-792-04 Molecular profile of drug resistance in bone and joint tuberculosis in China

G Wang,¹ H Huang¹ ¹Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Institute, Beijing, China. e-mail: 23332978@qq.com

Background: Bone and joint tuberculosis (BJTB) constitutes about 5-10% of the extrapulmonary tuberculosis (EPTB). Xpert MTB/RIF (Xpert) has been endorsed by WHO for diagnosis EPTB. Using Xpert, we investigated the drug resistance in BJTB patients.

Design/Methods: 208 pus specimens were obtained from orthopedics patients. Culture and Xpert were performed for each specimen, while MGIT960 based drug susceptibility testing (DST) was conducted for all the recovered isolates. The efficiency of Xpert was evaluated based on the bacteriological examination outcomes.

Results: Our results showed that 34.13% (71/208) of recruited cases had a positive result for *Mycobacterium tuberculosis* culture from pus, while 76.44% (159/208) of recruited cases showed positive results for Xpert. Xpert is not only an alternative diagnostic approach for BJTB but also can be further used for the detection of drug resistance, the results of which were consistent with the classic drug susceptibility test. However, it further provided the molecular profile of the mutations can be conducted much faster than the classic drug susceptibility test can. In the studied 208 pus samples from patients with BJTB, we found a rate of 14.08% for rifampicin (RIF) resistance, and 14.08% for multidrug-resistant tuberculosis, which is similar to the reported resistance in pulmonary tuberculosis. The molecular profile indicated that probes associated with the observed RIF-resistance were as follows: E (79.17%, 19/22), D (8.33%, 2/22), B (4.17%, 1/22) and no RIF-resistance was associated with probe A and C.

Conclusion: Our data suggest that Xpert is capable of detecting drug resistance for pus samples from BJTB. We recommend Xpert as routine assays for patients with suspected BJTB.

Table Demographic profile and clinical features of patients with BJTB who tested positive by culture and/or Xpert

Characteristics	No. (%) of culture- positive patients (n=71)	No. (%) of Xpert - positive patients (n=88)	P values
Median age, years (rang)	44(14-84)	29(3-80)	0.029
Male sex	35(49.3)	46(52.27)	0.709
Concomitant TB	36(50.7)	57(64.77)	0.073
History of TB contact	2(2.82)	4(4.55)	0.693
Smoking	13(18.31)	9(10.23)	0.142
Alcohol	8(11.27)	5(5.68)	0.201
Average treatment time at admission (day)	68	107	0.12
Clinical features at admission			
Fever	18(25.35)	40(45.45)	0.009
Night sweat	20(28.17)	29(32.95)	0.516
Weight loss	25(35.27)	30(34.09)	0.883
Lethargy	19(26.76)	12(13.64)	0.038
Localised pain	67(94.37)	79(89.77)	0.293
Swelling	19(26.76)	22(25)	0.801
Restriction of movement	57(80.28)	57(64.77)	0.031
Neurological deficit	27(38.03)	29(32.95)	0.443
MRI and CT abnormalities			
Bony destruction	64(90.14)	70(79.55)	0.068
Soft-tissue involvement	51(71.83)	67(76.14)	0.537
Histopathological features consistent with TB	62(87.32)	70(79.55)	0.194

PC-793-04 Comparison between fine needle aspiration cytology and GeneXpert® in the diagnosis of TB lymphadenitis in Ethiopia

T Gemechu,¹ M Aseresa Melese,² B Tessema,³
N Demmelash,² D Habte,² D J Dare,² P G Suarez⁴

¹Department of Pathology, College of Health Sciences, Addis Ababa University, Addis Ababa, ²Management Sciences for Health, Help Ethiopia Address the Low TB Performance (HEAL TB) Project, Addis Ababa, ³Department of Medical Microbiology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, USA.
e-mail: keeti.gemechu@gmail.com

Background: Lymphadenitis is the most common form of extra-pulmonary tuberculosis in Ethiopia. Fine-Needle Aspiration (FNA) offers a feasible and safe option for specimen collection for cytological examination, culture and GeneXpert tests. Cytology microscopic reading is an old diagnostic tool, which is simple, rapid, and performance-friendly method. However, FNA cytology is performed only in few hospitals in Ethiopia due to a limited number of pathologists and the introduction of Xpert might be an alternative test.

Design/Methods: A comparative cross-sectional study was conducted in a tertiary hospital between September 2014 and February 2015 to compare the cytological results of the senior pathologists and Xpert results. A senior pathologist took a split sample of FNA from patients clinically suspected of TB lymphadenitis. The cytology smears were stained with Wright's stain and read by the same senior pathologist. A senior microbiologist ran the Xpert test following the standard procedure. Both the pathologist and the microbiologist were blinded for the results of each other. We calculated the concordance rate of the two test results using Kappa statistics.

Results: A total of 118 TB lymphadenitis suspected patients were included in this study with male to female ratio of 0.72. From the total of 118 TB lymphadenitis suspects, 89 (75.4%) and 64 (54.2%) were diagnosed as TB by cytology reading and Xpert, respectively. Four (6.3%) of the TB patients diagnosed by Xpert were found to have Rifampicin Resistant Tuberculosis. Out of 89 patients diagnosed as TB lymphadenitis by cytology, 63 (70.7%) were diagnosed as TB by Xpert. The cytology labeled 29 of the suspects as no TB of which 28 (96.6%) were also negative for TB by Xpert. The agreement level between the two tests was moderate (Kappa 0.52, $P < 0.001$). The TB positivity rate is significantly less in caseous aspirates samples as compared to the pus (Cytology 65.3% vs. 88.3% and Xpert 38.8% vs. 70.5%, respectively)

Conclusion: Gene Xpert was also able to detect a larger proportion of the TB cases diagnosed by Cytology. In settings where there is no pathologist to provide cytology service, the new diagnostic tool could fill the gap. Getting enough samples for caseous aspirates was a challenge and the low yield among caseous samples could be due to insufficient sample.

Table Summary of readings of FNA Cytology and Gene Xpert test in the diagnosis of TB lymphadenitis

	Xpert TB	Xpert non-TB	Total
Cytology TB	63	26	89
Cytology non-TB	01	28	29
Total	64	54	118

PC-794-04 Need to adapt better diagnostic tools to improve the diagnostic accuracy of sputum-negative TB cases in India

S Dapkekar,¹ R Yeole,¹ S Kamble,² P Parmar,¹

A Sreenivas¹ ¹World Health Organization, Country Office for India, New Delhi, ²State Tuberculosis Office, Pune, India.
e-mail: drshankardapkekar@gmail.com

Background: National Tuberculosis Programme of India (RNTCP) has vision to accurately diagnose and effectively treat all TB patients including drug-resistant (DR) cases. From inception of RNTCP, diagnosis of TB depends on sputum microscopy. Presumptive pulmonary TB case found positive on sputum microscopy are typed as sputum positive TB and those tested negative on sputum microscopy but X-ray finding suggestive of TB are been typed as sputum negative TB as per current diagnostic algorithm under RNTCP. Previously treated pulmonary TB cases are been offered drug susceptibility testing through molecular diagnostic tool through programme assuming they are presumptive MDR-TB cases. Concerns have been raised about the high proportion of *Mycobacterium tuberculosis* not detected results on Xpert MTB/RIF testing for those already diagnosed as pulmonary TB cases in the field. We felt this study as unique opportunity to compare results of Xpert MTB/RIF test with basis of diagnosis of TB.

Methods: In this cross sectional study, we collected data on presumptive pulmonary MDR-TB cases with history of previous anti-TB treatment having MTB not detected results from January to December 2014 at 3 Xpert MTB/RIF lab sites and compared it with basis of diagnosis of TB in them.

Results: Total of 1553 pulmonary TB cases with past history of anti-TB treatment were tested for DST at 3 Xpert MTB/RIF lab sites in 2014. Among them 891 (57%) were sputum positive TB cases and rest were sputum negative. 603 (39%) of total tested for DST had *M. tuberculosis* not detected results. *M. tuberculosis* not detected results proportions were 19% and 66% among sputum smear positive and sputum smear negative previously treated pulmonary TB cases respectively.

Conclusion: World Health Organization has recommended use of Xpert MTB/RIF test for diagnosis of TB depending on its accuracy. It is concerning to know very high *M. tuberculosis* not detected results on Xpert MTB/RIF test among those diagnosed as TB on the basis of X-ray findings. Many studies have indicated that dependency on X-ray for diagnosis of TB has risk of false positive diagnosis to the extent of 40%.

Results of this study reiterate their findings. Though resource intensive, there is urgent need to adopt molecular tests like Xpert MTB/RIF instead of depending

on X-rays in RNTCP diagnostic algorithm for improved accuracy. Further research is needed to understand why 19% of cases in the study were sputum positive in the field but *M. tuberculosis* negative on Xpert MTB/RIF test.

PC-795-04 Diagnosis of drug-resistant tuberculosis by Xpert® MTB/RIF (CBNAAT) in extra-pulmonary samples: a retrospective analysis from Central India

P Desikan,¹ N Panwalkar,¹ S Dhawan,^{2,3} K Rade,³ S Mannan,³ L Mehendru,³ N Kulshreshtha,⁴ M Pandey¹

¹National Reference Library, Bhopal Memorial Hospital and Research Centre, Bhopal, ²International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ³World Health Organization, Country Office for India, New Delhi, ⁴Central TB Division, New Delhi, India. e-mail: prabhadesikan@yahoo.com

Background: 10 to 15% of TB cases in India are estimated to have extrapulmonary TB (EPTB). Its diagnosis is challenging due to the variety of sample types and protocols for sample processing. In March 2014, India's National TB Control Program adopted the Standard Operating Procedure for use of Xpert MTB/RIF in extrapulmonary (EP) samples. We aim to understand the performance of Xpert MTB/RIF on EP samples in the Central state of Madhya Pradesh, India.

Design/Methods: We retrospectively reviewed the results obtained on EP samples by Xpert MTB/RIF at a National Reference Laboratory for TB, Bhopal Memorial Hospital and Research Centre (BMHRC), Bhopal from April 2014 to March 2015. In addition to valid results, there were errors, invalids and no results. Samples with such results were retested from the samples kept in the refrigerator. We tried to understand the utility of retesting samples kept at 4°C till the time of retesting.

Results: 317 EP samples (86 tissue biopsies, 115 fluids, 46 aspirates & 70 pus) were tested by Xpert MTB/RIF. Of these, 18 (5.6%) were smear positive & 299 (94.3%) smear negative. From 317 samples, TB was detected in 88 (27.7%) samples-Rif resistant (19.3%, 17/88), Rif sensitive (80.6%, 71/88). TB was not detected in 175 (55.2%) samples, while there were 54 (17%) samples which needed retesting (8 indeterminates, 40 errors, 5 no results & 1 invalid result). Of the 17 Rif resistant samples, 2 were pleural fluids, 1 empyema pus, 2 CSF, 6 lymph nodes, 2 granulation tissue from spine, 3 osteomyelitic bones & 1 synovial fluid. Of the 54 samples needing retesting, 15 samples were not available for retesting. On retesting the remaining 39 samples kept at 4°C, 85 % samples (33 out of 39) could be resolved giving an additional gain of 5/ 54 (9%) TB cases. Unresolved results out of the 317 tests were 6 (2%) (2 pus, 1 CSF, 1 Ascitic Fluid, 1 Granulation Tissue, 1 FNAC).

Conclusion: Our results underline the utility of Xpert MTB/RIF in diagnosis of TB including Rif resistance in EP samples. Xpert MTB/RIF positivity over microscopy was 22% (70/317). By Xpert MTB/RIF, 19.3% Rif resistance was detected from EP samples within 2 hours and decision for initiation of treatment of drug resistant

TB could be taken early during the disease. Our results concur with the newly formulated national policy to provide Xpert MTB/RIF upfront for diagnosis of EPTB. To resolve test failures, procedures of retesting & time lag till retesting need further standardisation.

PC-796-04 Utility of GeneXpert® for diagnosis of rifampicin-resistant extra-pulmonary tuberculosis: a retrospective review of 70 cases, SGH, Pune, India

S Girish,¹ A Kagal,¹ S Dharmshale,¹ R Bharadwaj,¹ A Chandanwale,¹ R Lokhande¹ ¹Byramjee Jeejeebhoy Government Medical College, Pune, India. Fax: (+91) 20 2612 6868. e-mail: sunitagirish@rediffmail.com

Background: India lacks evidence-based guidelines for the diagnosis of extra-pulmonary TB (EPTB), resulting in empiric, standard TB treatment of patients, based on clinical symptoms and for prolonged duration of 12-24 months. Culture isolation rates are usually poor as is smear positivity. With the current MDR tuberculosis crisis, it has become even more important to not only isolate the organisms but also do a sensitivity testing. To address these issues we evaluated the sensitivity and specificity of GeneXpert diagnosis of EPTB and the prevalence of Rifampicin resistant tuberculosis in patients with extra pulmonary tuberculosis in a large, urban Indian hospital setting.

Design/Methods: During the period January 2013 to August 2013, Extra pulmonary samples (70) which included pus, pleural fluid, Urine, pericardial fluid, CSF, lymph node aspirate, endometrial tissue and ascitic fluid were obtained from patients, clinically diagnosed as EPTB. All specimens were tested by GeneXpert, Ziehl-Neelsen stained and cultured using standard protocol methods.

Results: A total of 70 patients of EPTB were identified. The mean age of the patients was 34 ± 16.4 years, and male to female ratio was 1:1. Lymph node aspirates (23), pleural fluid (20) and cerebrospinal fluid (13) were the most common samples. All 70 samples were subjected to processing by GeneXpert and 62 were cultured on LJ medium. GeneXpert could detect *Mycobacterium tuberculosis* in 29 samples (41.4 %) and 9 (31%) of these were Rifampicin resistant. Out of 62 samples, cultured growth was obtained in 16 (25.8%) samples. The sensitivity and specificity of GeneXpert as compared to culture was 81.3% and 72.7%. respectively and negative predictive value was 91.43 % (*) indicating probability that the disease is not present when the test is negative.

Conclusion: The current study showed the prevalence of 31% of Rifampicin resistant TB, and picked up an additional 13 cases which were negative by culture. Hence GeneXpert is a rapid and sensitive method for detecting *M. tuberculosis* in extra pulmonary samples which will allow early and appropriate treatment of TB. The National TB Program and chest and infectious disease societies should effectively implement GeneXpert for the early diagnosis and initiation of treatment of EPTB.

Table RIFA resistance and sensitivity in total EPTB cases

GeneXpert Report	No. of cases	%
not detected	41	58.6
MTB detected Rif sensitive	20	27.1
MTB detected Rif resistance	9	8.6
MTB detected Rif indeterminate	4	5.7
Total	70	100

PC-797-04 Clinical features of urogenital tuberculosis

E Kulchavenya,¹ D Kholto bin¹ ¹Novosibirsk research TB Institute, Medical University, Novosibirsk, Russian Federation. e-mail: ku_ekaterina@mail.ru

Background and challenges to implementation: Urogenital tuberculosis (UGTB) is one of the most common forms of tuberculosis (TB) after pulmonary TB.

Intervention or response: With purpose to estimate clinical features of UGTB we analyzed history cases of 131 patients who were under supervision in Novosibirsk anti-TB dispensary in 2008-2011 years.

Results and lessons learnt: Among 131 pts with UGTB 88 (67.2%) had isolated kidney TB (KTB): 10 pts (10.2%) – TB of parenchyma, 35 pts (39.8%) – papillitis, 22 pts (22.4%) – cavernous KTB, 21 pts (21.4%) – polycavernous KTB; in 10 pts alongside with polycavernous KTB male genital TB (MGTB) was diagnosed. In 33 pts (25.2%) MGTB only was revealed: in 14 – orchiepidydidimitis, and in 19 – prostate TB. Main clinical features were pain (flank or perineal), dysuria, hematuria, hemospermia, toxicity, but their frequency varied from 0 till 60.0% in different groups. Among all cohort of UGTB asymptomatic course was in 12.2%, among kidney TB – in 15.9%. Every third patient complained of flank pain and dysuria (accordingly 35.2% and 39.8%), 17% presented toxicity symptoms, 9.1% – renal colic, 7.9% – gross-hematuria. MBT was found in 31.8% in isolated kidney TB as whole. Sterile pyuria was in 25%. The onset of TB orchiepidydydmitis was in 35.7%, hemospermia – in 7.1%, dysuria – in 35.7%. Most common complaints for prostate TB were perineal pain (31.6%), dysuria (also 31.6%), hemospermia (26.3%). MBT in prostate secretion / ejaculate was revealed in this group in 10.5%.

Conclusions and key recommendations: UGTB is multi-variant disease, and standard unified approach is impossible. Join term “UGTB” has insufficient information in order to estimate therapy, surgery and prognosis – as well as to evaluate the epidemiology. Using clinical classification will improve the efficiency of the therapy of UGTB.

PC-798-04 Differential diagnosis of prostate tuberculosis

E Brizhatyuk,¹ E Kulchavenya,¹ A Baranchukova²
¹Novosibirsk TB Research Institute, Novosibirsk, ²Novosibirsk State Medical University, Novosibirsk, Russian Federation. e-mail: elena.brizhatyuk@yandex.ru

Background: Criteria to diagnose urogenital tuberculosis (TB) on its early stages except finding of *Mycobacterium*

tuberculosis and typical patomorphology are nonspecific and vague. The diagnosis becomes evident only with destruction, massive fibrosis and organs failure. Cases of isolated prostate TB are sporadic and accidental histological findings. This is why studying the early diagnosis of urogenital TB is important.

Design/Methods: A total of 83 males age from 36 to 72 years with prostate tuberculosis ($n = 45$; prostate TB group) and chronic inflammatory prostatitis ($n = 38$; chronic prostatitis group) were included in the study. All patients attended the Novosibirsk TB Research Institute between 2006 and 2014. Laboratory tests, ultrasound and radiological examinations, standard 6-12 cores prostate biopsies were done for all of them.

Results: Among the patients with prostate TB 66.7% had active TB in another localizations (lung, urinary system, scrotum). Additionally 8.9% had high density calcifications in a thoracic organ. Among the patients with chronic prostatitis the same signs were found in 7.9% and 15.7% of cases respectively. 35.5% of prostate TB cases has been confirmed by isolating of *M. tuberculosis* from ejaculate and prostatic fluid. Thus, sperm culture and MBT identification by PCR in ejaculate were more sensitive than the same study of prostatic fluid (sensitivity at 0.31 and 0.16, respectively). Specific symptoms which were identified only in prostate TB group patients were high density lesions and cavities in prostate (detected by X-ray examination) and hypoechoic lesions with high density wall (detected by ultrasonography). Large calcifications (28.8% vs. 7.9%; $P < 0.02$), hyperechogenic fibrosis areas (71.1 vs. 47.4%; $P < 0.05$) and seminal vesicles lesion (17.7% vs. 2.6%; $P < 0.05$) were detected more frequently in prostate TB patient. Leukospermia was detected with the same frequency in both groups (39.5% vs. 41.4%), but hemospermia was detected significantly more frequent in patients with prostate TB (in 22.2% vs. 7.8% of cases respectively; $P < 0.05$). Prostate biopsy with subsequent patomorphology, culture and PCR study of samples confirmed the diagnosis only in 20% of patients.

Conclusion: The diagnostic of prostate TB is difficult and based on *M. tuberculosis* detection, patomorphology, radiological examination and patient history (TB in another localization in present or past). But in the absence of specific symptoms indirect sign, such as large calcifications, hyperechogenic fibrosis areas in prostate, seminal vesicles lesion and hemospermia must be taken into account during the diagnostic.

PC-799-04 A randomised controlled trial of the impact of Xpert® on tracheal aspirates within a burden of disease study in South African intensive care units

G Calligaro,¹ G Theron,¹ H Khalfey,¹ J Peter,¹ M Miller,¹ L Michell,¹ I Joubert,¹ K Dheda¹ ¹University of Cape Town Lung Institute and Groote Schuur Hospital, Cape Town, South Africa. e-mail: greg.calligaro@uct.ac.za

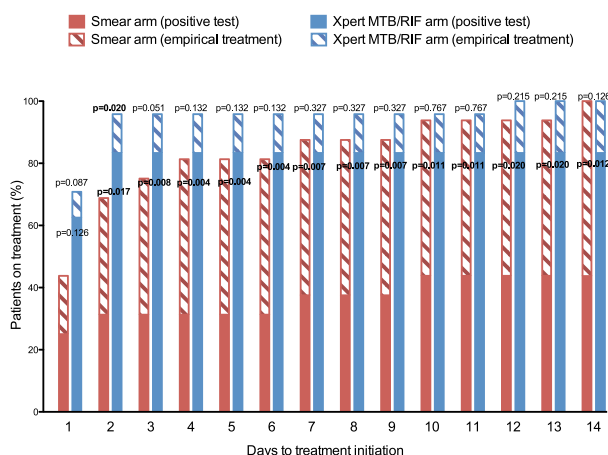
Background: There is limited prospective data about incidence and mortality associated with pulmonary

tuberculosis (PTB) in ICUs, and none on the accuracy and impact of Xpert-MTB/RIF in this setting.

Design/Methods: Ventilated patients with suspected PTB ($n=341$), admitted between August 2010 and July 2013, to 4 hospitals in Cape Town, were, irrespective of the reason of admission, prospectively investigated using microscopy, Xpert-MTB/RIF and culture A. In a sub-study, 242 patients were randomised to microscopy or Xpert-MTB/RIF. The proportion of culture-positive patients on treatment at 48 hours and mortality (28 and 90 days) were endpoints.

Results: 46/317 (14.51%) of TB suspects had culture-positive TB. Culture-positive patients who failed to initiate treatment (aHR 4.49, 95%CI 1.45-13.89) or received inotropes (AHR 4.33, 95%CI 1.62-12.54) were more likely to die, however, TB was not itself associated with death. In the RCT, Xpert-MTB/RIF sensitivity was higher than microscopy (100% vs. 43%; $P < 0.002$). Median time-to-diagnosis was shorter (0.2 days vs. 12.1 days, $P < 0.001$) in the Xpert-MTB/RIF arm. Xpert MTB/RIF resulted in more culture-positive patients on treatment only at 48 hours (92% vs. 53%, $P = 0.043$). There was no difference in stay duration, or overall 90-day mortality (32% vs. 42%, Xpert MTB/RIF vs. smear, $P = 0.1478$).

Conclusion: PTB amongst patients admitted to ICUs in South Africa is common, but mortality is unaffected by PTB. Although Xpert-MTB/RIF on TA is more sensitive, results in rapid treatment initiation and reduces incorrect treatment, it does not increase the number of patients on treatment due to high rates of empirical treatment.



13. Diverse diagnostics

PC-800-04 Can line probe assay be used directly on smear-positive extra-pulmonary samples?

P Dave,^{1,2} P Patel,¹ B Vadera,³ M Ghedia,⁴ H Thanki,³ A Amar Shah,⁴ K Pujara² ¹Intermediate Reference Laboratory, Ahmedabad, ²State TB Cell, Gandhinagar, ³World Health Organization Country Office, Gandhinagar, ⁴World Health Organization Country Office, New Delhi, India. e-mail: drpranavpatel09@gmail.com

Background: Line probe assay (LPA) has been endorsed for the use of first line drug susceptibility testing (DST) of smear positive sputum specimens of pulmonary TB patients. For extra pulmonary and smear negative TB patients, the samples are inoculated in culture and isolates of MTB are tested on LPA. This procedure results in considerable delay and loses the benefit of rapid diagnostics. Hence, in the present study smear positive extra pulmonary specimens were tested directly on LPA and its results was compared with LPA conducted on culture isolates of same specimens.

Design/Methods: In India, LPA has been used under Revised National TB Control Programme since 2009 for diagnosis of multi drug resistant TB patients. The study was conducted at Intermediate Reference Laboratory in the state of Gujarat which was one of the sites of validation study of LPA in the country and has experience of using technology since 2009. All extra pulmonary specimens received in 2014 were subjected to ZN smear microscopy and were inoculated on liquid culture. Smear positive samples were directly tested with LPA. Simultaneously, culture isolates of MTB were also subjected to LPA. Results of LPA conducted on both direct specimen and culture isolates were compared.

Results: A total 391 extra pulmonary specimens were tested on ZN smear microscopy and culture. Out of these, 177 were smear positive and direct specimen could be tested on LPA and among them 88 were culture positive and were tested on LPA. Among those specimen tested directly on LPA, 127 had valid results. This contributed to 32% of all extra pulmonary samples with median time to diagnose rifampicin resistance using direct sample was 5 days (IQR 2-7). In comparison, 88 (23%) extra pulmonary specimens with culture isolates tested on LPA with valid results and with longer turnaround time (18-40 days). Of these 88 specimens, 37 were smear negative and contributed to 14% valid results in addition to smear positive direct specimen. Of 51 specimens tested directly or on isolates with valid LPA results, 50 (98%) had concordance each for rifampicin and isoniazid resistance.

Conclusion: The present observation suggests the advantage of testing extra pulmonary smear positive samples directly on LPA and sequential testing of isolates on specimens which did not have results on direct specimen due to smear negative or invalid results.

PC-801-04 Evaluation of colorimetric detection based liquid culture system for rifampicin testing for *Mycobacterium tuberculosis*

R Singhal,¹ M Bhalla,¹ N Singh,¹ R Sarin,¹ D Behera,² P Sharma³ ¹National Institute of Tuberculosis & Respiratory Diseases, New Delhi, ²Post graduate Institute of Medical Education and Research, Chandigarh, ³Statistics, National Institute of Tuberculosis & Respiratory Diseases, New Delhi, India. e-mail: drritugo@gmail.com

Background: Colorimetric tests employ oxidation-reduction indicator methodology for detection of growth of an organism. World Health Organization has recommended use of these tests for detection of drug resistant tuberculosis as an interim solution in resource constraint settings. In our country, as there is limited experience of colorimetric tests, present study was undertaken to evaluate the accuracy of detection of rifampicin (RIF) resistance in *Mycobacterium tuberculosis* (MTB) in comparison with the results of 1% proportion method.

Methods: Total of 263 MTB positive cultures obtained over three months in the National Reference Laboratory were processed on solid Lowenstein Media. Positive cultures were considered for drug sensitivity by 1% proportion method and tetrazolium assay. Tetrazolium microplate assay was performed using Tetrazolium bromide [3-(4,5-dimethylthiazol-2-yl) - 2,5 - diphenyl tetrazolium bromide] prepared at the concentration of RIF at 1 mg/ml in absolute ethanol. Final RIF concentrations in the wells were set from 4 µg/ml to 0.06 µg/ml. Growth of MTB was detected by change of colour to purple and was confirmed by demonstration of cords in the break-point wells.

Results: The sensitivity, specificity, positive predictive value and negative predictive value were found to be 94.1%, 88.2%, 93.6% and 89.1% with 1% proportion method as the gold standard. Ten and 11 strains were found to be false sensitive and false resistant respectively. Cut off MIC for determining resistance was calculated at ≥ 0.05 µl using MedcalC software. Area under receiver operating characteristic (ROC) curve analysis was 93.1% (95% Confidence Interval 89.9% - 96.4%). The Diagnostic odds ratio (DOR) was 119 suggesting that test has high discriminatory ability. Average turn-around time from culture to drug susceptibility result was found to be 7.2 days whereas average turn-around time for 1% proportion method was found to be 42 days. The cost per patient for drug susceptibility by tetrazolium assay from culture was found to be \$ 2.1

Conclusions: The tetrazolium assay was found to be promising indirect susceptibility assay with turn-around time comparable to commercial liquid culture systems. The test is simple, inexpensive and sensitive for detection of resistance. However, it is desirable to confirm the RIF resistance by other methods. Stringent quality controls and standardization is required for interpretation of the result.

PC-802-04 Evaluation of the bacteriological diagnosis of adult tuberculous meningitis in Indonesia

L Chaidir,^{1,2} J Annisa,¹ S Dian,³ C Ruesen,^{2,6} B Alisjahbana,¹ I Parwati,³ A R Ganiem,³ R Van Crevel² ¹Universitas Padjadjaran, Bandung, Indonesia; ²Radboud University Medical Center, Nijmegen, Netherlands; ³Universitas Padjadjaran/Hasan Sadikin Hospital, Bandung, Indonesia. e-mail: litya.chaidir@gmail.com

Background: Tuberculous (TB) meningitis is the most severe form of TB and causes substantial morbidity and mortality in adults and children. Early recognition and treatment of the disease is believed to be able to reduce the burden of this disease, but this is hampered by the fact that it is often difficult to find bacteriological proof for TB meningitis. Relatively little is known about the performance of various methods for diagnosing TB meningitis in Indonesia.

Methods: We retrospectively evaluated diagnosis among all adult TB meningitis suspects at a referral hospital in West Java, Indonesia, between 2006 and 2013 ($n=916$). Signs and symptoms were recorded, and cerebrospinal fluid (CSF) was obtained for routine examination and microbiological testing. Different methods were applied over time, including Ogawa solid culture ($n=465$), MB/BacT ($n=449$) and MODS ($n=482$) liquid culture, and in-house IS6110 TB PCR ($n=207$).

Results: Head to head comparison showed a higher yield of liquid (40.6%) compared with solid culture (23.2%; $P < 0.01$), and a shorter time to positivity for MODS compared to Ogawa (14 vs. 33 days). Microscopy (ZN) was positive in 4.9 % of clinical suspects, and in 22.9% of Ogawa-positive and 13.8% of liquid culture-positive patients. In-house IS6110-PCR ($n=207$) was positive in 92% of culture-confirmed TB meningitis; and 68% of clinically diagnosed cases (vs. 44% for liquid culture; $P=0.262$); and 100% specificity in non-meningitis controls patients. HIV-infected patients (19.6%) had a lower yield of TB culture (21.2% vs. 34.1%, $P < 0.01$) but not microscopy (6.1% vs. 4.8%) compared to HIV-negative patients, with significant numbers of clinically suspected TB meningitis patients diagnosed with cryptococcal meningitis or PCR-positive cerebral toxoplasmosis (2.4%). Culture yield was higher with larger CSF volumes and lower when TB treatment had been started prior to lumbar puncture. CSF glucose more reliably predicted culture results than protein and cell count.

Conclusion: Microscopy was much less sensitive compared to other methods. Liquid culture was reasonably sensitive but not helpful in clinical decision making. In-house PCR had a good sensitivity for TB meningitis, but too complex to implement in routine practice. There is still an urgent need for faster and more sensitive diagnostic tests for TB meningitis.

PC-803-04 Genotyping of *Mycobacterium tuberculosis* isolated in a national reference laboratory in Baghdad

R Ali,¹ A Al Sudani,² L Salihi,² M Abdulrazaq² ¹Veterinary Directorate/ Ministry of Agriculture, Baghdad, ²Specialized Center for Chest and Respiratory Disease, Baghdad, Iraq. e-mail: ntp.mohammad@gmail.com

Background: Tuberculosis remains a major global health problem. Worldwide it ranks as the second leading cause of death from an infectious disease. Molecular characterization of *Mycobacterium tuberculosis* isolates has helped the study of dynamics transmission of such strains within defined geographical setting. Aim of the study: find molecular epidemiology and phenotypic and genetic characteristics of *M. tuberculosis complex* isolates

Methods: During January-May 2013, a study conducted in Baghdad, 2 genotyping methods spoligo-typing and Mycobacterial interspersed repetitive units – variable number tandem repeats (MIRU-VNTR), alongside with patients demographic data have been utilized to study samples from suspected TB patients.

Results: Spoligo-typing was performed for 106 *M. tuberculosis* strains, the results showed (2.7%) samples given negative and excluded from further investigation, the result of MTC isolates showed the most predominant genotype among tuberculosis strains were Delhi / CAS 37 (37.4%), TUR genotype was observed in (30.3 %) of spoligo-type, while (15.2%) classified as Ghana. (5.1%) isolates belong to Haarelem lineage. Uganda II was found in (3%) isolates, S lineage were found in (2%), NEW-1, LAM, lineage were observed in (1%) to each spoligo-type. Remaining (2%) spoligo-type patterns that did not match with any of the updated in the MIRU-VNTR plus database were classified as “Unknown” and multiple matches of genotypes respectively. MIRU-VNTR was used to assess the diversity of *M. tuberculosis*; there are no clustering rate of this method was observed from these strains. Five loci (QUB-11b, QUB-26, Mtub-21, Mtub-29 and Mtub-34) showed poor discriminatory power (HGDI<0.3). Six loci (MIRU-26, MIRU-39, MIRU-40, ETR-C, QUB-4156 and Mtub-04) were dispersed to discriminate the isolated moderately ($0.3 \leq \text{HGDI} \leq 0.6$). Lastly, thirteen loci (MIRU-2, MIRU-4, MIRU-10, MIRU-16, MIRU-20, MIRU-23, MIRU-24, MIRU-27, MIRU-31, ETR-A, ETR-B, Mtub-30 and Mtub-39) were highly discriminate (HGDI > 0.6).

Conclusions: Genotyping of *M. tuberculosis* is important in the identification of related strains and characteristic disease phenotypes. It can augment classic epidemiology and clinical practice to provide a holistic approach in the investigations, treatment and control of tuberculosis.

PC-804-04 Effectiveness of the detection of LTBI infection using tuberculin skin test and CFP-10-ESAT-6 allergen in children and adults in Moscow, 2013-2014

L Slogotskaya,¹ E Bogorodskaya,¹ O Senchihina,¹ G Nikitina,¹ V Litvinov,¹ P Seltsovs.ky,¹ D Kudlay,² N Nikolenko² ¹Scientific and Clinical Antituberculosis Center of Moscow Government Health Department, Moscow, ²RESEARCH, OJSC ‘Generium’, Moscow, Russian Federation. e-mail: chingy@bk.ru

Background: The Russian company has developed a preparation known as Diaskintest (DST), which represents *Mycobacterium tuberculosis*-specific recombinant proteins CFP10-ESAT6, which are absent in all *M. bovis* BCG substrains and in most of non-tuberculous mycobacteria. It is for skin testing (0.2 mcg/0.1 ml in the same way as the Mantoux test). Aim. To determine the size of the group at highest risk of TB using two different skin tests as a screening method in the children population.

Design/Methods: During 2013 in Moscow the Mantoux test with 2 TU PPD-L was performed in 1 420 084 children and adolescents (97.4% of general children population), positive reactions were observed in 1 019 814 individuals (71.8%), among them DST was performed in 131 361 or 12.9%, predominantly screened people with suspected TB infection, excluding post-vaccination allergy as much as possible. In Moscow more than 90% of children are BCG-vaccinated. During 2014 Mantoux test was performed in 1 429 395 children and adolescents (97.3% of children population), positive reactions were observed in 1 058 191 individuals (74.0%). Among them DST was performed in 88 000 people or 8.4%.

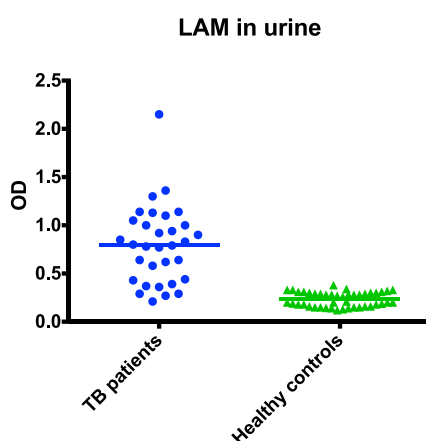
Results: In 2013 among 131 361 Mantoux-positive individuals DST-positive reactions were observed in 3304 cases (2.5%). Among DST-positive persons new cases of TB were identified in 163 (4.9%). Among 131 361 Mantoux-positive new cases of TB were identified in 0.12%. Detection rate was 40 times lower compared to positive DST, $P = 0.000$. In 2014 among 88 527 Mantoux-positive persons DST-positive reactions were in 3573 (4.0%) cases. Among DST-positive persons new cases of TB were identified in 138 (3.9%). Among 88 527 Mantoux-positive children new cases of TB were identified in 0.16%. Detection rate was 24 times lower compared to positive DST, $P = 0.000$. In 2013 among 131361 children examined by 2 skin tests DST-positive reactions were observed in 0.23% of the Moscow child population and in 2014 among 88 527 examined by 2 tests DST-positive reactions were observed in 0.25% ($P > 0.05$). In both years DST- positive reactions were observed in 0.31- 0.35% of the Mantoux-positive children.

Conclusion: Children with DST-positive reactions are the group with the highest risk of TB and this proportion in 2013-2014 was approximately 0.31-0.38% of the Mantoux-positive persons or 0.23-0.25 of the child population.

PC-805-04 A sensitive urinary lipoarabinomannan test for tuberculosis in HIV-negative patients

A Westman,¹ B Hamasur,¹ G Fröberg,¹ J Bellbrant,¹ M Correia-Neves,^{1,2,3} J Bruchfeld,¹ G Kallenius¹
¹Karolinska Institutet, Stockholm, Sweden; ²University of Minho, Braga/Guimarães, ³PT Government Associate Laboratory, Braga/Guimarães, Portugal. e-mail: gunilla.kallenius@ki.se

Background: We have previously developed a diagnostic test for tuberculosis (TB) based on detection of mycobacterial lipoarabinomannan (LAM) in urine.^{1,2} Commercial tests based on our findings have been developed, but a range of studies have shown a very low sensitivity in HIV-negative TB patients. We have now developed an easy to perform test based on a magnetic immunoassay platform, utilizing high avidity monoclonal antibodies for the detection of LAM in urine.³ With this method the analytical sensitivity of the assay was increased 50-100-fold compared to previous tests.³ The method includes a few pipetting and washing steps. A technician can handle 24-48 samples in about 2 h. An ELISA reader is used for a quantitative measurement of the LAM concentration, but can be replaced by either: 1) a battery operated portable ELISA reader or 2) by reading the colour change by the naked eye.



Design/Methods: The aim of the study was to evaluate the efficacy of the urinary LAM assay (Uri-TBdirect) in HIV-negative TB patients. The test was evaluated in adult HIV negative patients with either microbiologically verified TB or clinical TB at Karolinska University Hospital, Stockholm. Healthy individuals with no history of TB were included as controls. By reading the absorbance at 450 nm a cut-off value for the sensitivity and specificity of the test was set at an optical density (OD) of 0.35.

Results: In HIV-negative patients with microbiologically verified TB ($n=32$) the median OD value was 0.80 and in healthy controls ($n=44$) the median OD was 0.24. The sensitivity of the test was 91% and the specificity 98%. The LAM concentration decreased significantly over time in patients who responded to TB treatment.

Conclusion: Here we demonstrate the high sensitivity and specificity of our new urinary LAM detection test. This is in stark contrast to previous studies using available commercial tests with polyclonal anti-LAM Abs where the sensitivity in HIV-negative TB patients was very low.

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PC-806-04 Bedaquiline minimal inhibitory concentration quality control ranges for drug susceptibility testing in a multi-laboratory study

K Kaniga,¹ D M Cirillo,² S Hoffner,³ N Ismail,⁴ B Metchock,⁵ G Pfyffer,⁶ A Sloutsky,⁷ A Venter⁸ ¹Janssen Research & Development, LLC, Titusville, NJ, USA; ²TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Milan, Italy; ³Department of Microbiology, The Public Health Agency of Sweden, Solna, Sweden; ⁴National TB Reference Laboratory, Center for Tuberculosis, National Institute of Communicable Diseases, Johannesburg, South Africa; ⁵Reference Laboratory, Division of TB Elimination, U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁶Department of Medical Microbiology, Center of Laboratory Medicine, Luzerner Kantonsspital LUKS, Lucerne, Switzerland; ⁷Department of Public Health Massachusetts State Laboratory Institute, Jamaica Plain, MA, USA; ⁸TASK Applied Science, SA MRC Centre for TB Research, DST/NRF Center of Excellence for Biomedical TB Research, Division of Molecular Biology and Human Genetics, Tygerberg, South Africa. e-mail: kkaniga@its.jnj.com

Background: To successfully address the global challenge of multidrug-resistant tuberculosis (MDR-TB), reliable and reproducible DST results are critical, both for patient care and for surveillance. The advent of new anti-TB drugs including bedaquiline (BDQ) has highlighted this need. Two multi-laboratory studies were conducted to determine BDQ MIC QC ranges using standardized methods on solid and liquid medium.

Methods: Two multi-laboratory, reproducibility, tier-2, QC studies of BDQ DST were conducted in 8 geographically diverse laboratories following the CLSI M23-A3 and M24-A2 guidelines and using the standard QC reference strain *Mycobacterium tuberculosis* (MTB) H37Rv. Three separate lots of 7H10 and 7H11 agar from different manufacturers (agar dilution study) and 96-well frozen microtiter plates (Thermo Fisher; 7H9 broth microdilution study) were evaluated for the performance on BDQ DST. In each study, BDQ concentrations tested were 0.008–2 µg/ml and 0.008–4 µg/ml, respectively, and polystyrene ware was used. MIC was defined as the lowest BDQ concentration that completely inhibited growth by visual inspection. BDQ MIC frequency, mode, and geometric mean were

calculated. Three- or 4-dilution QC ranges targeted $\geq 95\%$ of the observed BDQ MICs centering on the mode or geometric mean. If one laboratory produced outlying data, their entire dataset (for all 3 media lots) was excluded, and the analyses repeated with the remaining laboratories.

Results: In the agar dilution study, a 4-dilution QC range (0.015 to 0.12 $\mu\text{g/ml}$) centered on the geometric mean included 95.8% of the BDQ MICs on 7H10 agar (204/213 observations with one dataset excluded) and 95.9% on 7H11 agar (232/242) (Table). In the 7H9 broth microdilution study, a 3-dilution QC range (0.015 to 0.06 $\mu\text{g/ml}$) centered on the mode included 95.1% (235/247) of BDQ MICs (Table). BDQ MICs were not affected by the sources of 7H10 or 7H11 agar lots or the frozen microtiter plate lot.

Conclusion: Based on the totality of the data from these two multi-laboratory, multi-country reproducibility studies, the BDQ MIC QC ranges against the MTB reference strain H37Rv were defined (Table). The 7H9 broth microdilution, 7H10 and 7H11 agar dilution methods and reference BDQ MIC QC ranges will provide a standard for BDQ DST in various settings.

Table: BDQ MIC QC ranges against MTB H37Rv

Quality control strain	MIC ($\mu\text{g/ml}$)		
	7H10 agar	7H11 agar	7H9 broth
<i>Mycobacterium tuberculosis</i> H37Rv	0.015 – 0.12	0.015 – 0.12	0.015 – 0.06

PC-807-04 Which attributes within target product profiles for TB diagnostics are the most important to focus on?

T Adepoiyi,¹ L Lillis,¹ H Greb,¹ D Boyle¹ ¹PATH, Washington, DC, USA. e-mail: topeadepoiyi@yahoo.com

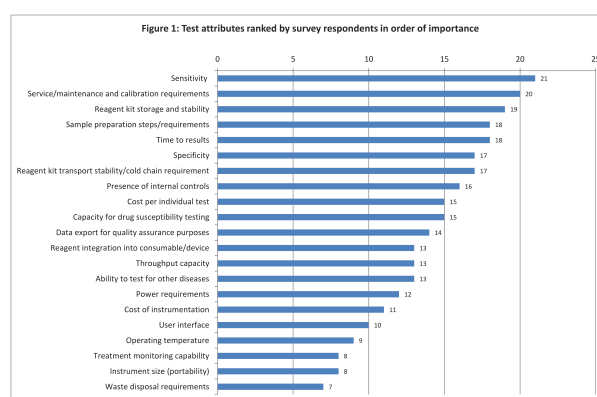
Background: In recent times, an unprecedented range of tuberculosis (TB) nucleic acid amplification technologies have entered the market, or are in late-stage development. To ensure that these tests meet the needs of the TB community, sufficient information should be made available to test developers in response to their key questions, and potential barriers to market entry should be addressed. In this regard, a 2013 publication outlined the top ten questions of 25+ surveyed TB test developers (Pai, 2013). Among the questions posed included; “What are the unmet diagnostic needs and target product profiles (TPPs) of greatest relevance?” There were also two sub-questions; “Which attributes within the TPP are the most important to focus on?” and; “What are the top four to five features that are needed in a TB diagnostic test for developing countries?” (Pai, 2013). In 2014 the WHO released a critical report following a consensus meeting, which identified the highest priority TPPs for new TB diagnostics. Using this information to assist in further addressing the two sub-questions, a range of stakeholders from high-TB burden countries were

surveyed and asked to rank TPP test attributes in order of importance.

Design/Methods: An online survey was administered to 43 purposively selected government and non-government participants representing 14 of the 22 TB high-burden countries. Respondents included laboratory personnel, national TB program managers, technical experts, patient representatives and researchers. Participants were asked to rank 21 TPP test attributes in order of importance using a maximum differential (max-diff) method.

Results: The max-diff approach ranked the 21 TPP attributes in order of relative importance, from most to least important (Figure). Respondents identified sensitivity as the most important TB test attribute, followed by maintenance/calibration, reagent kit storage/stability, sample prep steps, time to results, and specificity (in that order).

Conclusion: Developers can utilise the survey results to prioritize their investments and guide decision-making when trade-offs are required in test development.



PC-808-04 Use of automated MGIT culture tubes with a conventional incubator and manual reader for TB diagnosis in resource-limited settings

A Kruuner,¹ B Kosloff^{2,3} ¹University of Alabama at Birmingham, Birmingham, AL, USA; ²ZAMBART, UNZA School of Medicine, Lusaka, Zambia; ³London School of Hygiene & Tropical Medicine, London, UK. Fax: (+26) 211 254 710. e-mail: bkosloff@yahoo.com

Background: TB programs in resource-limited settings are often unable to equip all of their diagnostic laboratories with automated MGIT 960 instruments. Central laboratories might use a MGIT 960 instrument and automated tubes while peripheral laboratories use the manual MGIT system or solid media with a conventional incubator and manual reading. It would be simpler and more efficient to use the same tubes and reagents in all laboratories. Therefore, we compared use of 7mL automated MGIT tubes incubated in a conventional incubator and read manually to automated MGIT tubes incubated in a MGIT 960 instrument.

Design/Methods: 299 consecutive specimens (238 sputum, 59 urine, 1 bronchial lavage and 1 body fluid) were

processed for TB culture. Two automated MGIT tubes and one Löwenstein-Jensen (L-J) solid medium slope were inoculated with 0.5mL of sediment. One MGIT tube was incubated in a MGIT 960 instrument (automated method). The second tube was incubated in a conventional incubator and read manually on weekdays using a Micro-MGIT Fluorescence Reader (manual method). Negative results were reported after 42 days of incubation. Tubes with bacterial growth from any of the three culture systems were submitted for further workup to confirm the presence of mycobacteria. Identification of all AFB-positive cultures was performed using the Hain CM line probe assay.

Results: The recovery rates of *M. tuberculosis* using the automated method and the manual method were similar: 3% (9/299) for the automated method vs. 2.7% (8/299) for the manual method. Both methods detected the same number of environmental mycobacteria (MOTT). There was no difference in time to detection (TTD) of *M. tuberculosis complex* (16 vs. 16.4 days) or MOTT (16.5 vs. 16.7 days) between the two methods. Contamination rates of 21% for the automated method and 32% for the manual method were much higher than for solid medium (11%). The contamination rate after 35 days was much higher using the manual method compared to the automated method.

Conclusion: This study demonstrates that BD automated MGIT culture tubes incubated in a conventional incubator and read manually yield similar results to the same tubes incubated in a MGIT 960 instrument. The AFB-positivity rate and TTD of all AFB-positive cultures were not significantly different. Additional studies are needed to determine the reason for higher contamination rates after 35 days for culture tubes incubated in a conventional incubator.

14. Gene mutation: the engine behind drug resistance and TB strain diversity

PC-810-04 Genomic characterisation of multidrug-resistant (MDR) and non-MDR *Mycobacterium tuberculosis complex* from two urban referral centres in South Nigeria

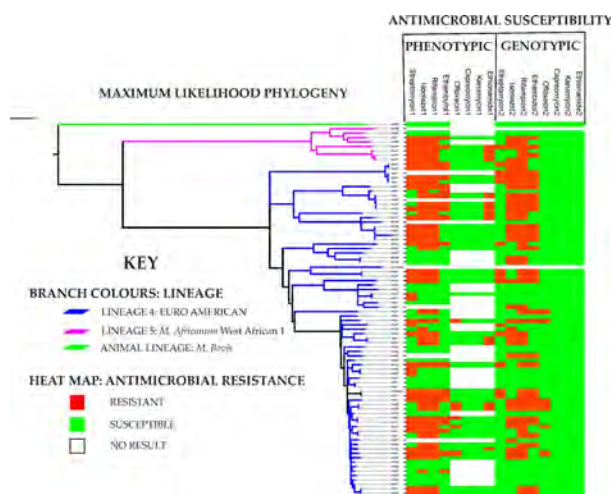
M Senghore,¹ J Otu,¹ A Witney,² A Kehinde,³ O Idigbe,⁴ B De Jong,⁵ M Pallen,⁶ M Antonio¹ ¹Medical Research Council The Gambia Unit, Bakau, Gambia; ²St George's University London, London, UK; ³University College Hospital, Ibadan; ⁴National Institute of Medical Research, Lagos, Nigeria; ⁵Institute of Tropical Medicine, Antwerp, Belgium; ⁶University of Warwick, Coventry, UK. e-mail: msenghore@mrc.gm

Background: The global emergence of multidrug resistant TB (MDR-TB) and extensively Drug-resistant TB (XDR-TB) in the context of HIV threatens to undermine the success that has been achieved in treating drug sensitive tuberculosis. Acquired drug resistance in *Mycobacterium tuberculosis complex* occurs due to chromosomal mutations. However, there is little infor-

mation on the molecular pattern of drug resistance of MTBC strains in West Africa.

Design/Methods: Isolates from the West African Nodes of Excellence for Tuberculosis Aids and Malaria (WANE-TAM) had previously undergone antimicrobial susceptibility testing. Whole genome sequencing was performed for 51 MDR and 40 non-MDR *M. tuberculosis complex* non-randomly selected from Nigerian. The maximum likelihood phylogeny of the isolates was reconstructed from single nucleotide polymorphisms (SNP) in the non-repetitive core genome. Resistance conferring mutations were detected by mapping sequencing reads to the H37Rv reference genome using the software KVARQ. Phylogenetic lineage was inferred using a typing method. Sequencing was unsuccessful for four isolates.

Results: The Euro-American lineage (lineage 4) was the most prevalent in the dataset ($n=78$). Within lineage 4, the Cameroon sub lineage ($n=40$) was the most prevalent. Others including Turkish, Latin American & Mediterranean, Ghana and Harlem were found. Eight isolates belonged to *M. Africanum* West Africa 1 lineage and one was from *M. bovis*. Out of 51 MDR isolates, 45 and 6 were found to belong to lineage 4 and Maf1 respectively. Rifampicin resistance was linked to mutations in *rpoB* while isoniazid resistance was linked to mutations in *katG* and the *inhA* promoter. In a third of isoniazid resistant isolates no resistance mutation was detected. Similarly a known resistance mutation was detected in only a third of streptomycin resistant isolates. In 20 instances mutations in *embB* did not correlate with resistance to ethambutol. Interestingly, in two patients, phenotypic resistance to either ethambutol or streptomycin was developed over the course of treatment. Despite the development of drug resistance there was no change in the genome sequence.



Conclusion: This preliminary data suggests that the molecular mechanisms of resistance in Nigerian *M. tuberculosis complex* may span beyond repository of known resistance-conferring mutations. Enhancing our knowledge of the molecular basis of resistance will aid in development of kits for rapid detection of drug resistance in clinical tuberculosis.

PC-811-04 Characterization of drug-resistant *Mycobacterium tuberculosis* complex species: higher rates of RMP resistance among *M. tuberculosis* patients in Northern Ghana

I D Otchere,¹ A Asante-Poku,¹ S Osei-Wusu,¹ S Aboagye,¹ A Forson,² F Bonsu,³ S Gagneux,⁴ D Yeboah-Manu¹ ¹Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, ²Korle-Bu Teaching Hospital, Accra, ³National Tuberculosis Control Program, GHS, Accra, Ghana; ⁴Swiss Tropical and Public Health Institute, Basel, Switzerland. Fax: (+233) 3021 502 182. e-mail: dyeboah-manu@noguchi.ug.edu.gh

Background: The control of TB is threatened by the emergence of strains resistant to anti-TB drugs. This study analysed for drug resistant conferring mutations among *Mycobacterium tuberculosis* sensu stricto (MTB) and *Mycobacterium africanum* (MAF) strains obtained from two regions (Greater Accra; GAR and Northern; NR) in Ghana.

Design/Methods: Isolates were tested for sensitivity to isoniazid (INH) and rifampicin (RIF) by the micro-plate alamar blue assay. Specific genetic elements of respective drug resistant isolates (inhApro, inhA, oxyR-ahpC, katG and ndh for INH and rpoA, rpoB and rpoC for RIF) were sequenced for mutation analyses. The proportions of drug resistant isolates were compared between species and the two regions

Results: A total of 111 (7.4%), 10 (0.7%) and 39 (2.6%) of the 1490 isolates analyzed were mono-resistant to INH, RIF and MDR. The likelihood of an isolate to be RIF mono-resistant was higher in the NR (1.4%; 2/140) than GAR (0.6%; 8/1350) ($P = 0.0000$) and a similar trend was seen with MDR even though not statistically significant ($P = 0.0636$). However, all the RIF mono-resistant strains were MTB. The propensity for an isolate to harbor katG S315T mutation was significantly higher in MTB (68.1%; 62/91) than MAF (63.6%) ($P = 0.0002$) whereas the opposite was the case for inhApro mutations 36.4%; 4/11 (MAF) and 23.1%; 21/91 ($P = 0.0082$). We detected two rpoC mutations (G332R and V483G), which occurred independently with rpoB S450L respectively. Among the 160 cases infected with strains resistant to at least one drug, 24 were lost to follow up and among those monitored, 36 were cured of which 35 were INH mono-resistant. In addition, treatment for 42 cases failed among which 38 were MDR cases.

Conclusion: The level of drug resistant TB is still fairly low in Ghana however, the rate of RIF mono-resistance (1.4; 2/140) and MDR (5.0%; 7/140) in the Northern region are above the national average. This calls for strengthening of control activities especially DOTs in the north by the NTP.

PC-812-04 Molecular epidemiology of extensively drug-resistant strains of *M. tuberculosis* in Southern Kazakhstan

A Alenova,¹ T Abildaev,¹ P Tarlykov,² D Raimbek,² E Zholdybayeva,² E Ramanculov² ¹National Center for Tuberculosis Problems, Almaty, ²National Center for Biotechnology, Astana, Kazakhstan. e-mail: arike.alenova@mail.ru

Background: The emergence of extensively drug-resistant tuberculosis (XDR-TB) in Kazakhstan compromises proper control of tuberculosis (TB) in the country. However, molecular characterization of XDR-TB isolates can be used for identification of mutations in the genes responsible for emerging patterns of antibiotic resistance.

Design/Methods: Genomic DNA was extracted from 58 XDR-TB isolates using thermolysis method. PCR amplification of nine genetic loci was performed, namely, rpoB, katG, embB, tlyA, eis, rrs, gyrA, gyrB and the fabG-inhA promoter region. PCR products were sequenced using Big Dye Terminator Cycle Sequencing Kit v3.1 (Life Technologies) with the same primers and run on 3130xl Genetic Analyzer (Life Technologies). Mutations were detected by comparison with the *M. tuberculosis* wild-type reference strain H37Rv using SeqScape software v2.6. In addition, VNTR-typing of 24 loci was performed by PCR (MIRU02, MIRU04, MIRU10, MIRU16, MIRU20, MIRU23, MIRU24, MIRU26, MIRU27, MIRU31, MIRU39, MIRU40, ETR-A, ETR-B, ETR-C, Mtub04, Mtub21, Mtub29, Mtub30, Mtub34, Mtub39, Qub-11b, Qub-26 and VNTR53).

Results: A combination of nine genetic loci has confirmed XDR-TB phenotype in 39 isolates (67.2%). The most frequent mutations among the XDR-TB isolates were 315 in katG; 531, 526 and 516 in rpoB; 94, 90 and 91 in gyrA and 1401 in rrs. Novel mutation was detected in 3 (5.2%) isolates causing change of aspartic acid to cysteine at codon 94 of gyrA. The mutation may represent additional molecular marker for fluoroquinolone resistance in *M. tuberculosis*. Also, among these XDR-TB isolates, 55 (94.8%) were classified as Beijing genotype, 2 (3.5%) – LAM and 1 (1.7%) – S genotype.

Conclusion: Sequencing has revealed the presence of major mutations in the genes responsible for resistance to the anti-TB drugs. This work may serve as a basis for new technique suitable for diagnosis and epidemiological control of XDR-TB in Kazakhstan.

PC-813-04 Detection of mutations among rifampicin- and isoniazid-resistant *Mycobacterium tuberculosis* isolates in Kazakhstan

Y Tursynbay,^{1,2} A Akhmetova,¹ L Chingisova,³ V Bismilda,³ A Akilzhanova,¹ U Kozhamkulov¹ ¹Center for Life Sciences, Nazarbayev University, Astana, ²School of Science and Technology, Nazarbayev University, Astana, ³National Center for Tuberculosis Problems, Almaty, Kazakhstan. e-mail: kzulan@mail.ru

Background: According to WHO data, Kazakhstan is positioned as 27th among the highest multidrug-resistant (MDR) TB burden countries worldwide. The aim of our study was to characterize mutations associated with drug resistance to the rifampicin and isoniazid among *Mycobacterium tuberculosis* isolates from Kazakhstan.

Design/Methods: *M. tuberculosis* strains were isolated in 2013 from new TB patients in three different regions of Kazakhstan (Almaty, Kyzylorda and Kostanay). Drug susceptibility of *M. tuberculosis* to isoniazid and rifampicin was determined using the absolute concentration method according to WHO recommendation. Genetic determination of *M. tuberculosis* drug resistance was identified through amplification and sequencing of the *rpoB* and *katG* gene regions and promoter regions of *mabA* (*fabG*)-*inhA*, *oxyR*-*ahpC* operons by automated ABI 3730 (Applied Biosystems) Genetic Analyzer, according to the manufacturer's instructions.

Results: For genetic research, 119 clinical isolates of *M. tuberculosis* was studied, including 92 MDR isolates, 23 isoniazid-resistant isolates and 4 rifampicin-resistant isolates. Among 96 rifampicin-resistant clinical isolates mutations were detected in 93.7% isolates. Six different variants of mutations in 4 codons (Ser531, Asp516, His526 and Leu533) were found. The majority of nucleotide substitutions have occurred at codon 531 on *rpoB* gene (82.3%), where 2 variants of single-nucleotide substitutions were discovered with a predominance of Ser531Leu (81.2%) replacement. In other cases, mutations were observed in less than 10% of cases and comprised: 9.3% at codon His526; 1.04% at codon Leu533; 1.04% at codon Asp516. In 6.2% cases mutations in *rpoB* gene were not found. Mutations that determine resistance to isoniazid were detected in 99.1% cases among 115 isoniazid-resistant isolates. Analysis of the *katG* gene revealed 112 isolates (97.4%) with mutation in codon 315, which leads to amino acid replacement of serine to threonine, including 6 cases (5.2%) with double mutation, when replacement simultaneously takes place in *katG* gene and in -8 and -15 positions of promoter *mabA* (*fabG*)-*inhA* operon. Two clinical isolates had a single mutation in the -15 and -8 positions in the promoter *mabA* (*fabG*)-*inhA*.

Conclusion: Mutations in Ser531Leu (81.25%) of *rpoB* gene and Ser315Thr of *katG* gene (97.39%) were the most prevalent among -rifampicin and -isoniazid resistant clinical isolates in Kazakhstan.

PC-814-04 Trends in pattern of resistance to first-line anti-tuberculosis drugs, Malawi

K Mbendera,¹ L C Chisuwo,¹ F Nyakwawa,¹ L Chaponda,¹ F Kassa,¹ B G Belaine,^{1,2} I Dambe,¹ J Mpunga¹ ¹National Tuberculosis Program, Malawi, Lilongwe, ²International Training and Education Center for Health (ITECH)-Malawi, Lilongwe, Malawi. e-mail: belaine@gmail.com

Background: Malawi is low MDR-TB burden country in southern Africa. The prevalence of MDR(TB was 0.48% among new and 4.8 % retreatment cases according to drug resistance survey conducted in 2010/11. Although the resistance level is low, there are different factors that put Malawi with an increased risk of drug resistance TB. Malawi has managed to shift to RH from EH just after the DRS survey, and there is a continuous interaction with countries in SADEC region that have high MDR(TB burden. Hence the purpose of this analysis is to review the pattern of resistance and inform decision.

Design/Methods: The national Tuberculosis program has established a surveillance system to monitor drug resistance among presumptive MDR TB cases in central reference laboratory. Drug susceptibility tests (DST) were performed on sputum culture positive isolates on four first-line anti-TB drugs: rifampicin, isoniazid, ethambutol and streptomycin. The pattern of resistance to first line anti TB drugs was reviewed. This was also compared to drug resistance survey result of 2010/11. Culture Registers were the source of information. Samples with any resistance for the aforementioned four drugs were included in the analysis.

Results: The total number of samples with any resistance for the four drugs was 68, 91 and 86 in 2012, 2013 and 2014 respectively. The number doesn't reflect the actual number of samples with any resistance as 2014 are still being processed. Resistance to rifampicin (67.44%) was higher among the drugs. Followed by INH (47.44%) and Streptomycin (25.58%) in 2014. This is contrary to DRS done in 2010/11 where resistance to INH was 58.5 % followed by streptomycin (42.3%) and Rifampicin (34.2%) among samples with any resistance collected from previously treated patients.

Conclusion: The analysis showed proportion of resistance to Rif is growing among presumptive MDR-TB cases in the last 3 years. Proportion exceeded resistance to INH. The change could be attributed to change in regimen shift from Ethambutol/INH to Rifampicin and INH. Proportion of samples with resistance to streptomycin has also declined. This may be related to reduce use of streptomycin and increased resistance the other drugs. Although, comparability of DRS with routine data may be affected by different biases including selection bias, the comparison revealed changes that signal alterations in drug resistance pattern and magnitude. Drug resistance survey will provide accurate information.

PC-815-04 The correlation between genetic mutations for isoniazid resistance by line probe assay and phenotypic resistance by drug susceptibility testing

Z Puyen,¹ H Ramirez,¹ E Pacheco,¹ J R Acosta Barriga¹
¹Instituto Nacional de Salud, Lima, Peru. e-mail: zpuyeng@gmail.com

Background: GenoType MTBDRplus is a commercial line probe assay (LPA) utilized in Peru since 2011. This assay allow the identification of the *M. tuberculosis* and its resistance to Rifampicin and/or Isoniazid. This probe is based on reverse hybridization of amplicons to immobilized membrane based probes covering wild type and mutation sequences. Isoniazid resistance is most frequently associated with mutations in *katG* gene and *inhA* gene. The detection of mutation in the *katG* gene is directly related with high level isoniazid resistance and the mutation in the promoter region of the *inhA* gene is related to the low level isoniazid resistance. The aims of this study is to determine whether detected genetic mutations for isoniazid (H) resistance by LPA GenoType MTBDRplus correlate with high or low level phenotypic resistance to isoniazid using Drug Susceptibility Test (DST).

Design/Methods: We compare the results of 8942 smear positive sputum specimens and 7227 culture sample tested with GenoType MTBDRplus, in the National Reference Laboratory of Mycobacteria in Peru from 2011 to 2013, against DST. We selected all the samples with valid result in DST and LPA, 2712 samples (excluding non-growing and contaminated samples). Data of these samples were exported to an EXCEL file and after analyzed with OpenEpi version 3. Comparisons between gene mutations for H resistance using LPA and the low and high phenotypic concentrations of H using DST will be done using Cohen's kappa coefficient, sensitivity and specificity, and positive and negative predictive values using DST as the referent. 95% confidence intervals were used throughout

Table Sensitivity and specificity of LPA (as compared to DST) for detection of levels of isoniazid resistance

	CDST	
	INH 0.2 ug/ml (Low)	INH 1.0 ug/ml (High)
Kat G mutation		
Sensitivity	64.2%	82.2%
Specificity	96.5%	95.6%
VPP	98.4%	96.3%
VPN	45.1%	79.2%
Kappa Cohen's	0.43	0.75
Inh A mutation		
Sensitivity	35.0%	27.6%
Specificity	96.53%	72.3%
VPP	97.06%	58.5%
VPN	31.2%	41.4%
Kappa Cohen's	0.18	<-0.01

Results: Mutation in *KatG* was present in 64.2% (1334) of the samples with low level isoniazid resistance, and 82.2% (1306) of the samples with high level isoniazid resistance. Mutation in *InhA* was present in 34.9% (727)

of the samples with low level isoniazid resistance, and 27.6% (438) of the samples with high level isoniazid resistance.

Conclusion: This study has been done under programmatic conditions. The VPP values of *KatG* mutations for predict resistance to H, are above 95% for low H resistance as for high H resistance. On the other hand, the VPP values of *InhA* mutations for predict resistance to H, are above 95% only for low H resistance, however the sensibility is only 35.0%. Finally, it is important to perform more detail analysis of the mutation implicated in these results.

PC-816-04 Potential of rifabutin in the treatment of rifampicin-resistant tuberculosis

A Van Rie,^{1,2} M Whitfield,³ L Scott,⁴ F Sirgel,³
 Y Voss De Lima,⁴ W Stevens,⁴ R M Warren³ ¹University of Antwerp, Antwerp, Belgium; ²University of North Carolina, Chapel Hill, NC, USA; ³SAMRC Centre for Tuberculosis Research / DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Stellenbosch, ⁴University of the Witwatersrand, Johannesburg, South Africa. Fax: (+1) 919 966 2089. e-mail: vanrie@email.unc.edu

Background: Resistance to rifampicin (RIF) greatly jeopardizes the success of tuberculosis (TB) treatment. WHO guidelines therefore recommend that patients diagnosed with RIF resistant TB initiate treatment with a 5-drug MDR-TB regimen, which is more expensive and has higher level of toxicity compared to first line treatment. Several *rpoB* mutations have been associated with isolates that are RIF sensitive or RIF resistant but rifabutin (RBT) sensitive. RIF or RBT could thus be used in selected patients diagnosed with RIF resistance on Hain MTBDRplus or Xpert MTB/RIF assay, two genotypic assays that are commonly to screen for RIF resistance. The proportion of such patient at population level is not known.

Design/Methods: Individuals diagnosed with RIF resistant TB by Hain MTBDRplus or Xpert MTB/RIF assay in 3 provinces in South Africa (Gauteng, Free State and Eastern Cape) were enrolled in a prospective cohort study. Samples of 314 patients were available for targeted sequencing of the *rpoB* gene and minimal inhibitory concentration (MIC) for RIF at concentrations 0.125-200 microgram/ml. MIC for RBT (at concentrations 0.125 – 2 microgram/ml) was performed on samples representing the different *rpoB* mutations and deletions and different levels of RIF MIC observed in the study population.

Results: Among the 314 enrolled patients, MIC for RIF and *rpoB* sequencing results were available for 291 (93%). Mutations in *rpoB* 531 (45%), 516 (30%) and 526 (13%) were the most frequent. RBT MIC was performed in 43 isolates. Isolates carrying *rpoB* mutations L511P, D516A, D516C, H526N, and 3bp deletion in 518 were sensitive to both RIF and RBT. Isolates carrying *rpoB* mutations D516V, D516Y, D516F, D516E, H526C, dual mutations 511&516 or 512&516 or a 3bp deletion

in 517 were resistant to RIF but susceptible to RBT. Isolates carrying mutation H526L were sensitive to RIF but mixed resistance results were observed for RBT. On population level, 8% of patients diagnosed with RIF resistance on Hain MTBDRplus or Xpert MTB/RIF can be treated with rifampicin and an additional 32% can be treated with Rifabutin.

Conclusion: Rifabutin holds great potential for treatment of patients diagnosed with RIF resistant TB by Xpert MTB/RIF or Hain but this would require knowledge of the exact rpoB mutation/deletion.

15. GeneXpert: the nuts and bolts of TB diagnosis

PC-817-04 Failing Xpert® MTB/RIF modules: When ? What warranty is needed from the customer's perspective? Experience in the DR Congo

E Renard,¹ E Andre^{2,3} ¹Université Catholique de Louvain, Louvain-la-Neuve, ²Université Catholique de Louvain, Brussels, ³Cliniques Universitaires Saint-Luc, Brussels, Belgium. e-mail: emmanuel.andre@uclouvain.be

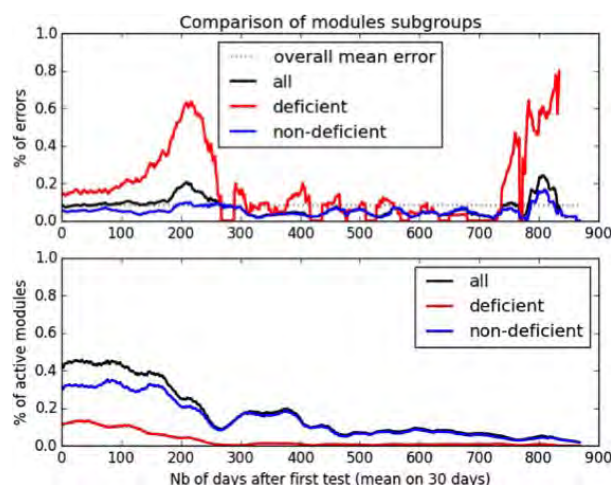
Background and challenges to implementation: Between 2012 and 2014, the Democratic Republic of Congo has gradually implemented 22 GeneXpert machines. The overall proportion of non-valid results (i.e. << error >>, << invalid >> and << no result >>) was 8%. Among the 68 analytical modules composing the 22 GeneXpert, 32% presented a significantly higher rate of non-valid results during the first 3 years of implementation, leading to unnecessary work and consumption of reagents as well as loss of diagnostic opportunities. The objective of this study was to determine whether it was possible to early identify modules presenting sub-optimal performance.

Intervention or response: Data was collected using the GenXchange (UC Louvain, Belgium; NTP, DRC) and XpertSMS (IRD, Pakistan) technology. We separated the modules in two groups: 22 modules identified with a high proportion of non-valid results, and 46 modules presenting normal figures. For each group, we computed the proportion of non-valid results based on time after implementation of the GeneXpert. We used a moving average on 30 days.

Results and lessons learnt: The figures below represent the percentage of non-valid results between the two groups of modules and the progressive decrease in activity of the modules with the time. In the group with a higher rate of non-valid results, all showed signs of dysfunction (proportion of not-valid results higher than 10%) from the first month after implementation and increased significantly with a peak of over 60% around month 7 (210 days). After 7 months of activity, virtually none of these modules was still in activity, compared to the "non-failing" group of modules, which continued reporting tests.

Conclusions and key recommendations: It had been previously reported that 32% of GeneXpert MTB/RIF

modules presented signs of dysfunction during the first three years after implementation. We showed that failing modules present early signs of dysfunction which can be identified as early as the first month after implementation by using adequate automatic reporting systems. We conclude that the one-year free-of-charge warranty from the manufacturer will cover the vast majority of costs related to sub-optimal equipment delivered. Nevertheless, as failing modules can be difficult to identify, it is recommended to implement the adequate surveillance solutions in order to maximize the benefit that can be made from this warranty.



PC-818-04 Stability of Xpert® MTB/RIF reagents in sub-optimal storage conditions: evaluation based on three years' experience in the Democratic Republic of Congo

C Vande Kerckhove,¹ E Andre^{2,3} ¹Université Catholique de Louvain, Louvain-la-Neuve, ²Université Catholique de Louvain, Brussels, ³Cliniques Universitaires Saint-Luc, Brussels, Belgium. e-mail: emmanuel.andre@uclouvain.be

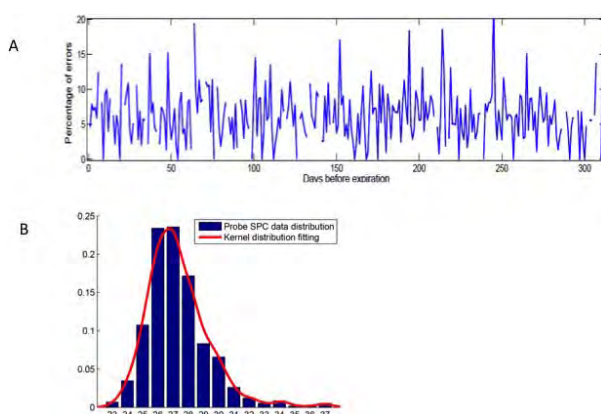
Background and challenges to implementation: Since 2012, the Democratic Republic of Congo (DRC) has performed 23,227 GeneXpert MTB/RIF tests. "Cartridges" are the main consumables for this technology and must be stored between 2 and 28°C. In DRC, these instructions cannot be fully controlled due to local climatic and infrastructure constraints. Based on international quality standards, medical laboratories must perform additional verifications when storage instructions cannot be strictly observed. The objective of this study was to determine the impact of the sub-optimal storage on the quality of reagents.

Intervention or response: Out of 22 lots of cartridges, 3 were considered as defective based on hypothesis testing and were excluded from analysis. Data was collected using the GenXchange (UCLouvain, Belgium; NTP, DRC) and XpertSMS (IRD, Pakistan) technology. We focused on two quality indicators. First, the evolution in the proportion of non-valid results (i.e. "Error", "Invalid", "No result"): we computed for each test the

remaining days left before the expiration date of the cartridge and whether the result was valid or non-valid. The second indicator was the distribution of the internal quality control (Cycle threshold or Ct of the SPC) among all tests.

Results and lessons learnt: Figure A represents the evolution of the proportion of non-valid results over time. The expiration date is the graph origin for all lots of cartridges. There was no significant increase of non-valid results observed when the expiration date was closer. The Histogram (Figure B) represents the Ct distribution for the SPC internal quality control. The empirical probability density function was obtained by fitting a distribution to the data histogram. The Ct values of SPC ranged between 23 and 37, with a mean value at 27.3. We observed a normal distribution of these values.

Conclusions and key recommendations: In this study, we evaluated the quality of Xpert MTB/RIF reagents during their life-cycle post-shipment by the manufacturer. We conclude that sub-optimal storing conditions did not seem to impact the quality of reagents over time, as there was no significant increase of non-valid results in the time and the distribution of SPC Ct was considered as normal, although we cannot definitively exclude from this analysis that high SPC values were not linked to cartridges exposed to particularly sub-optimal storage conditions or linked to cartridges approaching expiry date.



PC-819-04 Etude comparative de la sensibilité de *Mycobacterium tuberculosis* à la rifampicine sur MGIT 960 versus système Xpert®

M Y Fall Niang,^{1,2} A Ba Diallo,^{1,2} A Ndiaye Diawara,^{1,2} G W Ossoga,^{1,2} A Thiam,^{1,2} A Gaye-Diallo^{1,2} ¹Bacteriology and Virology Laboratory, Centre Hospitalier Universitaire Aristide Le Dantec, Dakar, Senegal. e-mail: ossogagedeon@gmail.com

Background: Le but de cet étude est de faire une comparaison des résultats des tests de sensibilité sur milieux liquides MGIT 960 vs. ceux obtenus sur le système Xpert à partir de souches provenant d'échantillons reçus au laboratoire de Bactériologie-Virologie de l'hôpital Aristide Le Dantec.

Design/Methods: 67 souches de *Mycobacterium tuberculosis* provenant de patients tuberculeux reçus pour diagnostic, suivi ou en échec de traitement ont été testés sur le système MGIT 960 (Streptomycine, Isoniazide, Rifampicine, Ethambutol) qui est un test qualitatif sur milieu liquide. Les résultats obtenus ont été ensuite comparés à ceux de l'automate GeneXpert qui est un test de diagnostic in vitro par PCR semi quantitatif en temps réel pour la détection de l'ADN du complexe tuberculosis et la mutation du gène rpoB associé à une résistance à la Rifampicine.

Results: Sur la totalité des souches testées par le système MGIT 960, 41 étaient sensibles à tous les antibiotiques testés et 26 présentaient une monorésistance à au moins un antibiotique. 16 souches avaient donné un profil de résistance à la Rifampicine sur le système MGIT 960 alors que le système Xpert en avait donné que 15 parmi ces derniers. Deux souches résistantes à l'Isoniazide et sensible à la Rifampicine sur MGIT 960 étaient résistantes à la Rifampicine sur le système Xpert.

Conclusion: La sensibilité de la détection des souches résistantes à la Rifampicine est plus importante avec le système GeneXpert que le système automatisé sur milieux liquides MGIT 960 et devrait être mis en place dans les laboratoires pour une meilleure prise en charge des patients tuberculeux sous traitement.

PC-820-04 Online Xpert® recording and reporting system in Kenya

J Ogoro,¹ E Masini,¹ M Kamene,¹ T Miura,² S Chebore,³ M Mburu⁴ ¹National TB Program Kenya, Nairobi, ²Japan International Cooperation Kenya, Nairobi, ³USAID, Centre for Health Solutions, Nairobi, ⁴Centre for Disease Control, Nairobi, Kenya. Fax: (+254) 271 3198. e-mail: jeergo@yahoo.com

Background: Kenya ranks 13th in 22 high TB burden countries and currently has 70 GeneXpert testing sites. For the last four years the recording and reporting has been paper based in diagnosis and surveillance of tuberculosis. Patient/clinician data collection is currently captured online and relay of results through email and text messages to the clinicians immediate they are available through automation. All the GeneXpert equipment are bundled to support the system at minimal costs

Design/Methods: All the generated laboratory request forms have patient demographics, clinicians' mobile numbers and their emails and tests required. Laboratory technologists transcript the request form details onto the same soft copy in the system before they commence running the test. After the testing is completed, the automated system relays results electronically to the emails and mobile numbers of the requesters. Consumption data is captured in the same system through site monthly updates.

Results: Out of the 70 sites trained and supported to use the system, 63 are actively utilizing the system. The online System has prevented missing records and reduced clerical errors. Management of Commodities has been made easier since sites update their monthly stock status before testing since this is an automatic prompt by the

system hence making Forecasting and Quantification process is accurate. Data on actual testing and commodity availability onsite is available too

Conclusion: The adoption of online recording and reporting tools into the testing system has markedly reduced TAT for TB diagnosis and DR-TB patients to be put on treatment faster. Additional benefits include reduction of missing laboratory results.

PC-821-04 Understanding the introduction of new laboratory technology in a poorly resourced setting: the case of GeneXpert® in Nepal

R Khatri,¹ K Dahal,¹ S Baral,¹ I Harper² ¹Health Research and Social Development Forum, Kathmandu, Nepal;

²University of Edinburgh, Edinburgh, UK. e-mail: rrekha.khatri@gmail.com

Background and challenges to implementation: Nepal, a country with a high TB burden, good TB treatment and cure rates, aimed to increase its case finding rate to over 80% by 2015.

Intervention or response: GeneXpert, endorsed by the WHO, was introduced in Nepal from 2011, in an attempt to target the unreached populations and increase the case finding rate through early detection of tuberculosis. A range of REACH funded projects introduced within the National TB programme through its various partners operated under various modalities. While some of the partners have static centers for GeneXpert, one of them is also running mobile services through labs in vans.

Results and lessons learnt: Extensive participant observation of the GeneXpert installation process in TB labs across the country was undertaken. In addition, interviews were conducted with a range of participants in the process, including lab staff, TB-leprosy officers and managers of the organizations implementing the TB REACH programmes. Although the technology does improve the speed of diagnosis and acts as a proxy for MDR diagnosis, broader issues of general laboratory capacity, sustainability and health systems strengthening remained unaddressed. Staff demanded incentives for the additional workload. The maintenance of the machine is a key challenge in poorly resourced settings where basic lab infrastructure is poor, was expensive, time consuming and undermined performance. Nepal currently lacks local capacity for maintaining the machine as the cartridges and modules have to be sent to France when there are problems. The cartridges are also expensive and the question of sustainability as the REACH grants end has yet to be addressed.

Conclusions and key recommendations: Examining the implementation of GeneXpert technology in a poor resource setting like Nepal offers valuable lessons for broader attempts at laboratory and health systems strengthening. Maintaining a technology like GeneXpert (or any other new technological intervention), requires certain preparedness on behalf of government to sustain its effective use. While new technology does support the detection and thus treatment of a disease, it should be

accompanied by wider efforts at strengthening the broader laboratory system itself.

PC-822-04 *Mycobacterium tuberculosis* in the laboratory: when the hunter becomes the hunted

B Magazi¹ ¹University of Pretoria, Pretoria, South Africa. e-mail: beki106@gmail.com

Background: In sub-saharan Africa tuberculosis is a significant occupational problem with the laboratory considered a work area with one of the highest risks regardless of immune status. Staff shortages, and drug resistance confound the problem. There is no safe level of exposure; often it is difficult to directly associate work exposure with disease. Resources limit optimal interventions but simple practical measures can mitigate risk.

Aims and Objectives: The aim was to investigate a potential tuberculosis outbreak in our laboratory with the objective of breaking transmission. A laboratory that performs 2500 *M. tuberculosis* cultures per month. Culture manipulation for drug susceptibility testing is done. 56 staff, including trainees, work here. One non-technical staff member had confirmed tuberculosis in 2015, 2 others had disease in the preceding 5 years.

Methods: Laboratory confirmation was by the Xpert MTB/RIF assay and culture. Staff education sessions on tuberculosis and biosafety were held and symptomatic screening administered. Xpert MTB/RIF and chest radiography was performed on screen positives. Review of previous safety audit reports, risk analysis and environmental testing was carried out. Respirator fit testing was performed. Procedure specific interventions were enhanced and some implemented.

Results: Work areas had no mechanical ventilation. Regularly serviced Class II Biosafety cabinets were in use. Only 5/31 (16%) workers passed fit testing using the TSI PORTACOUNT PRO. None had pre-employment chest X-rays. 100% had completed quarterly health questionnaire, 7 (12.5%) workers reported risk factors for TB. 4 suspects tested negative on Xpert MTB/RIF. Poor access control, inconsistent use of PPE and BSCs were among risky work practices identified through audit.

Discussion: An epidemiological link was not established but 12.5 % had high risk co-morbidity. While regular health surveillance of workers was done, processes for pre-employment and pre-placement assessments have had to be developed. Testing for latent TB infection was not established. Available respirators were unsuitable resulting in more expensive alternatives being sort. Ethnic variations in facial dimensions need to be considered when selecting this PPE. Education of staff and behavioural change was identified as important in ensuring a safety culture. Inadequate infrastructure and poor equipment should not be over emphasised to the neglect of these. Centralised testing is an option.

PC-823-04 Operational implementation of a quality assurance monitoring protocol for GeneXpert® in a hospital setting in Kampala, Uganda

L Asege,¹ D Armstrong,² A Andama,^{1,3} M Joloba,³ F Semitala,^{1,3} J Lemaire,⁴ A Cattamanchi,⁵ C Yoon⁵

¹Infectious Diseases Research Collaboration, Kampala, Uganda; ²Johns Hopkins University, Baltimore, MD, USA; ³Makerere University College of Health Sciences, Kampala, Uganda; ⁴Foundation for Innovative New Diagnostics, Geneva, Switzerland; ⁵University of California, San Francisco, San Francisco, CA, USA. e-mail: lucyasege@gmail.com

Background: GeneXpert MTB/RIF (Xpert), a semi-automated nucleic acid amplification assay for rapid tuberculosis (TB) diagnosis, has undergone widespread scale-up in high TB burden countries since 2010. We assessed the proportion of indeterminate results at the national referral hospital of Uganda, before and after implementation of a standardized quality assurance (QA) protocol.

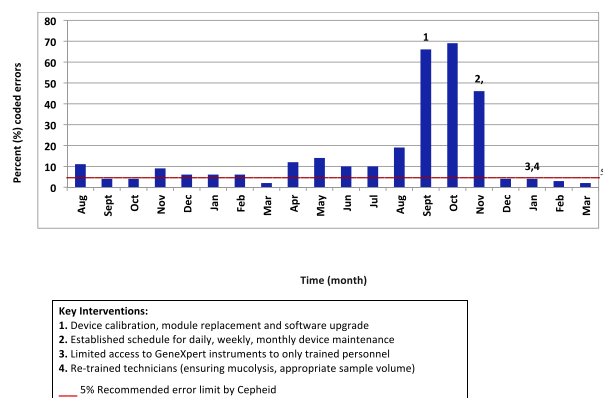
Methods: In July 2013, two Xpert platforms were installed in Mulago Hospital. Routine monitoring of test results and device maintenance was not performed until November 2014, when a standardized quality assurance (QA) protocol was implemented. QA activities included implementation of manufacturer-recommended daily, weekly and monthly device maintenance and the development of a monitoring toolkit to capture key quality indicators including the number of tests performed and the number of indeterminate results (errors and invalids), per month. To evaluate the impact of these QA activities, we extracted test results from archived data stored on both platforms to calculate the monthly frequency of indeterminate results. We then evaluated trends in the type and proportion of indeterminate results before and after implementation of the QA monitoring protocol.

Results: From August 2013 to March 2015, 4362 tests were performed (2448 on machine A, 1914 on Machine B) of which 727 (17%) were positive for *M. tuberculosis*, 560 (13%) showed test errors, and 70 (2%) were invalids. From August 2013 to March 2014, the median error rate was 6% (IQR 4-8%) and exceeded the 5% upper limit established by the manufacturer for 5/8 months (range 2-11%; Figure). Despite calibration and replacement of failed modules in September 2014, error rates continued to increase, peaking at 69% in October 2014. The most common error codes were #2127 (module communication loss, $n = 349$) and #1004 (internal instrument temperature out of range, $n = 83$). Following implementation of our standardized QA protocol, the median Xpert error rate decreased to 4% (IQR 3-4%; range 2-4%).

Conclusion: In the absence of an Xpert QA protocol, error rates rapidly increased and routinely exceeded 5%, resulting in wasted cartridges/lab resources and possible delays in TB diagnosis. For Xpert to achieve maximal impact, a systematic process for monitoring test results and routine device maintenance is required; annual calibration alone is insufficient. Future scale-up of Xpert

should include parallel implementation of a standardized QA protocol.

Figure 1. Proportion of GeneXpert errors by month, from August 2013 to March 2015



PC-824-04 Evaluation of the impact of Xpert® testing on the diagnosis and cascade of care of drug-susceptible tuberculosis in Epworth, Zimbabwe

R Harrison,¹ C Ssonko,² J Greig,² J Arhem,¹ T Maparo,¹ E C Casas,³ D Legrand,¹ D Fusco¹ ¹Médecins Sans Frontières (MSF), Operational Centre Amsterdam, Harare, Zimbabwe; ²MSF, London, UK; ³MSF, Amsterdam, Netherlands. e-mail: rebecca8harrison@gmail.com

Background: This retrospective study aimed to evaluate how the introduction of GeneXpert in 2012 influenced the diagnosis, treatment and outcomes of patients with drug sensitive Tuberculosis in Epworth, Zimbabwe. In 2013, Zimbabwe reported an HIV prevalence of 14% and a TB incidence rate of 409 per 100 000. 69% of TB patients were HIV co-infected. TB case detection rate was estimated at 42%.

Design/Methods: All smear microscopy and GeneXpert results recorded for the 4683 patients registered for any type of TB treatment in Epworth and Overspill polyclinics from 15/3/2010 until 31/12/2013 were recorded. GeneXpert was introduced in 2012 to the onsite laboratory in one of the clinics, whereas previously only fluorescent Smear Microscopy was utilised for bacterial confirmation. Summary descriptive statistics were calculated comparing the pre-GeneXpert and GeneXpert era.

Results: After the introduction of GeneXpert the number of sputum confirmed patients put on TB treatment per month rose from 39 to 49, but the total number of treatments started went from 117 to 88 per month. The median time from sputum test to treatment initiation for smear positive patients was 3 days before and after GeneXpert implementation. Before the implementation, 196 people were tested for TB per month vs. 189 after. 84% (95%CI: 82-86%) of the first sputum submitted during the pre-GeneXpert era were of good quality compared to 67% (95%CI: 64-69%) during the GeneXpert Era. Of all the patients starting treatment at Epworth Polyclinic, 72% (95%CI: 70-73%) successfully

completed treatment before implementation compared to 66% (95%CI: 64-69%) after. Treatment success for pulmonary confirmed MTB went from 71% (95%CI: 68-74%) to 69% (95%CI: 65-72%) and for smear negative cases from 70% (95%CI: 67-73%) to 65% (59%-70%). Death rates of MTB confirmed went from 5% (95%CI: 4%-7%) to 8% (95%CI: 6%-10%), LTFU from 12%(95%CI: 10%-15%) to 9%(95%CI: 7%-11%) and patients with outcomes not evaluated went from 8%(95%CI: 6%-10%) to 12%(95%CI: 10%-14%).

Conclusion: In this context, the introduction of GeneXpert was associated with an increase in number of sputum confirmed TB patients but not with an increase in total TB treatments started. Median time between test and start of treatment remained unchanged while treatment success rate for all cases decreased slightly. Further investigations will be carried out into changes in TB prevalence, false positives amongst smear negative cases and changes in quality of care provision.

16. Retaining our patients in care

PC-825-04 Factors contributing to good TB treatment adherence among patients in North West Region of Cameroon

A Z Achidi,¹ W Mbacham,² I Ndong,¹ M Sander,³ L Ayuk,⁴ P Aseh¹ ¹Catholic University of Cameroon, Bamenda, ²University of Yaounde 1, Yaounde, ³Bamenda Regional Hospital, Bamenda, ⁴Regional Delegation of Public Health, Bamenda, Cameroon. e-mail: achidiasanga@gmail.com

Aim: To investigate aspects of patient and healthcare worker knowledge and behaviour that is contributing to high adherence to TB treatment in the Northwest region of Cameroon, where only 3% of patients are lost to follow-up as compared to the national average of 8% (NTP data).

Methods: A convenient sample of 38 adult TB patients and 18 TB treatment nurses were recruited in the study. In-depth semi-structured interviews were conducted for all study participants. In addition, four focus group discussions (FGDs) were held for three groups of 10 patients each and one group of 10 TB nurses.

Results: From this qualitative assessment, several factors were identified that may potentially contribute to the relatively high TB treatment adherence in this region. From the in-depth interviews administered to TB patients, a majority of patients reported taking their medicine on their own, without a designated treatment supporter, by using an alarm system to remind them of the time to take their treatment (21 of 38 respondents). In addition, the TB nurses surveyed indicated a high level of knowledge about the correct administration of TB treatment including the importance of TB treatment adherence. The patients surveyed also had good knowledge of most aspects of tuberculosis treatment reported little or no feeling of stigmatization by their families or

communities due to the disease and reported a good patient-health service staff relationship during the FGDs. **Conclusion:** These results suggest that in similar settings where TB treatment administration is not directly supervised by a healthcare worker, high rates of treatment adherence and completion may be achieved by other methods, including patient use of mobile phone alarms as treatment reminders and strong engagement by health care workers in patient education at treatment initiation.

PC-826-04 Use of counselling to retrieve and retain lost to follow-up multidrug-resistant patients in India

S Waikar,¹ A Kapoor,¹ B Entoor Ramachandran,² S Chadha² ¹Population Services International, New Delhi, ²International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. Fax: (+91) 114 106 8779. e-mail: swaikar@psi.org.in

Background and Challenges: India accounts for 64 000 MDR-TB cases accounting for 22% of global burden. One of the major challenges in the management of MDR-TB is lost to follow-up (LTFU) patients. Evidence from HIV/AIDS programming indicates that counselling can support adherence to long-term treatment by addressing psychosocial issues. Yet the RNTCP program in India does not offer counselling services for TB and MDR-TB cases.

Intervention: Since April 2014, Population Services International (PSI), under the Global Fund supported Project Axshya is implementing MDR-TB counselling in 28 districts across 12 States. PSI recruited and trained professional counsellors with masters' degrees in social work and 2-3 years of experience in counselling. The key roles of MDR-TB Counsellors include providing facility and home based counselling to all MDR TB patients currently on treatment with an objective to ensure adherence and treatment completion, linking MDR TB patients to appropriate social welfare schemes and retrieving lost to follow up patients before and after the initiation of treatment.

Results and Lessons Learnt: A total of 9878 MDR-TB cases are registered in 28 intervention districts as of December 2014. 275 patients were recorded as LTFU in intervention districts before April 2014. From May'14 to Dec'14, MDR Counsellors tracked and counselled 55% (153) of patients LTFU. Non availability of proper addresses and migration are two major factors for not being able to track the remaining 45% of LTFU cases. 49% (74) of tracked LTFU cases were retrieved by MDR counsellors and brought back on treatment. Empathetic counselling, regular follow-up, catalysing family and social support and MDR patient support group meetings helped to bring these patients back on treatment. MDR counsellors continue to make efforts to retrieve the remaining LTFU cases in the districts, however loss of faith in treatment, intolerance to side effects, substance abuse and regular supply of MDR medicines are some of the key barriers that limit success.

Conclusion: Empathetic counselling, regular follow up, facilitating family and social support and MDR patient support group meetings helps to retrieve LTFU cases. Counselling should be an integral part of RNTCP program. Based on the initial success in MDR-TB counselling, the counselling component is going to be scaled up at 30 additional districts under Project Axshya.

PC-827-04 Poverty induced migration causes TB treatment default in tribal district, Lohardaga, Jharkhand, India: calls to enforce TB and migrant strategy

S Nayak,¹ R Dayal,² S Chadha,¹ V Ghule,³ O Bera,¹ R Pathak,³ A Das,¹ P Mishra,² K Rout⁴ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²State TB Cell, Ranchi, ³World Health Organization Country Office India, Ranchi, ⁴Catholic Health Association of India, Lohardaga, Jharkhand, India. Fax: (+91) 114 605 4430. e-mail: snayak@theunion.org

Background: Jharkhand (India) a tribal dominated state with 26% tribal population (of 35 million) live in hilly & hard to reach terrains, registered 72 227 TB cases including 44 874 (62%) smear positive (S +ve) in 2012 & 13. Lohardaga with 0.5 million population, is a tribal district & comes under 5th schedule of the Indian Constitution with 56% tribal. The paradox is while default rates of new (5%) & re-treatment (RT) (10%) S +ve cases of Jharkhand remains same of 2012 & 13, that of Lohardaga was 10% (new) & 21% (RT) in 2012; 16% and 22% respectively in 2013. The objective of this study is to find out the barriers to high default in tribal areas & strategy to overcome those.

Method: It includes desk review of 811 cases (527 S +ve) with 610 (75%) tribals registered during 2012 & 13 in the context of tribal vis-à-vis non-tribal whose outcomes declared. 25 default patients selected out of 75 S +ve defaulted in a proportion 1:3 and interviewed through a semi-structured questionnaire; 3 Focused Group Discussions (FGDs) were conducted among 7 DOTs Providers, 6 NGOs & 8 programme implementers to address the objective.

Results: Among 811 (550M, 261F) cases, 117 defaulted (15%) that include 94M (17%) & 23F (9%). The case ratio of tribal to non-tribal is 3:1 and in case of default, it is 3.7:1. Among male, default is 17% & 9% in female. Male to female ratio is 2:1 in total case & 4:1 in defaulters, the same in case of tribals are 2:1 & 9:2 respectively. Out of 25 tribal default patients interviewed, 10 (40%) defaulted because of migration to other states for felt need of survival. All (100%) are of education of below 10th standard with less than \$100 monthly income. Further, 16% found to be chronic alcoholic & 12% defaulted due to drug side effect and shifted to private. Most have inadequate knowledge on TB & think of cure after 3/4 months. 7 cases (28%) found dead after defaulting, 3(12%) complete the treatment after re-registration and 1 switched to MDR. The FGD findings stressed upon addressing issues of migration & alcohol practice. It suggests for monetary/

food incentive to check migration along with adequate counselling facility during treatment.

Conclusion: Default in tribal area is deep rooted with issues of migration/poverty, knowledge gap, poor health seeking behaviour & systemic gaps in counselling, follow-up & barrier managements. Tribal TB control needs an integrated style with policy/strategy for migrants, extra HR, fund, admin commitment & linkage mechanism.

Table Cases registered and default status in Lohardaga Tribal district of Jharkhand, India

Particulars	2012			2013			Total		
	Male	female	Total	Male	female	Total	Male	female	Total
Total									
Number of TB cases									
Registered	297	135	432	253	126	379	550	261	811
Tribal	226	96	322	191	97	288	417	193	610
Non-Tribal	71	39	110	62	29	91	133	68	201
Smear									
Positive TB Cases	198	67	265	185	77	262	383	144	527
Tribal	156	52	208	140	63	203	296	115	411
Non-Tribal	42	15	57	45	14	59	87	29	116
Total Default	47	11	58	47	12	59	94	23	117
Tribal	34	6	40	41	11	52	75	17	92
Non-Tribal	13	5	18	6	1	7	19	6	25
Smear									
Positive Default	28	4	32	35	8	43	63	12	75
Tribal	20	2	22	30	7	37	50	9	59
Non-Tribal	8								
Tribal		2	10	5	1	6	13	3	16

PC-828-04 Axshya Project (TS&AP): experience of retrieval of potential TB drug interrupters

A Kumar,¹ P Varma,¹ PSundares,¹ V Panibatl,¹ S Mukhopadhyay,² S Cornelius,² B Samuel² ¹TB Alert India, Hyderabad, ²World Vision, New Delhi, India. e-mail: emailtoarunk@gmail.com

Background and challenges to implementation: Sub Recipient (SR) for Global Fund for Andhra Pradesh State, TB Alert India is implementing Axshya India Project in 7 districts of Telangana & Andhra Pradesh states. The phase 2 of project is being implemented since April 2013. Despite decades of intense drive two deaths occur every 3 min from tuberculosis (TB). The drug resistant cases threaten to undermine the program at various levels. At one level there is the difficulty in treating the cases and on another level are the misconceptions in the community. In the present scenario of universal access to TB care and TB declared a notifiable disease, a look into the challenges faced by the ones struggling to complete the treatment.

Intervention or response: One of project activity objectives is to increase TB treatment adherence among potential Drug Interrupters (missing one week dosage to More than 2 months) retrace them and bring them

back to DOTS treatment. Retrieval of Drug Interrupters, bringing them back to DOTS and ensuring that they have taken the medicines at least for one week time (minimum 3 doses). The project collected the information about the reasons of default during Drug Interrupter retrieval activity. As a part of activity, project staff advise the TB patient on importance of continuation of long TB treatment regimen and counsel addressal of side-effects of drugs, nutritional education, family education, anger management, usage of motivation card for self-motivation, confidence building and restoring self-esteem.

Results and lessons learnt: Between Apr'13 to December 2014, TB Alert has retrieved 619 Potential TB Drug Interrupters (age <18 Yrs- 4%, 19-45 Yrs- 46%, 46-60 Yrs -30% and >60 Yrs -20%, Average 42). Of them 472 (74%) number male, and 147 (24%) were females. The major reasons mentioned for interrupting the drugs is due to side effects 65% (Male- 405 and Female-96) and 21% (Male-35 Female -97) interrupted thinking that they got cured after initiation of treatment.

Conclusions and key recommendations: The experiences of Drug Interrupter Retrieval analysis stressed the need for prompt assistance and greater addressal of side effects and counselling of patients on importance of TB treatment completion.

PC-829-04 Risk factors for loss to follow-up among DR-TB patients on second-line treatment in Kyrgyzstan

A Toktogonova,¹ A Estebesova,^{2,3} E Kotysheva,⁴ S Fedorova,⁵ E Maliukova,¹ N Kurmanova,⁶ A Kadyrov,¹ S Verver^{7,8} ¹National Phthisiatry Center under the Ministry of Health, Bishkek, ²KNCV Tuberculosis Foundation, Country Office, Bishkek, Kyrgyz Republic; ³Open Society Foundations, New York, NY, USA; ⁴Kyrgyz State Medical Academy, Bishkek, ⁵International University of Kyrgyzstan, Bishkek, ⁶Kyrgyz State Medical Institute on Postgraduate Education and Re-training, Bishkek, Kyrgyz Republic; ⁷KNCV Tuberculosis Foundation, Hague, ⁸Academic Medical Centre, AIGHD, Amsterdam, Netherlands. e-mail: aida.estebesova@gmail.com

Background: Kyrgyzstan has one of the highest rates of MDR-TB in the world, with 68% MDR-TB among previously treated patients and 26% MDR-TB among new cases. About 20% of MDR-TB patients are lost to follow-up of treatment (LTFU). Reasons and risk factors are often unknown. The objective of this study was to assess risk factors associated with loss to follow-up from TB treatment among drug resistant patients on second line treatment in Kyrgyzstan.

Design/Methods: Four out of nine regions (oblasts) in Kyrgyzstan were selected for feasibility reasons. Within these regions all new and previously treated drug resistant (DR) TB patients who were over 18 years of age and started second line drugs (SLD) in 2011 and first half 2012 were included from the main national level registry. We studied risk factors by comparing patients successfully treated with patients LTFU.

Results: Out of the expected 625 patients fulfilling the selection criteria, 347 patients' records were found

(56%). Among the 347 records, 288 patients were included for risk factor analysis including 73 LTFU (21%) and 215 successfully treated (62%). 59 patients had other treatment outcomes. The following factors were associated with LTFU in multivariate analysis: being treated in the intensive phase in ambulatory care had a lower risk of LTFU vs. those hospitalized (OR for 0.34, 95% CI 0.13-0.91), having sputum conversion after 6 months or never had a higher risk of LTFU vs. those with sputum conversion within 6 months (OR 1.72, 95% CI 0.93-3.19).

Conclusion: In Kyrgyzstan, drug-resistant TB patients getting ambulatory treatment in intensive phase and patients with early sputum conversion have a lower risk on LTFU than other DR patients. It should be more often considered to treat DR patients on ambulatory care. Patients who do not have sputum conversion after 6 months should get extra attention to prevent LTFU.

PC-830-04 Common difficulties in tracing tuberculosis treatment interrupters

M Mohamad,¹ N A Noor,¹ N Abdullah,¹ W Al-Kubaisy-Abd-Al-Qahar¹ ¹Universiti Teknologi MARA, Sungai Buloh, Malaysia. e-mail: yammo33@yahoo.com

Background: It is stated in the International Standards for TB Care, that healthcare providers (HCP) have the responsibility to address factors of treatment interruption (TI) or discontinuation which failure in doing so is considered as not meeting the international standard. Managing TI is vital in preventing relapse, drug resistance and death due to TB. It is an important activity and that it should be done in organized manner in order to meet the standard care. Our intention in this study is to get our HCP perceptions on the difficulties in tracing TB cases with TI. We hope from the information gathered in this study, we could aid our local health system in addressing any difficulties in tracing TI cases.

Design/Methods: A cross sectional study was carried out in one of the states in Malaysia involving primary HCP who were involved in managing TB patients. Each of the HCP was given a self administered questionnaire which contained demographic profile and their rankings on the reasons of difficulties in tracing TI. The respondents were required to rank 1-10 where 1 being the most important and 10 the least important of 10 reasons of difficulties in tracing TI.

Results: From the 236 healthcare personnel responded in this study, 162 (68.4%) admittedly had some involvement in managing TI. Majority of them are Malays (84.0%), more than half (55.6%) are females and 89.5% of them have attended TB management course. Their median age was 30 years old (IQR 9) and median duration of service was 5 years (IQR 7). The median duration of involvement with TB care was 24 months (IQR 36months). The median number of days for the HCP to act after noticing a TI was 3 days (IQR 6). Only 86 (53.1%) of the HCP, responded to the questions on ranking the reasons of difficulties in tracing TI. The reasons of difficulties according to the most top to the

lowest ranks (mode) were as follows: 1. Incomplete address, 2. Homeless, 3. Non-existent address, 4. Wrong address, 5. Patient from other district, 6. Legal Immigrants, 7. Drug abusers, 8. Illegal immigrants, 9. Patient busy working, and lastly, 10. Patients in detained institutions.

Conclusion: The common difficulties in tracing TI in our setting seem to be around the address issues and being homeless. The incomplete, wrong and non-existent address can be dealt with during the first encounter with TB patients. We recommend that our HCP to develop a system to verify the addresses given by the patients and also obtained other addresses.

PC-831-04 Social issues are an important contributor to lost to follow-up during TB treatment: experience from the North and Northeast of Namibia

L Petersen,¹ S Dalebout,² S Neri,¹ D Moongo,¹ R Indongo,³ F Mavhunga,⁴ T N Shilongo⁴ ¹Project HOPE, Windhoek, Namibia; ²Project HOPE, Millwood, VA, USA; ³United States Agency for International Development, Windhoek, ⁴National TB and Leprosy Programme, Windhoek, Namibia. e-mail: sneri@projecthope.org

Background and challenges to implementation: Project Hope Namibia (PHN) supports the MoHSS in the provision of community-based TB care in 6 districts across 4 Regions. Our work focuses on advocacy, treatment adherence, early identification and referral for TB treatment as well as continued adherence support through DOT and follow up. The program is successful with LTFU of under 5%, but this still represents a significant number that warrants review.

Intervention or response: Community health workers implement the DOT strategy and trained DOT supporters reach the household providing adherence support during treatment. When interruption occurs, tracing is conducted. Once the patient is traced, interventions include restart or continuation of treatment, referral for adherence counselling, and revisiting the role of the treatment supporter.

Results and lessons learnt: Patient records over the past three years indicated 4760 patients registered for TB treatment, of which a total of 95 (2%) were lost to follow-up (LTFU) with more than half lost for less than 4 weeks. Of the 95, 91(96%) were successfully traced. 55% of them gave socio-economic problems as a reason for treatment interruption, 21% gave no reason for interruption, and 14% relocated. LTFU occurred after the initial intensive phase of treatment, the first two months. Side effects that may be experienced during this initial phase did not seem to contribute, however patients may feel clinically better and thus may think treatment is no longer required. The socio-economic problems indicated by 55% of patients were either not identified or attended to prior to initiation or during treatment. In more than 80% of cases, referral for problems, such as lack of finances to travel, alcohol abuse, lack of treatment support, relocation for better

economic opportunities, and others, did not have the desired outcome.

Conclusions and key recommendations: Review the current DOT strategy. Programming should be strengthened and tailored to address social issues at the onset of treatment with structured counselling, referral and follow up and on-going adherence education.

PC-832-04 Improving continuum of care for mine workers on TB treatment across borders during holidays

N Sigwebela,¹ A Hani² ¹University Research, Pretoria, ²Aquity Innovations, Pretoria, South Africa. e-mail: ntombim@urc-sa.com

Background and challenges to implementation: Managing TB across borders presents a challenge to National TB programs (NTP) in Southern Africa. The circular migration to and from labor-exporting countries exacerbates TB transmission across communities. For mine workers with TB, the disruption in the continuum of care results in treatment interruptions caused by various challenges relating to unequal access to care and perceived poor quality of health care services, specifically treatment medicines.

Intervention or response: Aquity Innovations/URSA with funding from the DGF project of the World Bank, implemented a large scale intervention targeting miner workers diagnosed with TB to ensure continued provision of comprehensive TB treatment services across the borders. The primary objective was to promote continued patient support and ensure uninterrupted care for mine workers on TB treatment during holidays. The intervention was implemented in partnership with two mining companies in South Africa as well as the NTPs in each of the 4 countries. The 3 interventions implemented were 1) provision of a "survival kit" to each mine worker which contained educational materials on TB adherence, TB medicines available in their country and a list of health facilities 2) provision of an incentivized mobile phone to receive sms reminders, confirm compliance with treatment and call for help if needed 3) Follow up by nurses to remind the mine worker to take their medications. The nurse was incentivized with \$3 worth of airtime for each follow up made. In addition local media was used to broadcast messages on TB treatment and importance of adherence.

Results and lessons learnt: 399 mine workers with TB participated, >900 sms reminders sent over 10 days, 540 mobile phone responses received from mine workers confirming treatment was taken

Conclusions and key recommendations: The existing systems are adequate for ensuring continuum of care for mine workers with TB. However, for optimal care and support to be achieved, a multi stakeholder approach involving employers, workers and the ministries of health is critical. Incentives for both service providers and patients can also be an effective way of ensuring uninterrupted care.

PC-833-04 Involvement of sub-county health workers in improving cure rates

A Batwaula,¹ A Mugume,¹ R Kimuli,¹ H Ndagire¹ ¹John Snow Inc JSI Research and Training Institute, JSI/STAR-EC, Jinja, Uganda. e-mail: abatwaula@starecuganda.org

Background and challenges to implementation: The national cure rate stands at 40% 2012/2013 National TB and Leprosy Programme (NTLP) reports. Whereas At inception of STAR-EC program in 2009, the overall cure rate stood at 30% for the nine districts of East-central Uganda. The low cure rate was attributed to failure for patients to turn up to facilities for follow up, inadequate information given to the patient at initiation and absenteeism of laboratory staff at time of patient visit.

Intervention or response: JSI with funding from USAID is implementing the STAR-EC program that supports the National TB and Leprosy program (NTLP) to strengthen TB control activities in the nine districts of East Central Uganda. STAR-EC supported a training of Sub-county health workers (SCHW) on smear preparation and TB infection control. This was followed by attachment to a diagnostic facility with in their respective sub-counties for several days to perfect smear preparation skills. The SCHWs were then supported to follow up patients in the communities on a monthly basis to collect sputum and prepare slides from clients that were due for sputum follow up then transported to facilities to be examined by the lab staff

Results and lessons learnt: Over a period of 5 years, there has been progressive improvement in the cure rate cure rate from 30% to 70%%. Active involvement of lay providers trained on slide preparation in the communities in TB control activities improves cure rates as opposed to waiting for patients to visit facilities

Conclusions and key recommendations: In resource constrained settings where human resource for health is a challenge, utilization of community volunteers to support community TB sputum follow is a cost effective strategy.

PC-834-04 An ethnographic account that assesses drug-resistant tuberculosis patients' ability to adhere to treatment in Cape Town, South Africa

L Winterton^{1,2} ¹University of Cape Town, Cape Town, South Africa; ²University of Edinburgh, Edinburgh, UK. e-mail: winterton.laura@gmail.com

Background and challenges to implementation: Approximately 13 000 new cases of Drug-Resistant Tuberculosis (DR-TB) are reported in South Africa every year. Treating DR-TB requires an intensive drug regimen for the duration of the 18-24 months. The pharmacological benefits of the treatment cannot be understated. However, adherence to treatment remains a profound challenge for both patients and their health care providers. I explored how DR-TB patients not only understand and cope with the extreme side effects, but how they develop processes and strategies that alleviate

some of the physical and psychological symptoms that surface during treatment.

Intervention or response: This was a four-month, qualitative ethnographic study conducted in Khayelitsha, Cape Town in 2012. I observed weekly DR-TB support group sessions. I conducted 18 illness history interviews with patients drawn from the support group sessions. I also conducted 5 in-depth case studies where I witnessed patients in their day-to-day lives moving from the clinic, their homes, shopping centres and church. At the end of my research I performed 2 female focus group discussions (FGD) and two male FGDs to elaborate on themes of gender and identity that surfaced during interviews and observations. All interviews and FGD were voice recorded and detailed field notes were kept throughout the research.

Results and lessons learnt: Participants in this study were not labeled as Loss to Follow UP (LTFU), but all participants expressed moments of pausing or experimenting with their treatment as a coping strategy. The patients viewed DR-TB treatment as a conflicting process whereby the side effects felt more damaging than the infection. The profound psychosocial effects from toxic drug regimens destabilise a patient's sense of self and it restructures their most intimate valued relationships.

Conclusions and key recommendations: This research reveals the need for more and continued qualitative research that can capture the social and psychological complexities of treatment seeking behaviour. Side effects are the most significant reason for DR-TB patients LTFU. Patients expressed the need for more psychological and social support that recognises the profound and complex journey from diagnosis to cure. TB treatment strategies require more robust psychological support that can speak to range and complex side effects that surface during treatment and after treatment is complete.

17. Including those affected in care

PC-835-04 Improved urban DOTS strategy: strengthening referral linkages between tertiary hospitals and treatment (DOTS) centres

S Islam,¹ T Hirayama,² M Akramul Islam,¹ S Reza,¹ N Ishikawa,² M Haque,³ M Siddiqui¹ ¹BRAC, Dhaka, Bangladesh; ²Research Institute of Tuberculosis, Tokyo, Japan; ³National Tuberculosis Control Programme, Dhaka, Bangladesh. Fax: (+88) 2988 8026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: Urban TB control is a major challenge for a developing country like Bangladesh. The National Tuberculosis Control Programme (NTP) of Bangladesh first adopted the directly observed treatment short course (DOTS) strategy in 1993 as World Health Organization declared TB as a global emergency. The programme rapidly scaled up in the following years to almost all areas of the country and DOTS was expanded to Dhaka metropolitan city in 2002 through partnership with different NGO partners

including BRAC. Initiatives taken to establish referral linkage between tertiary hospital and peripheral DOTS centres to initiate early treatment.

Intervention or response: TB symptomatic from different corners of the city comes to these 15 tertiary hospitals for diagnosis which is run by BRAC. After diagnosis TB patients residing closely to the hospital are registered and given DOT from the hospital DOTS corners. Medicine is also given to the admitted TB patients. Discharging patients are referred to the peripheral DOTS center according to patients' convenience. Counseling to the TB patient is done to report the referral center in time and to initiate treatment promptly. A referral form (TB-07) is given to the patient to send its part back after reporting into the peripheral DOTS centre.

Results and lessons learnt: In 2014, a total of 7589 TB patients were diagnosed in 18 tertiary level hospitals of Dhaka city. Among them, only 122 (1.6%) were registered in the hospital and most of the TB cases (6789; 89%) were referred to different DOTS centres according to the patients' convenience. Among the referred patients 4667 (69%) were reported to the different DOTS centers following NTP established referral system, 280 (3.6%) left from hospital after discharge without referral slip and others 398 (5%) are died/medicine stopped/self medicated. In 2010, reported case in different DOTS centres was 28% which has been improved in 2014 (69%).

Conclusions and key recommendations: As a large proportion of TB patients are diagnosed from these tertiary hospitals, linkage with the DOTS centers is crucial following NTP established referral mechanism which reduces the number of missing cases after diagnosis. Proper counseling of TB patient is necessary during referral to peripheral DOTS centres.

PC-836-04 Can contact investigation play a role in missing one million in India?

B Entoor Ramachandran,¹ S Chadha,¹ S Waikar²

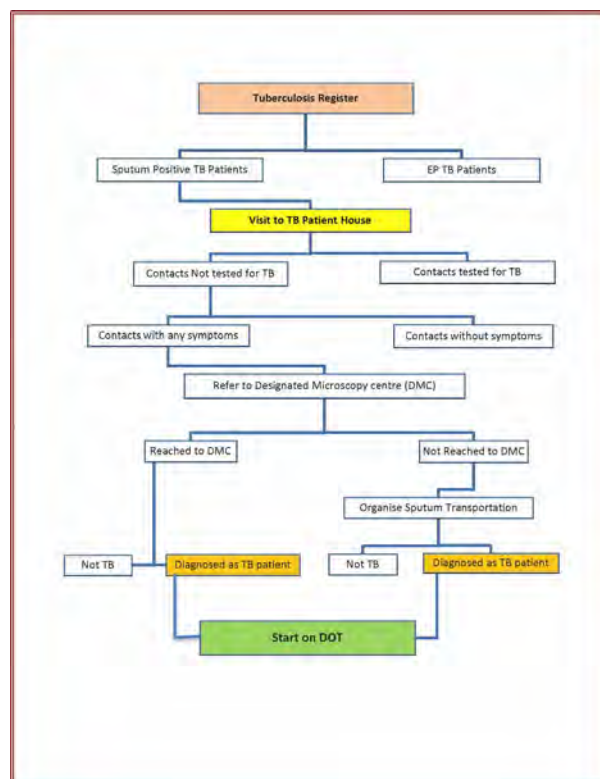
¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ²Population Services International, New Delhi, India. Fax: (+91) 114 605 4430. e-mail: ebaru@theunion.org

Background: The Global TB Report 2013 estimates 2.9 million cases are missed every year (out of the estimated 9 million incident cases) and 31% of these missing cases (~ 1 million) are in India. A recent study in India found 8.7% of household contacts were diagnosed with TB. As per policy, contacts of TB cases should be screened. However, the practice is not systematic across the country.

Intervention: 'Project Axshya' focuses on engaging all sectors to strengthen TB care and control in 300 districts across 21 states of India. This project is implemented by The Union with support from the Global Fund. In order to facilitate early diagnosis, customized Contact Investigation (CI) intervention was designed and implemented in 120 Tuberculosis Units (TU) in 60 project districts with the involvement of community based volunteers

Results: In project locations, 19 269 TB patients (all types) were registered during the period Jul – Dec 2013. The project aimed to reach 12 126 (63%) smear positive TB cases (30 % female) with contact investigation services but only 8425 (69%) TB patients have been reached. There were 5866 children household contacts and 26% (1489) of them were on Isoniazid Prophylaxis Treatment (IPT). 1857 (4%) contacts out of 51 411 (including 12% children below 6 years) were having symptoms during the visit. 997 (54%) adult persons have undergone the diagnosis and 74 (7.42%) of them were diagnosed as having TB. The prevalence of TB among symptomatic children was 7.32%. It was found that 8.02 % of persons were having TB out symptomatics tested under special intervention. Services and cost of CI activity implemented by Project Axshya in India Services offered Rates (covering travel and honorarium) Visit to TB patient household Creating awareness on TB Preparing symptomatics for TB diagnosis 1 US\$ (0 - 20 kilometer) per household 2 US\$ (beyond 20 km) per household Sputum collection and transportation symptomatic from persons to designated microscopy center (DMC) Sharing of lab reports with symptomatics Refer Not TB patients to health facilities Linkage of identified TB patients with treatment centers 2 US\$ (0- 10 km) per symptomatic 3 US\$ (beyond 10 km) per symptomatic.

Conclusion: In India 1 410 880 total TB cases were notified during the year 2014. As per this study, systematic implementation of CI strategy could have identified additional 17 337 TB patients during the year 2014 and this will also increase in proportionate to index case identification.



PC-837-04 A study on awareness and stigma related to tuberculosis among patients attending a district TB centre, Kollam, India

P Teena,^{1,3} P Rakesh,² K Viswanathan,⁴ C Joltin,³ V Sameer,³ P Bhat,³ T Thomas³ ¹School of Medical Education, Kottayam, ²District TB Control Office, Kollam, ³Catholic Health Association of India, Secunderabad, ⁴Indian Medical Association, Delhi, India. e-mail: sameer-valsangkar@chai-india.org

Background: TB stigma leads to TB diagnostic delay and treatment non-completion and has a more significant impact on women and poor or less-educated community members, which is especially concerning given that these groups are often at higher risk for health disparities. TB stigma may worsen pre-existing gender- and class-based health disparities. The study was conducted to evaluate stigma related to tuberculosis among patients in District TB Centre, Kollam.

Design/Methods: The study was conducted over a period of three months among patient attending the District TB Centre, Kollam. Convenience sampling method was used to select 50 of the 120 TB patients attending the center during the study period. Data was collected through personal interview with the help of a structured schedule.

Results: The sample consisted of predominantly (20%) elderly population between the age of 60 to 65 years, among whom 72% were males and 28% were females. Awareness was measured by asking simple questions regarding TB disease and only 30% of people were well aware of TB. 14% of the people agreed and 18% of people strongly agreed that they felt ashamed for having TB disease.

Conclusion: Stigma and lack of awareness are still a factor in tuberculosis which impact the life of these patients and can hinder seeking care. Awareness generation and stigma redressal components must be a part of initiatives against tuberculosis in India.

PC-838-04 Civil society TB forum gears up to protect the rights of TB patients and help ensure social security of TB patients

S Nayak,¹ S Chadha,¹ S Mohanty,¹ A Das,¹ S Diwakar,² P Banuru Muralidhara,¹ K Deepak,² J Thithio³ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ²Catholic Health Association of India, Ranchi, ³Emanuel Health Association, Jharkhand, India. Fax: (+91) 114 605 4430. e-mail: snayak@theunion.org

Background: The Union implements Project Axshya (Global Fund supported) through its eight sub recipients in 21 states of India covering 300 districts. The project is in operation in 15 districts of Jharkhand. Catholic Health Association of India (CHAI), Emanuel Health Association (EHA) and Population Service International (PSI) are the Sub Recipients (SRs) to The Union in Axshya Project in Jharkhand. As part of the project strategy, district TB Forums have been formed in each district with representatives from various cross-sections of the society, such as social reputé opinion leaders,

Doctors, Media persons, retired bureaucrats, business men, philanthropists and more importantly cured TB patients.

Intervention: Axshya Project through its SRs has formed district TB forums in all 15 district of the state. The TB forum's mission is to work for ensuring rights and entitlements of TB patients and strengthening the TB control measures as civil society representatives. The forum advocates with TB patient, TB department, other departments for convergence and social protection of TB patients and civil society groups including media. This paper is an outcome of the qualitative analysis of visit and discussion with members of five District TB Forums in Jharkhand.

Results and lessons Learnt: The forums are successful in taking the cause of TB emergency to the higher level and dissemination at the public by advocating for social security schemes for TB patient, sensitising patients on patient charter, meeting and local political representatives for involvement in TB, providing nutritional support to TB/MDR TB cases (from red cross, their own fund, corporates and advocate with Social Welfare, PRI & Women Child departments) and raising the issues in the media. In Hazaribagh, Garwa & West Singhbhum districts, the forum has raised nutritional support for MDR patients. In Palamu and West Singhbhum districts, the forum has given memorandum to the administration for financial support from the district welfare fund to below poverty line TB patients. Across the state ~30 patients benefitted during 2014. The forum in Hazaribagh has taken up issues of notification.

Conclusion: The District TB Forum represents a solid body representing civil society for the benefits of the TB patients and equally supports to the TB control measures as well. More representation of TB patients in the forum will further strengthen in taking up gaps and barriers starting from cough to cure.

PC-839-04 Systematic screening of contacts of DR-TB patients in Andhra Pradesh: results of a rapid survey

C Chatla,¹ J Jaju,¹ S Achanta,¹ C Purad,¹ R Chepuri Nagaraj,¹ R Samyuktha,² A Sreenivas,¹ P Parmar¹ ¹World Health Organization Country Office India, New Delhi, ²State TB Cell, Hyderabad, India. e-mail: chatlac@rntcp.org

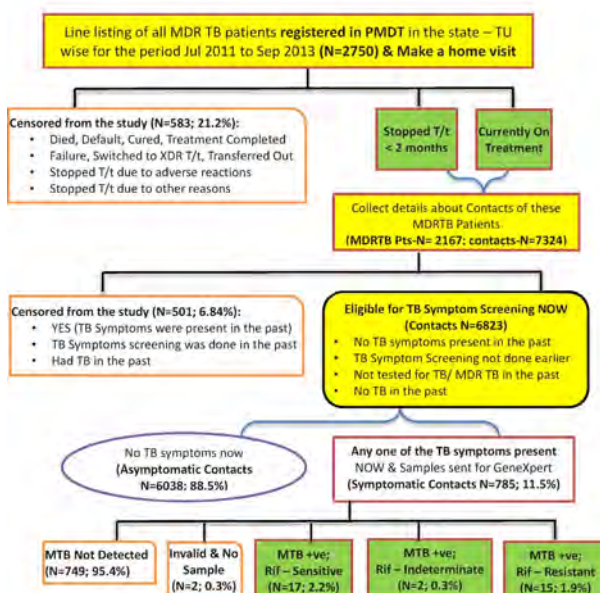
Background: India has the world's highest estimated burden of multi-drug-resistant tuberculosis (MDR-TB). While prevalence of MDR-TB is known to be 2–3% among new TB cases and 12–17% in previously treated cases, programmatic information on the prevalence of MDR-TB/ TB among contacts of known MDR-TB cases is not available. A state wide, house to house systematic screening of household contacts was conducted by RNTCP (Revised National Tuberculosis Control Program), Andhra Pradesh to understand the prevalence of TB/MDR-TB among contacts of known MDR-TB patients under treatment.

Intervention: All MDR-TB patients in the State registered between July 2011 and Sep 2013 and currently on treatment under the programme were listed. House to house visit was made as per pre-defined survey protocol by the programme supervisory staff. All household contacts were screened for symptoms and if found positive, 2 sputum samples were collected (one spot and one morning) and transported for testing on GeneXpert.

Results: A total of 2750 MDR-TB patients were registered between July 2011 and Sep 2013. Of these, 2167 MDR-TB patients were included as per survey protocol and 7324 contacts of these patients were screened for past history of diagnosis or treatment of TB. After excluding those with past history of diagnosis or treatment for TB, a total of 6823 contacts were screened for current signs and symptoms of TB. Of these, 785 had at least one of the symptoms suggestive of TB and their sputum samples were transported and processed on GeneXpert. A total of 34 contacts among 785 tested (4.3%) were diagnosed with TB. Of these 17 were Rif. sensitive (2.2%), 15 were Rif. resistant (1.9%) and 2 were indeterminate results. Of the diagnosed TB cases, 50% ($n=17$) were found to be Rif sensitive TB cases, and 44.1% ($n=15$) Rif resistant TB while the remaining 5.9% Rif indeterminate TB cases.

Conclusions: Based on the estimation of 203 TB cases/lakh population as per Annual Risk of Tuberculosis infection in India and estimation of 2% MDR-TB among new cases (4 MDR-TB cases/lakh population); it can be concluded that being a contact of MDR-TB patient increases the chance of being diagnosed with TB by 2.4 times and MDR-TB by 55 times. Rapid diagnostics must be utilized for early diagnosis in this vulnerable group. It reinforces the need of regular contact screening for early detection and prompt treatment besides educating the patients and family on infection control measures.

Algorithm of selection of eligible contacts and GeneXpert Testing



PC-840-04 Factors associated with performance of tuberculosis support volunteers in Lusaka, Zambia, 2014–2015

Y Toyama,¹ M Ota,^{2,3} Y Onoe,^{1,3} I Njovu,³ Y Takemura,^{1,3} A Ito,^{3,4} G Samungole,⁵ S Hirao,^{2,3} H Ogata,^{2,3} ¹Japan Anti-Tuberculosis Association, Tokyo, ²Research Institute of Tuberculosis, Tokyo, Japan; ³RIT/JATA-Zambia, Lusaka, Zambia; ⁴Japan International Cooperation Agency, Tokyo, Japan; ⁵Lusaka District Community Health Office, Lusaka, Zambia. e-mail: ytoyama@jatahq.org

Background: Mobilising tuberculosis support volunteers (TSs) is a widely employed approach for tuberculosis (TB) control especially in communities that traditionally suffer shortages of health care workers. Yet, individual performance of the TSs and its associated factors have not been fully identified. Since 2012, Japan Anti-Tuberculosis Association conducted a project aiming at early detection of presumptive TB cases as well as providing treatment support through mobilising TSs for urban marginalized sectors at the selected health centres: Bauleni, Chelston, and Chilenje in Lusaka, Zambia through Japan International Cooperation Agency Partnership Programme. Objective of this study is to identify associated factors influencing attendance of TSs to their activities after 3 years of project implementation.

Methods: A cross-sectional study was conducted among TSs at the three clinics. Data were collected through structured interviews. TSs' individual performance was measured by latest 6 month attendance rate to weekly patients' support activities, such as health education and drug adherence support. Descriptive and multiple logistic regression analyses were done to identify factors influencing individual attendance of TSs.

Results: Of the 74 (97% of the total) respondents, the average monthly attendance rate between September 2014 and February 2015 was 83.2% (95% Confidence Interval (CI) 79.2–87.2). The attendance over 80% was likely to be achieved by the TSs who were in a temporary or no work (adjusted odds ratio [aOR]: 8.9, 95%CI 6.8–45.5) and have experienced the executive members among the groups (aOR: 7.0, 95%CI 5.4–37.3). However, the TSs who had secondary education or above were less likely to attend over 80% than those who did not completed the primary education (aOR: 0.10, 95%CI 0.083–0.77). No associations were found between the level of attendance and gender, distance to the designated health facilities, marital status, TB knowledge and satisfaction of project activities.

Conclusion: The study suggested in recruiting TSs, the priority should be those who have a temporary or no work, rather than a fulltime work. Selecting an individual as an executive member of the TSs may facilitate the person to more commit the activities. Those who have secondary education might be more likely to commit other activities, such as income generation activities, than the TS activities and should be selected as TSs with caution.

PC-841-04 Adherencia al tratamiento anti-tuberculoso en pacientes de un ensayo clínico que recibieron acompañamiento comunitario vs. pacientes que reciben tratamiento en condiciones programáticas

J Jimenez,¹ R Yataco,¹ B Martel,¹ D Garcia,¹ L Panduro,¹ E Osso,² C C Contreras,¹ C Mitnick² ¹Socios En Salud Sucursal Perú, Lima, Peru; ²Harvard Medical School, Boston, MA, USA. e-mail: jjimenez_ses@pih.org

Antecedentes: La adherencia al tratamiento y resultados oportunos para TB, disminuyen los riesgos de morbilidad, mortalidad y adquisición de drogoresistencia. El acompañamiento comunitario a través de promotores de salud busca mejorar la adherencia al tratamiento, brindar soporte emocional y educación al paciente durante y después de la administración del tratamiento. El presente estudio describe los resultados de tratamiento de pacientes que se incluyen a un ensayo clínico con acompañamiento comunitario vs. pacientes que reciben tratamiento en condiciones programáticas.

Metodología: Se incluyeron pacientes nunca tratados que iniciaron tratamiento anti-TB, esquema 1, en el periodo setiembre 2013 - agosto 2015, en Lima - Perú. En el mes de marzo del 2015 se revisaron las condiciones de egreso del tratamiento de 160 pacientes, identificándose: pacientes que se incluyeron a un ensayo clínico con acompañamiento comunitario y pacientes que recibieron tratamiento en los EESS de acuerdo a los estándares programáticos. Se colectaron datos de los registros de tratamiento, registrados por personal de investigación o por el personal de salud de los EESS.

Resultados: 127 pacientes fueron incluidos a un ensayo clínico y 33 pacientes recibieron su tratamiento en los EESS del MINSA. De los 127 pacientes que participaron en el ensayo clínico, todos accedieron a un resultado de Prueba de Sensibilidad (PS) Rápida antes de iniciar el tratamiento; y las condiciones de egreso fueron: 94 (74%) curados y 33 (26%) se transfirieron a su EESS por terminación temprana (9 criterios de exclusión del estudio, 17 presencia de eventos adversos, 3 retiro voluntario, 1 recluso en penal, y 3 abandonaron el tratamiento debido al consumo de drogas). De los 33 pacientes que recibieron tratamiento en los EESS, sólo 17 (52%) tuvo un resultado de PS, siendo las condiciones de egreso: 18 (55%) curados, 9 (27%) continúan en tratamiento (3 irregulares y 6 iniciaron tratamiento tardíamente, 2 (6%) cambiaron de esquema de tratamiento por resistencia a INH, y 4 (12%) no tienen datos.

Conclusion: El acompañamiento comunitario y el acceso a la prueba de sensibilidad rápida podrían mejorar la adherencia al tratamiento obteniéndose un mayor porcentaje de curación y término de tratamiento en los tiempos establecidos.

PC-842-04 Improving TB control in urban settings through engagement of community linkage facilitators: the case of Kampala City

C Nanziri,¹ D Lukoye,¹ A Etwom,¹ S Ntudhu,² D Okello,³ B Woldemariam,¹ P G Suarez,¹ E Birabwa⁴ ¹Management Sciences for Health, Kampala ²AIDS Information Centre, Kampala, ³Kampala City Council Authority, Kampala, ⁴USAID UGANDA, Kampala, Uganda. Fax: (+256) 414 235 035. e-mail: cnanziri@msh.org

Background and challenges to implementation: Over 20% of patients that were registered for TB treatment in Kampala were lost to follow up in 2012, DOT was less than 27% and cure rate at 24%, barely half of the national target of 65%. With a daily 1:20 health worker patient ratio (TRACK-TB quarter 2015 report), patient retention and provision of sufficient patient counseling and adherence support through the course of TB treatment was very challenging.

Intervention or response: Kampala Capital City Authority with support from USAID funded TRACK TB project, received 46 community linkage facilitators (CLFs) who actively followed up bacteriologically confirmed TB patients at 20 selected high TB burden health facilities. A monthly average of 12 patients were assigned to each CLF to monitor directly observed treatment (DOT) and sputum smear follow ups at months 2, 5 and 6/8. DOT was considered if the patient treatment supporter was counseled, received health education and ascertained daily patient observation of swallowing TB medicines within the first 6 weeks of treatment. Counseling and health education was done by the CLFs at first contact, at a home visit during the intensive phase of treatment and the biweekly phone calls during the course of continuation phase treatment. Follow up fortnight telephone calls were made to ensure continuity of DOT, track patients who missed appointments and remind patients to keep sputum monitoring appointments.

Results and lessons learnt: By December 2014, the number of new bacteriologically confirmed TB patients receiving directly observed treatment had increased to 95% and the cure rate to 73%. The improvement was consistent at health facilities that were allocated CLFs compared to those that had no CLFs. This was attributed to follow up efforts for DOT and sputum monitoring through home visits and telephone calls. Follow up activities were affected by patient mobility in Kampala; 5% were lost to follow up, 1% were transferred out, 5% died and 16% had a treatment completed outcome. Patients who maintained residence and contacts were easily followed up at CLF supported sites.

Conclusions and key recommendations: Community linkage facilitators helped to improve DOT and cure rates for TB patient in Kampala. This may be a useful intervention that needs to be expanded to other facilities and urban settings with similar challenges.

PC-843-04 Self-reported health of TB patients in Republic of Macedonia: is less more, or is it even more complicated?

D Gudeva Nikovska,¹ F Tozija^{1,2} ¹Faculty of Medicine, University Ss Cyril and Methodius, Skopje, ²National Institute of Public Health, Skopje, Macedonia, Yugoslav Republic. Fax: (+389) 2317 7983. e-mail: dgnikovs.ka@gmail.com

Background: Studying self-reported health is considered an indicator for morbidity and mortality that may be used in primary health care to detect poor health in certain population groups that predicts health care utilization. Prognostic value of self-rated health is particularly important among older adults and literature acknowledge self-rated health as lying at the cross-roads of culture and biology, therefore it needs a collaborative effort between different disciplines to improve understanding of this key measure of health status. The goal of the survey is to assess the socio-economic self-rated health gradient and to describe contribution of behavioral risk factors to this gradient among TB patients in Republic of Macedonia.

Design/Methods: Data is collected through a “nested case-control study”, conducted in the period March – December, 2013. “Cases” are households with TB patient(s) registered in the period July, 2012 – June, 2013 and “controls” are households randomly chosen in cases’ immediate vicinity. The total study population is 605 households with total of 2720 respondents. Self-reported health is assessed through the question *How will you rate your health status today?* with a five-point scale ranging from 1 – very satisfied to 5 – very dissatisfied. Data was analyzed with SPSS 19.0, utilizing logistic regression to measure predictive value of most important factors that determine self-reported health.

Results: Self-rated health was reported as excellent or good by only half of the respondents, with slightly less positive answers among TB cases compared to controls and evident differences in responses for poor or extreme difficulties in everyday life provided by TB patients. Analyzed by group of respondents, 50.8% cases and 49.1% controls assess their health status as good, but differences are significant in categories bad with dominant responses by TB cases with 9.3% vs. 4.9% controls and very bad with 10.3% positive answers among TB cases vs. no such response in controls with statistically significant difference in answers among groups ($X^2=26.410$, $df=4$, $P < 0.001$). Positive association was found between poor rated health and longstanding diseases, such as asthma and arthritis, and education was associated with poor self-rated health. Adding questions on mobility, self-care, pain, cognition, interpersonal activities and affect has only reaffirmed poorer health of TB patients, with statistically significant differences among study groups along all six dimensions assessing mobility.

Conclusions: The study is the first step towards establishment of evidence that self-rated health is an important indicator to be followed by both clinicians and health planners in Republic of Macedonia. Further research is needed to determine if self-rated health

assessment in routine clinical setting can be used to identify groups at risk for increased mortality and other important health outcomes.

18. Don't forget us: migrants and indigenous populations

PC-844-04 Do migrants from developing countries transmit *M. tuberculosis* to locals in the host country? Results of a molecular epidemiology study in Israel

Z Mor,^{1,2,3} E Rorman,⁴ D Chemtob,¹ P Freidlin,⁴ N Cedar,^{1,4} H Kaidar-Shwartz^{1,4} Z Dveyrin,⁴ D Goldblatt⁴
¹Ministry of Health, Jerusalem, ²Ministry of Health, Ramla, ³Tel Aviv University, Tel Aviv, ⁴Ministry of Health, Tel Aviv, Israel. Fax: (+972) 3683 6632. e-mail: turkiz1@netvision.net.il

Background: Health authorities in developing countries raise the concern of a possible transmission of *M. tuberculosis* from migrants who originate in high incidence countries to the local population. This study aimed to assess the penetration of imported isolates of migrants to the local Israeli population and describe the predominant strains in Israel.

Methods: Molecular characterization was employed by 43-spacer spoligotyping and 16 loci MIRU-VNTR typing to all new culture-positive strains reported between 2008 and 2010. Patients were classified by those who were members of a cluster, and to those who were not. In case Israeli-born patients were members of a cluster of *M. tuberculosis* isolates with non-Israeli born patients, they were questioned if they could recall a possible contact with a non-Israeli born individual.

Results: Of 741 culture confirmed cases reported during the study period, 684 (92.3%) were genotyped and 83 different clusters were identified. The major spoligotype families in Israel included Central Asian (CAS) ($n = 140$, 20%), Beijing ($n = 101$, 15%) and T ($n = 160$, 23%). CAS strains were mainly (74%) from Ethiopia, Eritrea and Sudan, while most (66%) Beijing strains were isolated from patients originating from former Soviet Union. Membership in a cluster was more common among younger patients, males, Ethiopian-born, migrants who had longer stay in Israel, smear positive and MDR cases. Of all 83 clusters, 30 (36%) were “mixed”, and included 40 Israel-born and 291 non-Israeli born patients. Of these Israeli-born patients, 24 (55.8%) shared the cluster only with non-Israeli born citizens, 12 (27.9%) shared the cluster with both non-Israeli born citizens and non-Israeli born non-citizens and 4 (9.3%) shared the cluster with non-Israeli born non-citizens. Of all the Israeli-born, 15 (37.5%) could recall a close contact with an individual who was non-Israeli born citizen, but not with non-Israeli born non-citizen.

Conclusions: Cluster analysis indicated that membership in a cluster was more common in migrants, suggesting a probable transmission among communities of foreign-born. Despite the concern of a possible penetration of *M.*

tuberculosis from migrants to Israeli-born in the host country, only limited transmissions were observed from non-Israeli born citizens, yet none from non-Israeli born non-citizen.

PC-845-04 Spatiotemporal analysis of tuberculosis in South American immigrants in Sao Paulo municipality, 2006-2013

P Pinto,¹ M Ribeiro,¹ M J Penon Rujula,¹ C Silveira¹

¹Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brazil. e-mail: priferscaff@hotmail.com

Background: São Paulo is the biggest municipality in Brazil and the principal economic center in the country. Since 1980, São Paulo has been an important destination to immigrants from other countries of South America, especially Bolivia. These immigrants are attracted to work in sewing workshops, where they are subjected to a working system of semi-slavery. This precarious situation exposes them to many health risks and therefore to the tuberculosis (TB) infection. The aim of this study is to describe the spatiotemporal distribution of tuberculosis in South American immigrants in São Paulo from 2006 to 2013.

Methods: Secondary data were obtained from an information system of São Paulo State called TB-WEB. It was considered to the survey all new TB cases in South American immigrants, residents in São Paulo municipality. Socioeconomic variables associated to the monitoring of TB were used to describe the sample. Data were analyzed on EpiInfo. The geocoding of the cases was performed through the QGIS software.

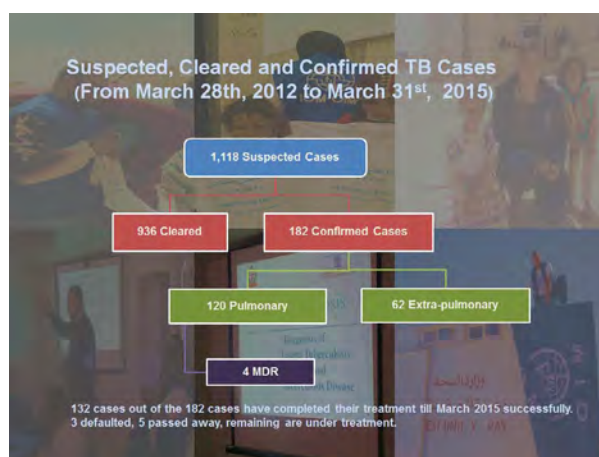
Results: During the study period, 1904 cases of tuberculosis in South American immigrants were reported, representing 4.2% of total cases in São Paulo. In 2006, there were 155 cases, in 2011, there were 307 cases. 63% were male, the dominant age group was 20-39 years (76.5%), the most reported skin color was indigenous (26.7%). In 30.8% of the cases, the education level was 8-11 years of study. 87% were employees and 46% were couriers. The majority of cases (84.3%) were classified as pulmonary tuberculosis, the subjects discovered they were ill after finding a primary health care service (57.2%) and an emergency care service (25.1%). 9.5% did not realize the sputum smear examination, 62.2% had manifestations of TB in results of chest X-ray, 63.4% did the TB supervised treatment, the abandon rate was 15.2% and the cure rate was 74%. On the beginning of the survey, the geocoding showed that the South American immigrants with TB were concentrated in the downtown region, but over the years they are moving to the suburbs especially in the Northern part of the city.

Conclusions: The number of South American immigrants with TB is increasing in São Paulo municipality, and the municipal health system must establish a strong policy to control the disease in these vulnerable groups and improve cure rates. It must also direct health interventions to the most affected areas of the city.

PC-846-04 Enhanced tuberculosis management among Syrian refugees in Jordan

L Kutkut,¹ A Galev¹ ¹International Organization for Migration, Amman, Jordan. e-mail: lkutkut@iom.int

Background and challenges to implementation: Four years of civil war has depleted the health infrastructure in Syria; the exposure to tuberculosis (TB) emerges as a grave public health concern for the Syrian refugees & host populations throughout Jordan (including Za'atari Camp {83 501 refugees} & Azraq Camp{17 738} of the 628 427 registered Syrian refugees in Jordan). Due to the dynamic movement of Syrian refugees, some TB patients migrate to other countries without prior notice, making them difficult to trace. The International Organization for Migration (IOM) in collaboration with Jordanian National Tuberculosis Program (NTP) & with funding support of partners (United Nations & Global Fund), work towards strengthening NTP's capacity to address TB-related challenges that exceed the existing capacities of Jordanian health authorities.



Intervention or response: Targeted TB activities include: - TB Prevention: Starts through IOM's First Health Screening as refugees arrive at the Jordanian Transit Center. Awareness is raised about signs & symptoms of TB & some effective practices to avoid the spread of TB. IOM conducts TB training to primary health care providers to ensure effective referrals of presumptive TB cases. TB Screening: IOM medical mobile teams conduct CX-rays with a portable CX-ray unit coordinated by Jordanian Ministry of Health. TB Diagnosis & treatment: IOM facilitates diagnostic investigations: CX-ray, 3 direct sputum smears, cultures & GeneXpert. All confirmed cases are then referred to NTP to confirm the diagnosis & avail drugs. IOM medical teams monitor Directly Observed Treatment (DOT), side effects & treatment progress. Challenges arise when TB patients do not adhere to treatment thus needing close follow up. 50 % of the 62 extra-pulmonary TB patients suffered from comorbidities & complications like vertebral deformities & paralysis, requiring costly medical interventions ranging from 70-14,000 \$. Transportation for follow

up visits & nutritional support with a high protein diet are provided.

Results and lessons learnt: In spite of all the challenges, the treatment success rate for 2013 cohort was 96% with 1 death & 3 % default rate. The figure summarizes data from March 2012- March 2015.

Conclusions and key recommendations: Joint efforts by the NTP & International community are necessary to address challenges of TB & reduce susceptible TB transmission, morbidity & mortality among Syrian refugees residing in Jordan.

PC-847-04 Overview of the TB situation among migrants in Kazakhstan

S Ussembayeva,¹ E Berikova,¹ S Pak,² T Markabayeva²

¹National Tuberculosis Center, Almaty, ²Representative Office of the Royal Netherlands Tuberculosis Association (KNCV) in Central Asia, Almaty, Kazakhstan. Fax: (+7) 727 291 8658. e-mail: saule_usesm@mail.ru

Background: The successes on stabilization and improvement of TB epidemiological situation were achieved since implementation of WHO strategy in Kazakhstan. For last 10 years the rate of TB population morbidity was reduced for 54.9% and mortality for 77.4%. At the same time for the last years due to economic growth Kazakhstan shifted to category of the countries with active inflow of migrants who are related to vulnerable population with high risk of TB. According to various expert evaluations Kazakhstan annually receives from 300-500 thousand up to 1 million working migrants, the flow of which is weakly regulated by the state.

Design/Methods: In the frame of implementation of 8 Round of the Global Fund project the operational research on the spread of TB, MDR-TB and the TB-HIV among migrants in Astana and Almaty. One of the goals of the research is investigation of the socio-demographic and health characteristics in external migrants diagnosed with tuberculosis for the period 2009-2012.

Results: Results of the research allowed to define the portraits of migrants arrived in Kazakhstan and taken for treatment to TB facilities. Usually they are young people at able-bodied and reproductive age (81%), at the age of 21-50 with secondary education (63.6%). The mostly are males (63.6%) arrived from Uzbekistan, Kyrgyzstan and Russian Federation (86.3%). 42,7% of migrants do not have families and majority (80%) of them are living in Kazakhstan less than 1 year. Third of them are working migrants and more than half (60%) have legal status of staying in the country. More than 90% arrived migrants are renting dwelling with accommodation of more than 3 people. 87% of migrants have duration from the moment of identifying the first symptoms to medical treatment about more than 1 month. TB diagnosis often takes 1 week. Treatment success registered in 72.2% cases but violation of regime is observed in 7,3% cases. Results of cases outcomes of defaulters demonstrated that all of them were lost and went out of the country to unknown direction.

Conclusion: There is a need in Kazakhstan of development and implementation of complex measures on prevention of TB spread among migrants service, PHC network, international and non-government organizations. The activities on quality of TB care for migrants are provided in the Complex Plan to combat Tuberculosis in Kazakhstan for 2014-2020 years.

PC-848-04 Challenges in managing MDR-TB in Dadaab refugee camp on the Kenya-Somali border

D Miriti,¹ H Mohammed,¹ Y Mohamed,¹ A Abdullahi,¹

D Nyachieo,¹ B Opare,¹ N Marwan¹ ¹International Organization for Migration, Nairobi, Kenya. Fax: (+254) 272 2818. e-mail: dmiriti@iom.int

Background: Dadaab refugee camp is located near the relatively porous Kenya-Somalia border with 351 446 registered refugees as of March 2015. Various agencies and partners under the overall coordination of UNHCR provide various services to refugees in the camp including health. The MDR-TB treatment centre is located within the camp. It was opened in 2009 with 20 beds capacity and later expanded to now cater for an average 100 patients. In a partnership with Kenya NTP, CDC, UNHCR, IOM took over the provision of clinical services at this MDR-TB ward in January 2013. The NTP provides the TB medicines and some laboratory reagents, while UNHCR supports the infrastructure maintenance and feeding patients through its implementing health partner in the camp.

Intervention: A dedicated clinical team of 1 clinician, 2 nurses and 6 incentive workers carry out the daily tasks of patient care and management. External consultation services requested as needed. Security provisions with armed escort accompany staff to the ward daily. Directly Observed therapy of TB treatment, continued education, clinical review with adverse effects monitoring and scheduled investigations form part of daily routine tasks. Diagnosis is based on clinical evaluation, sputum testing with smear microscopy, molecular gene Xpert testing as well as culture and DST for both first line and second line TB medicines. The ward is supported by IOM TB laboratories with capacity for all above TB investigations. Baseline blood tests are done in partner laboratories in the city - Nairobi and results sent back to health care worker by email. Moving to a larger facility 2014 made it possible to separate infectious/intensive phase patients from those long converted. The ongoing patient care and management seems to act as a pull factor continually attracting ever increasing patient flow.

Results: 2009 to date, the facility has enrolled a total of 184 patients for MDR-TB treatment. 47 (26%) of these were enrolled in the first four years 2009-2012, 137 (74%) were enrolled in 2013-2015. All the 184 patients tested HIV negative. Female to male ratio is 1:3 (50 and 134 respectively). 5 out of 184 patients were <15 yrs old. 144 patients (78%) are NOT registered refugees but are migrants who crossed into Kenya solely in search of MDR-TB treatment. 94% of all patients were treatment-

after-failure patients. GeneExpert tests supported by DST confirmed MDR-TB for all the patients. No XDR patient identified so far. Approx 80% were malnourished at initiation of treatment. Currently 101 patients have come to a definitive outcome (84% cured, 5% defaulted, 12% died). 83 are still ongoing with treatment. The influx of patients from Somalia continues.

Conclusions: There is need for all partners in Kenya, Somalia and beyond to source for funds to strengthen management of TB both pan susceptible and drug resistant & cut down transmission.

PC-849-04 Tuberculosis among the key health hazards of labor migrants from Central Asia in Moscow

D Kashnitsky,¹ E Demintseva¹ ¹Higher School of Economics, Moscow, Russian Federation. e-mail: kashnitsky@gmail.com

Background: Previous studies of migrants from Central Asia living and working in Russia suggest that their life is characterized by limited resources and social exclusion. Lack of health insurance, scarce information about medical infrastructure and discrimination practices turn out as barriers on migrants' way to timely and quality medical care. Heavy physical work, cramped living conditions and poor nutrition are the factors that largely contribute to the new cases of tuberculosis. Central Asian countries have much higher prevalence of TB than Russia (Kyrgyzstan – 190 per 100 000, Russia – 121 per 100 000).¹ [

Design/Methods: The study is based on the analysis of qualitative interviews with 30 caregivers working in Moscow-based medical facilities including TB clinics.

Results: We have identified several strategies of seeking medical care in Moscow. Migrants tend to disregard an occurring disease as they often do not have time, money and information to seek treatment. Only emergency care is fully accessible to migrants in Moscow free of charge. When diagnosed with an open form of TB migrants still had to be accorded permission from the Moscow city health department before they could be placed in the TB clinic. This often took time so migrants had to remain without treatment while waiting. During this period they continued to work being exposed to their colleagues and roommates and posing a threat to their health. Migrants diagnosed with TB most often preferred to leave Russia to pursue treatment in their home country. Young female migrants are most vulnerable. Besides the pressure of limited resources and discrimination they also experience double stigma both from the host society and from their community.

Conclusion: Migrants with TB lack prompt access to treatment while working in Russia. Their health condition is greatly endangered as well as they pose a serious threat to their roommates, co-workers and all who are around them. The study provides recommendations for city health authorities with regards to addressing the needs of migrants living and working in Moscow including the health rights of migrant TB patients.

1) World Health Organization Country Data 2013. www.who.int/tb/data. Accessed 22 January 2015.

PC-850-04 Utilizing existing health care workers to find TB cases in high-risk migrant populations in Swaziland

V Masuku,¹ P A Dlamini² ¹University Research South Africa, Mbabane, ²National TB Control Program, Manzini, Swaziland. Fax: (+268) 2505 3248. e-mail: victoriam@urc-sa.com

Background and challenges to implementation: Swaziland has highest burden of TB with an incidence of 1349/100 000. The National Tuberculosis Strategic Plan 2015-2019 lacks community approaches that can increase active case finding. The existing treatment supporters' cadre focuses only on TB DOTS and the National TB program (NTCP) sought to investigate the potential use of this cadre in improving active TB case finding (ACF), including amongst high risk groups such as miners and ex miners.

Intervention or response: In June 2014, University Research South Africa (URSA) under the regional Development Grant Fund worked with ex miners associations in Swaziland to identify members to be trained as community TB treatment supporters with an ACF role. The training was done in collaboration with the NTCP and covered basic TB facts, treatment adherence and the TB screening tool. Treatment supporters were deployed to 14 communities (with hot spots identified through ex-miners registration data) and community entry was led by the ex-miners associations. Health facility introductions were done by URSA at 14 health facilities identified to receive referrals for all TB presumptive ex miners identified at household level. Door to door activities were done focusing on TB education, TB screening and referral for all TB presumptive for follow up diagnosis. Care givers were given a target of 10 households each month.

Results and lessons learnt: From July to December 2014, across 2500 households, more than 6000 ex miners were reached with TB education, 5013 screened for TB, 307 found to be TB presumptive and 56 bacteriologically confirmed and initiated on TB treatment, and 148 were already on TB treatment. As a result, the NTCP is now introducing community TB screening as another function for the MoH supported treatment supporters.

Conclusions and key recommendations: The pilot among ex-miners demonstrated that community cadres can be utilized to improve national TB ACF efforts.

PC-851-04 Improving access to TB care services with community extension workers in tribal populations in Central India

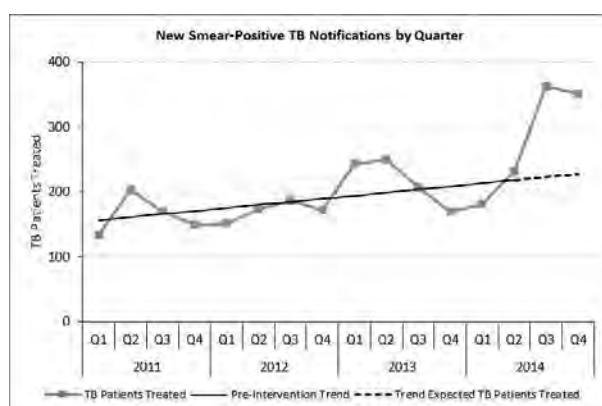
A Vyas,¹ V Jain,¹ C Andrew,² C Jacob,² S Sahu² ¹Asha Kalp, Gwalior, India; ²Stop TB Partnership, Geneva, Switzerland. e-mail: andrewc@stoptb.org

Background: India's tribal and indigenous people often have poor access to TB care services because they live in

isolated and insular communities; the Saharia tribes of Madhya Pradesh province are no exception. Many of their villages are only accessible by foot and are more than 40km away from the closest government health facility. As a result of these barriers, TB prevalence in Saharia communities is thought to be many fold higher than India's national prevalence estimate and few TB patients in these communities receive the care they need. **Design/Methods:** A case finding initiative was set up which employed community health workers (CHWs) to act as an extension of the RNTCP in Saharia communities. CHWs verbally screened the tribes people for symptoms of TB and symptomatic individuals were either referred to the closest microscopy centre or a sputum specimen was collected in the community and transported by CHWs to the laboratory. Smear-positive patients were started on treatment in the community. CHWs were initially given a fixed salary, but salaries were later revised downward and an incentive of INR 225 (USD 3.5) was provided for each patient started on treatment.

Results: 25 679 individuals were verbally screened over 6 months, resulting in the detection of 4744 suspected TB patients. 913 (19.2%) individuals were simply referred to the microscopy centre for further evaluation. This strategy was quickly stopped as it became clear zero referred individuals were tested. 3831 (80.8%) people were asked to provide a sputum sample in the community. 2574 sputum specimens were transported and tested at the nearest laboratory, resulting in the detection of 454 (17.6%) smear-positive TB patients. 447 (98.4%) of these patients were then started on treatment in the community by CHWs. These activities resulted in a +89.4% increase in the number of people treated compared with the year prior, indicating that the patients detected by this initiative would likely not have been treated without CHWs.

Conclusion: This initiative shows that large numbers of previously missed TB patients can be detected and treated using CHWs as an extension of existing health facilities to target tribal populations. We must move past the clinic-based model of care and strengthen community engagement to achieve our ambitious post-2015 targets. Community interventions which show impact, such as this one, should be prioritized for scale-up and replication in other tribal populations.



19. TB in children: epidemiology - I

PC-852-04 Tuberculosis in children in Brazil, 2014

D Gomes Dell'orti,¹ A Torrens,¹ F. Dockhorn,¹ M S Evangelista,¹ R Ruy De Souza,¹ N M Saita,¹ F M Reis,¹ D Barreira¹ ¹National Tuberculosis Programme Brazil, Brasilia, Distrito Federal, Brazil. e-mail: danielle.dellorti@saude.gov.br

Background: The magnitude of childhood tuberculosis (TB) has not been well established yet. It is estimated that, each year, more than half a million TB cases affect children around the world. Consequently, the disease is an important cause of childhood morbidity and mortality in endemic countries, which makes it a public health problem. The objective of this study is to describe tuberculosis cases in children in Brazil during 2014

Design/Methods: A cross-sectional study was developed of new TB cases in children of up to 14 years of age in Brazil. The data were obtained from the National Notification System, based on the tuberculosis cases notified to the National Tuberculosis Control Program (NTP). The clinical and demographic characteristics of tuberculosis were analyzed, as well as the case outcomes. To compile the data, the software Microsoft Excel® was used

Results: In 2014, 67 885 new cases of tuberculosis were registered in Brazil, 3.3% of which were children (2263 cases). The highest incidence occurred in the age group from 10 to 14 years (39.9%) and the lowest in children under one year of age (17.8%). Most children were male (52.8%) and mulatto (46.8%). Concerning the clinical form, 76.0% of the cases were pulmonary and 24.0% extrapulmonary. When considering the total number of pulmonary and extrapulmonary cases per age group, most TB cases affected the age group from 10 to 14 years, with 39.8% and 40.6%, respectively. In addition, an increase was observed in the number of pulmonary TB cases between the ages of less than one year and the group from 10 till 14 years. Most notified cases had a favorable outcome, with 84.7% of cure. Treatment abandonment corresponded to 6.1% and death due to tuberculosis to 1.9%

Conclusion: Different strategies need to be considered to strengthen the disease control and surveillance actions in this vulnerable group, mainly in children under one year of age and in the age group between 10 and 14 years, which showed significant differences in the case incidence rates. Although the outcome of the cure indicator was favorable, it should be highlighted that the abandonment percentage is a source of concern for TB control in children.

PC-853-04 Lessons learned in a children's tuberculosis clinic

A Rossoni,^{1,2} C Oliveira Rodrigues,¹ T Tannus Tahan,¹ B Gabardo,³ M Rossoni,² A Ruffino-Netto⁴ ¹Federal University of Parana, Curitiba, Paraná, ²State University of Ponta Grossa, Ponta Grossa, Paraná, ³State Department of Health of Parana, Curitiba, Paraná, ⁴University of São Paulo, Ribeirão Preto, SP, Brazil. Fax: (+55) 41 3339 1002. e-mail: dearossoni@gmail.com

Background: The diagnosis of tuberculosis (TB) in children is difficult to perform and all efforts to improve it should be encouraged.

Design/Methods: This is a descriptive study, which analyzed data of children treated at an outpatient references for children with suspected of tuberculosis in south of Brazil. We followed up children from 0 to 14 years, from January 2005 to July 2010. The Research Ethics Committee of the hospital approved this study.

Results: In this period in the study 186 children were included: 30 cases (16.1%) were classified as TB and 127 (68.3%) with latent infection and 29 (15.6%) with other diagnoses; 50.5% were male, 81.1% white and median age was 5.8 years. Regarding the demographic characteristic there was no difference between the children sick and not sick. In the TB group 85% showed history of contact with tuberculosis case (especially parents), with a higher frequency of multiple contacts ($P = 0.02$); 85.7% had signs or symptoms and, when present, all of them were statistically more frequent in this group. But when observing the reason for referral the child, only 19% were due to clinical symptoms. Among all children directed by clinical symptoms, after detailed analysis of the case and in some cases performed therapeutic measures nontuberculous, only 30% remained as symptomatic (found lower in the TB group $P < 0.01$). Among the tests performed 41.5% of children who had abnormal X-ray, with repetition of the exam only 1 remained abnormal; 23.2% of TST need to be repeated for being initially non-reactors, of which 14% turned positive.

Conclusion: The main reason patients' referral was the history of contact with tuberculosis, thus concluded the importance of active search of cases. As well, the importance of judicious analysis of these children, by trained professionals, because a lot of tests or clinical symptoms may be erroneously interpreted as suggestive of TB, when in reality there aren't; being necessary, sometimes, the repetition of the exams and previous therapies before the specific drugs for TB.

PC-854-04 Risk factors for unfavorable treatment outcomes in DOTS-treated pediatric tuberculosis patients

S Shelke,¹ R Bollinger,² A Chandanwale,¹ A Deluca,³ N Gupte,² P Adhav,¹ D Kadam,¹ A Gupta² ¹B.J. Medical College, Pune, India; ²Johns Hopkins University School of Medicine, Baltimore, MD, ³Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: drshelke@rediffmail.com

Introduction: Indian children with tuberculosis (TB) treated with DOTS under programmatic conditions have 10–20% unfavorable treatment outcomes. Ascertaining risk factors for poor outcomes will help authorities take corrective actions to improve the program.

Methods: We conducted a retrospective analysis of children with TB diagnosed and treated in the year 2013, in 6 TB Units of Pune city, India. Unfavorable treatment outcome was defined as failure to respond clinically, death or loss to follow-up. Categorical variables were compared by Fisher's exact test. Treatment completion rates, adjusted odds ratio (AOR) with confidence intervals (CI), univariate and multivariate logistic regression analysis was done. We included age, sex, clinical category, type of TB treatment, HIV infection and type of TB in the model.

Results: A total of 3645 TB patients were registered in 2013, under the Revised National TB Control Programme (RNTCP) in Pune city. Of these, 212 (5.82%) were children and 125 (59%) of these were female. Pulmonary TB was diagnosed in 110 (50.5%) and 102 (46.8%) were diagnosed as extra pulmonary TB (EPTB). Among the EPTB 71 (69.6%) had lymphadenitis. Twenty (9.4%) of the children were HIV-infected. Twenty (9.4%) of children had an unfavorable treatment outcome. Of these 8 were loss to follow up, 9 died and 2 failed to respond clinically. WHO Category II TB patients were at greater risk for unfavorable treatment outcome, compared to category I newly diagnosed patients (AOR=8.4, CI: 2.1–12.4, $P < 0.001$). Compared to uninfected children, HIV-co-infected children had a greater risk of unfavorable outcome (AOR= 3.1, CI: 1.2 – 3.3, $P = 0.045$).

Conclusions: The study illustrates HIV+ children and Category II patients had increased odds of unfavorable outcomes and these patients may benefit from more stringent frequent monitoring and counselling. This indirectly accentuates that patients in Category I should also be thoroughly encouraged and supervised so that we have very few Category II patients. New guidelines by RNTCP recommends daily regimen to HIV + pts. As an extension of this policy, we recommend daily observation of category II patients, as they may benefit from the same. Further studies need to be done to understand whether daily treatment for Cat II and HIV+ children reduces unfavorable outcomes.

PC-855-04 The epidemiology of childhood tuberculosis in Japan

S Yoshimatsu,¹ A Ohkado,^{1,2} K Uchimura,¹ K Izumi,^{1,2} L Kawatsu,¹ K Ito¹ ¹Research Institute of Tuberculosis (RIT)/ Japan Anti-Tuberculosis Association (JATA), Kiyose, Tokyo, ²Biomedical Sciences, Nagasaki University Graduate School, Nagasaki, Japan. e-mail: yoshoji@jata.or.jp

Background: Annual numbers of newly notified tuberculosis (TB) cases and its rate have been decreasing in Japan, but the notification remains high (16.1/100 000 population in 2013) because of the high notification among the elderly. Although TB is prevalent in the society, childhood TB cases have become very rare in Japan. We report the current epidemiological trend of childhood TB in Japan to identify its uniqueness and the factors relating to childhood TB control.

Design/Methods: The childhood TB data from 1987 to 2013, derived from the data posted on a website of the Tuberculosis Surveillance Centre, the Research Institute of Tuberculosis and data from a statistical yearbook on TB in Japan and other publicly available, were analyzed.

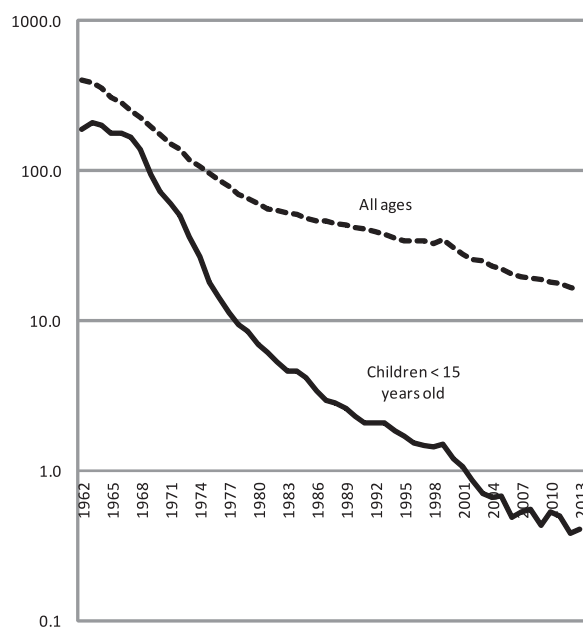


Fig. 1 Time trend of Tuberculosis notification rate in children under 15 years of age per 100,000 child population and in all ages per 100,000 general population.

Results: The annual number of notified childhood TB patients has been less than 100 since 2006 and notification rate has been less than 1.00 per 100 000 child population since 2005 (Figure). In 2013, there were 66 newly notified childhood tuberculosis patients aged 0–14 years, corresponding to a notification rate of 0.40 per 100 000 child population, which were 957 and 2.9 in 1987, respectively. The notification rate of childhood TB in Japan is one of the lowest in the world in spite of high notification rate among the elderly. Only one or no cases of TB meningitis had been found in children since 2006, though two cases were reported in 2013. In 2009, 4

miliary TB were reported; only one or two miliary cases have been found in children since 2006. Regarding the modes of detection, almost half of the childhood cases were found by household contact investigation and one third were identified at medical institutions in the recent years. BCG coverage among TB patients aged 0 to 5 months was extremely low (0 – 50 %), because current vaccination policy in Japan recommends not to give BCG for infants less than 3 months old. This is to avoid BCG vaccination for immunodeficient infants before their diagnosis and its fatal side effects. BCG coverage among TB patients aged more than 6 months was above 90 %. **Conclusion:** Japan is a still middle burden country of TB as a nation, but achieved very low notification rate among children. This may partially be attributable to BCG vaccination, along with contact investigation based on routine monitoring and evaluation.

PC-856-04 Treatment outcomes among children with tuberculosis in Malawi

B G Belaine^{1,2} I Dambe,¹ K Mbendera,¹ L Mlauzi,¹ J Mpunga¹ ¹National Tuberculosis Programme, Malawi, Lilongwe, ²International Training and Education Center for Health (ITECH) -Malawi, Lilongwe, Malawi. e-mail: belaine@gmail.com

Background: Children account for more than 10 % of notified TB cases in Malawi. Childhood Tuberculosis is also one of the thematic areas addressed in the Malawian national strategic plan 2015 to 2020. As part of the national strategy, NTP focus on case finding mainly using contact investigation, IPT provision and provision of first line Anti TB treatment. The treatment outcome of children with TB has not been monitored and reported regularly. Hence this analysis was done to inform performance and identify gaps to improve performance. **Methods:** NTP has revised the national TB-HIV supervision tool to allow collection compilation and review of treatment monitoring and follow up among children. As part of the first cycle of supervision, 109 health facilities were covered. The treatment outcome module covered treatment outcome by category, diseases classification and age category. Treatment outcome was assessed for patients enrolled during Oct- Dec 2013. The source of data was TB unit register. Comparison was made among children aged 0-4 yrs, 5-14 years and all age groups.

Results: During the period under review, a total of 347 children were evaluated for their treatment outcome. Of these 133 were children (0-4 years old). The treatment success rate was higher among children (5-14 yrs). Children with < 5 yrs tend have higher risk of death than children with 5-14 years old. The unfavorable treatment outcome among 0-4 years were death (10.52%) and lost to follow up (6.79%) and these were higher than those children (5-14 years).

Conclusion: More than 80% of children with tuberculosis have successfully completed treatment. Younger children have increased risk of having unfavorable outcome. The risk of death was 3 times higher in 0-4 years than older children. They also had increased risk of being lost to follow up than older children. Specific cause

of death among young children needs to be explored. Prevention of new tuberculosis infection and early diagnosis and treatment initiation among these populations need to be strengthened through strengthening of TB contact investigation and IPT provision.

Item	0–4 years	5–14 years	All age groups
Number in the cohorts, <i>n</i>	133	214	3748
Treatment success rate, %	81.9	86	79.88
Death rate, %	10.5	3.72	9.52
Lost to follow-up, %	6.79	3.25	6.96
Not evaluated, %	6.76	6.5	2.88

PC-857-04 Epidemiology of childhood tuberculosis in Malawi: what more can we do?

J Mpunga,¹ I Dambe,¹ L Vito,¹ K Mbendera,¹ F Kassa,¹ B G Belaine^{1,2} ¹National Tuberculosis Control Programme, Malawi, Lilongwe, ²International Training and Education Center for Health (ITECH) -Malawi, Lilongwe, Malawi. e-mail: belaine@gmail.com

Background: Malawi is one of the high TB and HIV burden countries. The latest national TB prevalence survey revealed that Tuberculosis is 2 times higher than the current estimate. However, the national prevalence survey doesn't provide estimate of the magnitude of Tuberculosis among children. Addressing childhood TB is a high priority agenda for the Malawian tuberculosis control program. Hence, analysis of the notification data is vital to understand TB epidemic and come up with appropriate measures.

Methods: A descriptive analysis was done using routine TB surveillance data for period of January 2014 to December 2014. All TB cases are diagnosed according to national TB diagnostic algorithms. AFB microscopy, GeneXpert, clinical assessment, Chest X-ray and FNA are the main diagnostic tools that assist TB diagnosis. The data was summarized by age group, disease category and district. Percentage of children among notified cases was determined for each district.

Results: Of 17 353 TB cases notified in one-year period, childhood tuberculosis constituted 10.65% of all cases. There was a wide variation in the proportion of childhood Tuberculosis cases across districts. The highest proportion of childhood TB was noted in Lilongwe district (19%) followed by Zomba (17%) and the least was noted in Chiradzulu (4.5%). Children 0-4% contributed the least among all age group (27/100 000 vs. all age group (104/100 000). Among children (0-4 yrs), smear negative pulmonary TB cases dominate (69.8%). And the highest proportion EPTB (extrapulmonary TB case) (37.9%) cases were reported among children age 5-14 yrs.

Conclusion: Children contribute to 10.69% of the notified TB cases. Notification doesn't seem to correlate with overall notification rate. The variation among districts seems to be related to the capacity to diagnosis and compliance to national algorithm. With a strong surveillance and access to service the notification rate of

TB among children may serve as a proxy indicator of Tuberculosis transmission in the community. NTP is planning to improve capacity of health workers in diagnosis and management of children. The contact investigation and expansion of IPT provision will also be strengthened.

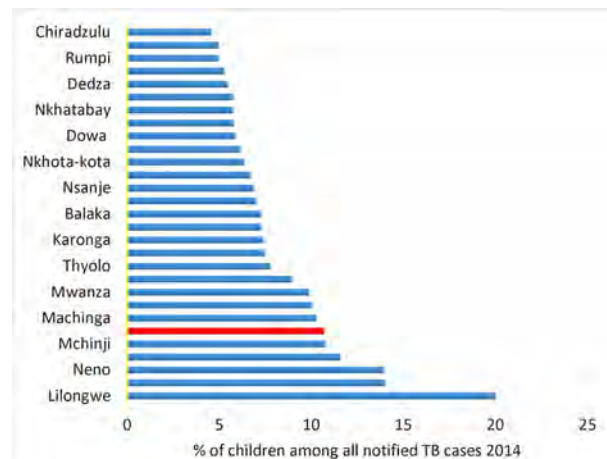


Figure Per cent of children among notified TB cases in Malawi, 2014

PC-858-04 3-year analysis (2012–2014) of childhood TB notification in Akwa Ibom State, Nigeria: implications for childhood TB scale-up in a resource-limited area

A F Omoniyi,¹ A Awe,¹ V Obot,² G Akang,³ J Kuye,³ R Eneogu,³ M Gidado,⁴ E Oyama¹ ¹World Health Organization Country Office, Abuja, ²Akwa Ibom State TBL Control Programme, Uyo, ³NTBLCP, Abuja, ⁴KNCV, Abuja, Nigeria. e-mail: omoniyifadare@yahoo.com

Background: Akwa Ibom state has a population of about 5.9 million, a higher percentage of whom belongs to the relatively young age group (age 0-9 years). TB services are provided in about 150 health facilities across all the 31 LGAs in the state. The state is considered as one of the 6 high TB-HIV burden states in Nigeria. There has been an increased in the proportion of childhood (0-14 years) TB cases notified in the state from 5% in 2012 to 7% in 2014, with some LGAs reporting as high as 18%. The aim of this study is therefore to review the childhood TB notifications in each of the 31 LGAs in the state with the aim of providing evidence based information to enhance childhood TB programme in resource limited settings.

Design/Methods: A retrospective review of childhood TB notifications reports from all the DOTS centers in the 31 LGAs in the state from 2012-2014.

Results: There was an increased in the proportion of childhood (0-14 years) TB cases notified in the state from 5% in 2012 to 7% in 2014, the proportion of childhood TB cases notified range from 0% to 15% in 2012, from 0% to 12.1% in 2013 and from 0% to 18.2% in 2014. 10% (3) of the LGAs did not report any cases of childhood TB in 2012, 32% (10) did not report in 2013 and 23% (7) did not report in 2014. The LGA with the tertiary institution recorded the highest number of

childhood TB cases in the state while the rural LGAs recorded the lowest number of cases. LGAs with 100% smear positivity rate among notified cases in 2014 reported no case of childhood TB, this is because the diagnosis of TB still largely depends on medical officers. The implication of this is that most childhood TB are still being missed in the state.

Conclusion: Notification of childhood TB cases is higher in urban LGAs and LGA with tertiary facility where a high number of medical officers are located. The TB programme must therefore urgently task shift diagnosis of TB among children to Nurses and other cadre of health workers for the programme to be able to rapidly increase childhood TB notification, the use of rapid diagnostic test tool for TB diagnosis among children must be scale up in resource limited settings to address the low childhood TB case finding.

PC-859-04 Assessment of management of tuberculosis among HIV-infected vs. non-infected children at Kalembe-Lembe Pediatric Hospital, Kinshasa, R D Congo

P Lelo,¹ C Akele,¹ A Shoma,² D Muteteke,² G Bakaswa²
¹Kalembelembe Pediatric Hospital, Kinshasa, ²Programme National de Lutte contre la Tuberculose, Kinshasa, Democratic Republic of the Congo. e-mail: fkitetele@hotmail.com

Background and challenges to implementation: To assess the management (clinical profile, evolution and issue) of tuberculosis (TB) treatment among HIV infected vs. uninfected children.

Intervention or response: Retrospective chart review of children treated for TB at Kalembe Lembe Pediatric Hospital in Kinshasa, Democratic Republic of Congo, between January 2008 and December 2012. Data was collected on use of status HIV, TB presentation and outcome of treatment.

Results and lessons learnt: During the study period, 1009 children were treated for TB. Median age was 4.33 years (range 0.08 to 15); 46.6% were female. Screening HIV test was realized to 809 (80.2%) children after parent's consent. 441 (54.5%) of them had a positive serological result for HIV. In clinical presentation, among HIV infected children treated for TB, 252 (57.1%) were aged less than 5 years, 106 (24.0%) were between 6 - 10 years and 83 (18.9%) were between 11 and 15 years. Among them, 52 (11.6%) children had extra-pulmonary TB, 5 (1.1%) had a positive sputum, 28 (6.3%) died during the TB treatment whom 17 (60.7%) aged between 0.08 and 5 years and 18 (4%) were loss to follow up. Compared to HIV uninfected children treated for TB, the profile of age was nearly similarly (76.4%, 16.3% and 7.3%), no sputum positive and the rate of loss to follow up was similarly (5.2% vs. 4.0%). However the cases of extra-pulmonary TB was higher (19.9% vs. 11.6%), No deaths in those non-infected by HIV.

Conclusions and key recommendations: In our population, HIV infection is one of considerable causes of morbidity and mortality for children coinfecting by TB.

To promote HIV testing of children treated for TB and screening of TB of HIV children infected should be an integral component of the care of children in TB endemic areas.

20. TB in children: diagnosis

PC-860-04 The diagnosis of tuberculosis in children in the province of South Kivu, Democratic Republic of Congo

Y Lufungulo Bahati,^{1,2} F Zech,¹ E Musafiri,⁴
 D Kalumuna,³ G Bakaswa,³ A Murhula,²
 D Van Der Linden,^{1,4} E Andre^{1,4} ¹Cliniques Universitaires Saint-Luc, Brussels, Belgium; ²Université Catholique de Bukavu, Bukavu, ³Programme National de Lutte contre la Tuberculose, Kinshasa, Democratic Republic of the Congo; ⁴Université Catholique de Louvain, Brussels, Belgium. e-mail: emmanuel.andre@uclouvain.be

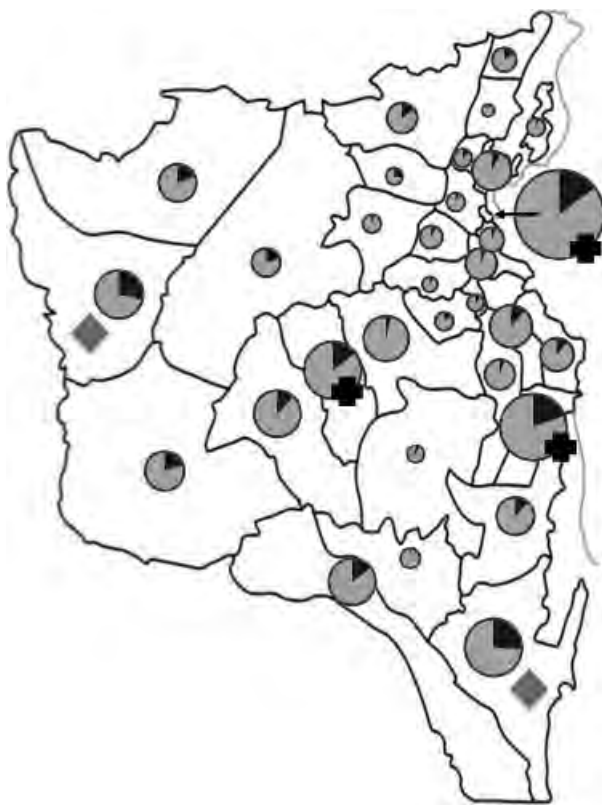
Background and challenges to implementation: Tuberculosis (TB) in children is particularly difficult to diagnose. In Africa, while the paediatric population often represents the majority of the population and has the same degree of exposure as adults, the infection is often under-diagnosed. The aim of our work is to analyse the epidemiology of paediatric TB and the determinants of diagnosis in the province of South Kivu of DRC.

Intervention or response: We carried out our analysis on TB detection data from the National TB Program covering a period of 12 calendar quarters from 2010 to 2012. We also evaluated the impact of interventions specifically targeting detection of difficult forms of TB. The changes over the period covered by the study were examined using quasi-least squares (generalised linear regression). We chose the hypothesis of an autoregressive between-year correlation matrix. The cases in each area had a gamma-Poisson distribution with a risk correction depending on the population size of each health area. The percentages followed a beta-binomial distribution.

Results and lessons learnt: During this period, the incidence of TB per 100 000 inhabitants in the general population showed no significant change. A significant fall was, however, seen during the period in the number of notified cases of TB in the population under 15 years of age, with the incidence falling from 14.7 to 10.4 during the period being studied. The proportion of paediatric TB varies significantly between urban and rural health areas, with predominantly urban health areas (Bukavu, Uvira and Kamituga) showing the highest proportion of paediatric cases. In the rural areas, the health areas supported by a non-governmental organisation and those in which Xpert MTB/RIF is available had the largest proportion paediatric TB, while the other rural health areas had lower detection rates.

Conclusions and key recommendations: This study makes it possible to highlight the difficulties encountered in the diagnosis of paediatric TB in rural areas in the Democratic Republic of Congo. The presence of a higher density of qualified healthcare workers and access to

appropriate diagnostic tools are factors that positively impact the detection rate of TB in children. We have also shown that the performance of health areas in terms of detection of paediatric TB was linked to their performance in terms of detection of other forms of TB that are considered difficult to diagnose.



PC-861-04 Utility of a clinical model for predicting the risk of tuberculosis in child contacts of tuberculosis cases in The Gambia

T Togun,¹ U Egere,¹ M P Gomez,¹ A Sillah,¹ M Daramy,¹ J Sutherland,¹ P Hill,² B Kampmann^{1,3} ¹Medical Research Council (MRC) Unit - The Gambia, Banjul, Gambia; ²University of Otago School of Medicine, Dunedin, New Zealand; ³Imperial College London, London UK. Fax: (+220) 449 5919. e-mail: ttogun@mrc.gm

Background: It has been suggested that clinical features may offer good prognostic value if they are well defined and appropriate risk stratification is applied. A documented history of TB exposure in a child changes the pre-test probability of disease and the positive predictive value of subsequent investigations, therefore it provides an appropriate parameter for risk stratification. We established a multivariable clinical prediction model for active TB disease in symptomatic TB-exposed children identified from an active case-finding study in The Gambia.

Methods: Backward stepwise logistic regression and bootstrapping techniques were used for development and internal validation of a clinical prediction model for active TB in a prospective cohort of actively-traced

symptomatic TB-exposed children, with suspected intra-thoracic TB disease. Model discrimination was assessed by area under the receiver operator characteristic curve (AUC).

Results: Overall, 150 symptomatic TB-exposed children with suspected intrathoracic TB disease were included in this analysis with a median age of 6 years (IQR 3 – 9 years), an approximately equal gender distribution and none were HIV infected. Thirty-five (23%) were diagnosed with active TB disease and started on TB treatment, while 115 (77%) had other respiratory tract infections (OD). In the final, most parsimonious clinical prediction model, the combination of age <5 years (AOR 4.8; 95% CI 2.0 – 11.5) and lymphadenopathy on clinical examination (AOR 4.9; 95% CI 1.8 – 13.0) discriminated active TB from OD with an AUC of 0.70 (95% CI 0.61 – 0.80). Internal validation using bootstrapping technique with 1000 repetitions gave a normal-based 95% confidence interval of the AUC (AUC 95% CI 0.61 – 0.79; bias 0.014; bootstrap SE 0.048) that was similar to those of the non-bootstrapped clinical prediction model.

Conclusion: We developed a simple and internally validated clinical algorithm that includes age <5 years and lymphadenopathy on clinical examination which reliably classified 70% of active TB from OD among TB-exposed children and could be an efficient screening tool in resource limited settings.

PC-862-04 Pediatric population: expediting the diagnosis of Intra-thoracic, multidrug-resistant tuberculosis

U Singh,¹ S Kabra,¹ R Lodha,¹ H Gautam,¹ Y Verma,¹ R Jain,¹ G Mehta,¹ P Pandey¹ ¹All India Institute of Medical Sciences, AllMS, New Delhi, India. e-mail: drurvashi@gmail.com

Background: Rapid and accurate diagnosis of Intra-thoracic Tuberculosis (TB) in children is challenging due to difficulties in obtaining good quality sputum specimens, pauci-bacillary nature of disease, low sensitivity of smear microscopy and poor access to culture. We compared the diagnostic accuracy of Xpert MTB/RIF assay with microscopy and culture for diagnosis of PTB and multi-drug resistant TB (MDR-TB) in children.

Design/Methods: Two hundred eighty-eight children (mean age, 7.2 yrs.) with suspicion of TB were grouped as Confirmed, Probable and No-TB based on microbiological and clinical findings. Patients were classified as progressive pulmonary disease (PPD, parenchymal lesion/pleural effusion/ pneumothorax) and primary pulmonary complex (PPC, hilar lymphadenopathy alone) on Chest X-ray. Gastric aspirates and induced-sputum samples were taken on two consecutive days and subjected to Ziehl Neelsen stain, Xpert MTB/RIF-assay and MGIT-960 culture (reference standard) with Drug sensitivity testing.

Results: Thirty-seven children (12.8%) were confirmed TB, 224 (77.7%) were probable TB and 27 (9.3%) were No-TB. Eight children (2.7%) were positive by smear, 70 (24.3%) tested positive by Xpert assay and 37 (12.8%)

by culture. Xpert- assay detected 30 of 37 culture confirmed cases (sensitivity 81% and NPV 96%). Xpert assay detected 62 cases more than smear microscopy and was more sensitive (81% vs. 18%). Xpert assay detected rifampicin resistance in additional 4 cases which were negative on culture. Among Xpert-MTB/RIF Positive cases, 26/30 (86.6%) had parenchymal involvement in Confirmed TB group, and 36/40 (90%) in Probable TB group.

Conclusion: In our study, up-front access to Xpert-MTB/RIF testing in clinically suspected pediatric Intra-thoracic TB cases demonstrated approximately two-fold increase in microbiologically-confirmed PTB, and increased detection of MDR-TB cases. Xpert proved to be more useful in patients with parenchymal involvement. Patients with only hilar lymphadenopathy but no parenchymal lesion had fewer microbiological confirmations. Xpert assay significantly improved case detection among probable TB cases hence improving early detection and treatment. Nevertheless a negative Xpert outcome does not always rule out TB, hence culture continues to be the gold standard. In addition, good clinical correlation is needed for treatment initiation. Research should continue for better diagnostics.

PC-864-04 Radiological findings in young children investigated for tuberculosis in Mozambique

A L Garcia-Basteiro,^{1,2} E Lopez Varela,^{1,2} O Joaquim Augusto,¹ K Gondo,¹ J Sacarlal,¹ J Muñoz,² P Alonso,^{1,2} J L Ribó³ ¹Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique; ²Barcelona Institute for Global Health (ISGlobal), Barcelona, ³Hospital Sant Joan de Deu, Hospitalet De Llobregat, Barcelona, Spain. e-mail: alberto.garcia-basteiro@manhica.net

Background: Chest radiography remains a critical tool for diagnosing intrathoracic tuberculosis (TB) in young children who are unable to expectorate. We describe the radiological findings in children under 3 years of age investigated for TB in the district of Manhiça, southern Mozambique, an area with a high prevalence of TB and HIV.

Design/Methods: Digital antero-posterior and lateral projections were performed and reviewed by two independent readers, using a standardized template. Readers included a local pediatrician and a pediatric radiologist blinded to all clinical information. International consensus case definitions for intra-thoracic TB in children were applied.

Results: A total of 766 children were evaluated of whom 43 (5.6%) had TB. The most frequent lesion found in TB cases was air space consolidation (65.1%), followed by suggestive hilar lymphadenopathy (17.1%) and pleural effusion (7.0%). Air space consolidation was significantly more common in TB cases than in non-TB cases (odds ratio 8.9; 95%CI: 1.6-50.5), as were hilar lymphadenopathy (OR 17.2; 95%CI: 5.7-52.1). The only case with miliary infiltrates and 3 with pleural effusions occurred in HIV-infected children.

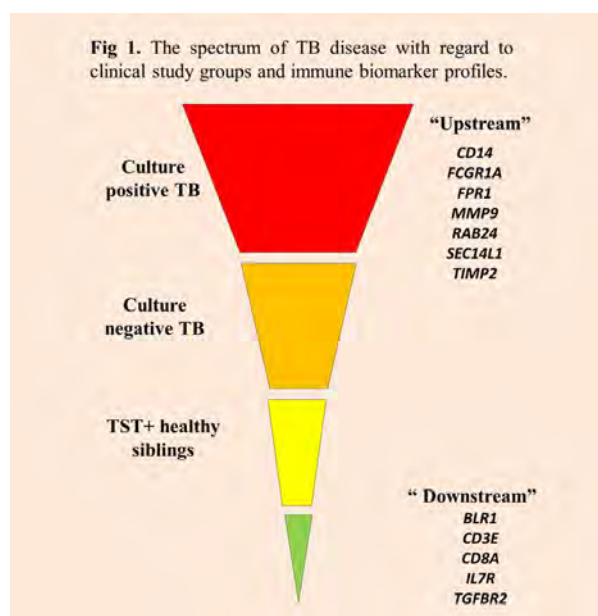
Conclusion: Frequent air space consolidation complicates radiological distinction between TB and bacterial pneumonia in young children, underscoring the need for epidemiological contextualization and consideration of all relevant signs and symptoms.

PC-866-04 Approaching a diagnostic point-of-care test for pediatric tuberculosis through evaluation of immune biomarkers across the clinical disease spectrum

S Jenum,¹ S Dhanasakaran,¹ A Mukherjee,² S Singh,² R Lodha,³ S K Kabra,² C Ritz,³ H Grewal¹ ¹University of Bergen, Bergen, Norway; ²All India Institute of Medical Sciences, New Delhi, India; ³University of Copenhagen, Copenhagen, Denmark. e-mail: harleen.grewal@gades.uib.no

Background: The World Health Organization calls for an accurate, rapid and simple point-of-care (POC) test for the diagnosis of childhood TB in order to make progress "Towards Zero Deaths". A POC test based on detecting the presence of MTB is likely to have poor sensitivity in childhood TB as 70-80% of children having culture-negative disease. Host biomarkers reflecting the on-going pathological processes from *Mycobacterium tuberculosis* (MTB) infection throughout the spectrum towards TB disease might hold greater promise.

Design/Methods: We analyzed transcriptional immune biomarkers direct ex-vivo applying dual-colour Reverse Transcriptase-Multiple Ligation-dependent Probe Amplification (dcRT-MLPA) in 88 Indian children with probable intra-thoracic TB (40 culture confirmed, 48 culture negative) aged 6 months to 15 years and 39 healthy siblings, having a positive ($n = 15$) or negative ($n = 24$) for the Tuberculosis Skin Test (TST).



Results: We identified 12 biomarkers consistently associated with clinical groups "upstream" towards culture-positive TB on the TB disease spectrum or "downstream"

towards a decreased likelihood of TB disease (Figure). Differences in biomarker profiles between the groups were assessed by hierarchical clustering and Lasso regression analysis. Notably, the latter method identified a biomarker signature with a very satisfactory capacity to discriminate children with intra-thoracic TB from healthy siblings regardless of culture result (area under the receiver-operator characteristic curve of 88%).

Conclusion: Consistent correlation with the identified biomarkers with MTB-related pathology, indicates a relevance to future POC-test for pediatric TB. Furthermore, the specific biomarker signature reported could fulfill the requirements for a POC-test, which, if validated, would contribute significantly towards a reduction of the worldwide TB attributable deaths in children.

PC-867-04 Effectiveness of screening questions used in enhancing pediatric TB detection in a rural setting

S Saleem,¹ M Jaswal,¹ A Malik,^{1,2} F Amanullah,¹ H Hussain¹ ¹The Indus Hospital, Karachi, ²Interactive Research & Development, Karachi, Pakistan. e-mail: saniya.saleem@industbcontrol.org

Background: Pediatric tuberculosis comprised 10% of all new case notification in Pakistan in 2013, which is an underestimate. We implemented a mass screening program to enhance child TB detection in rural Sindh, Pakistan. The objective of this study was to assess the effectiveness of screening questions in identifying presumptive TB patients and likelihood of TB confirmation in this cohort.

Design/Methods: A chart review was conducted of all children <15 years screened and identified as presumptive TB patients by trained screeners and referred to the physician for further evaluation, at three participating treatment centers in Jamshoro, Sindh from October 2014 to March 2015. The screening questions included presence of cough, fever, night sweats and weight loss.

Results: We found that out of the 859 children screened and identified as presumptive TB patients, 25.7% (221/859) were later diagnosed with TB and started on TB treatment. The most commonly reported symptom by the children identified as likely TB patients was fever in 66% (567/859) and 20% (113/567) of these children were diagnosed with TB by the physician. Female children were more likely to report fever >2 weeks as a presenting symptom, 61% (61/100) compared to 43% (52/121) male children ($P < 0.01$). In the 0-4 year age group 29% female children presenting with fever were diagnosed with TB compared to 16.7% male children ($P < 0.05$). Cough >2 weeks was a more specific TB screening question reported by 23.7% of children who were later diagnosed with TB compared to 12% children who reported cough <2 weeks and were found to have TB ($P < 0.05$). Also of interest was the finding that 26.8% (29/108) children who presented with cough >2 weeks and no fever were diagnosed with TB making it an important stand-alone symptom.

Conclusion: In mass screening efforts to find previously undiagnosed children with TB, symptom screens are an invaluable tool. We found that fever and/or cough of greater than two weeks duration were presenting symptoms in 98.2% of children diagnosed with TB. Fever and/or cough of two weeks or more are essential screening questions and the presence of either symptom in a child can be an entry point for TB evaluation in high burden settings.

PC-868-04 Advanced TB diagnostics in a resource-limited setting: findings from the first two years of the pediatric TB Centre of Excellence in Mbeya, Tanzania

J Bacha,¹ J Benjamin,¹ L Mwita,¹ P Clowes,² C Mangu,² A Dinardo,³ K Ngo,³ A Mandalakas³ ¹Baylor College of Medicine Children's Foundation - Tanzania, Mbeya, ²National Institute of Medical Research - Mbeya Medical Research Centre (NIMR-MMRC), Mbeya, Tanzania; ³Baylor College of Medicine, Houston, TX, USA. e-mail: bacha@bcm.edu

Background: In 2013, the Baylor Tanzania Center of Excellence (COE) in Mbeya, NIMR-MMRC and the Mbeya Referral Hospital created a centre providing advanced TB diagnostics and treatment for children with presumptive TB. The program offers sputum analysis, tuberculin skin testing (TST), fine needle aspiration (FNA), and chest X-ray (CXR) interpretation as well as treatment. This abstract provides a description of robust patient assessments, diagnostic findings and treatment during the first 22 months of the program.

Design/Methods: Retrospective chart review at the COE between March 2013 and December 2014. Baseline and outcome data were captured using a standardized data collection tool and unique data base. Diagnostic test performance used clinical diagnosis of "TB disease" as a reference standard, which incorporates both CXR and TST results.

Results: Baseline: 504 patients with presumptive TB were referred. 48% female (241/504); age 0.3-19.7 years (median 4.8yr). 57% (288/504) HIV-infected, 4% (20/504) HIV-exposed, HIV-uninfected, and 39% (196/504) HIV-negative. Of HIV-infected, 63% (181/288) were on ART when referred. 20% (103/504) reported a known TB contact, and 3% (16/504) had history of prior TB treatment. Of all evaluated, 70% (355/504) provided sputum (42% induced, 58% spontaneous), 93% (470/504) completed TST, 5% (26/504) FNAs, and only 56% (281/504) had CXR results due to mechanical and logistical challenges. Outcomes: 176 of the 504 (35%) were diagnosed with TB disease and 98% (172/176) initiated TB treatment. 19% (33/176) were bacteriologically-confirmed TB, 62% (109/176) probable TB, and 19% (34/176) possible TB. 14 patients were LTFU or died (1 of which had bacteriologically-confirmed TB results). Of those diagnosed, 86% (152/176) had pulmonary TB, 5% (8/176) lymph node TB, and 9% (16/176) extrapulmonary TB (EPTB). HIV-infected accounted for 60% (91/152) of PTB, 38% (3/8) of LNTB and 44% (7/16) EPTB. The Table lists the results and performance of the TB diagnostics. Median time

from referral for TB diagnostics to initiation of TB therapy was 3 days (range 0-142 days).

Conclusion: Effective pediatric TB diagnosis is possible in our resource-constrained setting and improves TB case finding and prompt initiation of TB treatment. However, despite access to state of the art diagnostics, performance of GeneXpert and culture are still sub-optimal, regardless of HIV and referral status, stressing the importance of clinical TB diagnosis in children.

Table TB diagnostic test results and test performance for pediatric patients with presumptive TB (with "TB Disease" diagnosis used as reference standard)

Diagnostic Test (# Performed)	% Tests with positive result (n)	PPV	NPV	Sensi- tivity	Speci- ficity
All patients (n=504)					
Sputum GeneXpert (n=355)	3% (11/355)	1.00	0.63	0.07	1.00
Sputum smear (n=355)	4% (13/355)	1.00	0.66	0.10	1.00
Sputum culture (n=308)	7% (21/308)	0.95	0.68	0.18	0.99
TST (n=470)	14% (65/470)	0.78	0.71	0.31	0.95
FNA (n= 26)	35% (9/26)	0.89	0.64	0.57	0.92
Chest x-ray (n=281)	31% (87/281)	0.94	0.80	0.68	0.97
HIV-infected patients only (n=288)					
Sputum GeneXpert (n=216)	3% (6/216)	1.00	0.67	0.08	1.00
Sputum smear (n=220)	2% (5/220)	1.00	0.67	0.07	1.00
Sputum culture (n=194)	7% (15/194)	0.93	0.69	0.20	0.99
TST (n=250)	11% (27/250)	0.85	0.69	0.25	0.97
FNA (n=16)	38% (6/16)	0.83	0.70	0.63	0.88
Chest x-ray (n=156)	34% (53/156)	0.94	0.82	0.72	0.97
Inpatient Referrals (n=227)					
Sputum GeneXpert (n=128)	4% (5/128)	1.00	0.67	0.11	1.00
Sputum smear (n=129)	3% (4/129)	1.00	0.66	0.09	1.00
Sputum culture (n=108)	2% (2/108)	1.00	0.68	0.06	1.00
TST (n=204)	9% (19/204)	0.63	0.68	0.17	0.95
FNA (n= 8)	38% (3/8)	1.00	0.80	0.75	1.00
Chest x-ray (n=111)	28% (31/111)	0.94	0.76	0.60	0.97
Outpatient Referrals (n=277)					
Sputum GeneXpert (n=223)	4% (8/223)	1.00	0.66	0.10	1.00
Sputum smear (n=226)	3% (7/226)	1.00	0.65	0.08	1.00
Sputum culture (n=200)	10% (19/200)	0.95	0.67	0.23	0.99
TST (n=245)	19% (46/245)	0.85	0.74	0.43	0.95
FNA (n=18)	33% (6/18)	0.83	0.58	0.50	0.88
Chest x-ray (n=170)	33% (56/170)	0.95	0.83	0.74	0.97

TST-Tuberculin Skin Test; FNA- Fine Needle Aspirate; PPV- Positive Predictive Value; NPV- Negative Predictive Value

PC-869-04 Barriers to childhood tuberculosis diagnosis: a qualitative study

S Chiang,¹ S Roche,² C C Contreras,³
A Valentina Antonieta,⁴ H Del Castillo Barrientos,⁵
M Becerra,^{3,6,7} L Lecca³ ¹Baylor College of Medicine,
Houston, TX, ²Boston University School of Public Health,
Boston, MA, USA; ³Socios En Salud (Partners In Health), Lima,
⁴Ministerio de Salud, Lima, ⁵Instituto Nacional de Salud del
Niño, Lima, Peru; ⁶Harvard Medical School, Boston, MA,
⁷Brigham and Women's Hospital, Boston, MA, USA. e-mail:
schiang@alumni.stanford.edu

Background: According to Peru's National Tuberculosis Program (NTP), children aged 0-14 account for 7.9% of the country's tuberculosis (TB) incidence. This figure likely reflects suboptimal diagnosis of childhood TB. The challenges of childhood TB diagnosis have been well described by clinical studies and expert opinion. However, the perspectives of front-line healthcare providers and affected families have been infrequently reported. An understanding of these groups' experiences is crucial to increasing case detection. In this qualitative study, we sought to identify obstacles to childhood TB diagnosis faced by primary care providers and patients' families in Lima, Peru.

Design/Methods: El Agustino and La Victoria, two of Lima's 43 districts, were chosen as the setting because of their high TB incidences: 224 per 100 000 person-years in El Agustino and 195 per 100 000 person-years in La Victoria. We purposefully sampled NTP providers, community health workers, and parents of children with TB at the eight (of 16 total) health centers in El Agustino and La Victoria with the highest pediatric TB caseloads. Using semi-structured guides, moderators conducted ten focus group discussions with 53 primary care providers, community health workers, and parents. In addition, moderators conducted nine in-depth interviews with NTP administrators and pulmonologists to add a broader perspective to the issues explored in the focus groups. Two authors independently performed inductive thematic analysis and identified emerging themes.

Results: Participants identified six barriers to the diagnosis of childhood TB. These barriers were (1) ignorance and stigma among the community; (2) insufficient contact investigation; (3) limited access to diagnostic tests; (4) insufficient health center staff; (5) inefficient specialist referrals; and (6) provider shortages. While participants mentioned the challenge of sputum collection and the low sensitivities of smear microscopy and culture, these issues received less attention than the other six barriers.

Conclusion: Recent efforts to increase childhood TB detection have centered on the development of new technologies. However, our findings demonstrate that many diagnostic barriers are rooted in socioeconomic and health system problems, which must be addressed alongside efforts to improve technological tools. Strengthening providers' ability to diagnose childhood TB at the primary care level may be the best starting point for intervention.

Table 2: Focus group eligibility criteria and composition

Focus Group	Eligibility Criteria*	Number of participants	Number (%) of female participants
1	NTP physicians working at a health center in El Agustino for ≥ 3 months	6	2 (33)
2	NTP physicians working at a health center in La Victoria for ≥ 3 months	4	1 (25)
3	NTP nurses working at a health center in El Agustino for ≥ 3 months	7	7 (100)
4	NTP nurses working at a health center in La Victoria for ≥ 3 months	3	3 (100)
5	NTP nursing technicians working at a health center in El Agustino for ≥ 3 months	6	5 (83)
6	NTP nursing technicians working at a health center in La Victoria for ≥ 3 months	6	6 (100)
7	Community health promoters in El Agustino with ≥ 6 months' experience in TB control activities	6	6 (100)
8	Community health promoters in La Victoria with ≥ 6 months' experience in TB control activities	6	6 (100)
9	Parents of children who had received treatment for TB disease in the past six months. Treatment must have been administered at a health center in El Agustino.	4	3 (75)
10	Parents of children who had received treatment for TB disease in the past six months. Treatment must have been administered at a health center in La Victoria.	5	4 (80)

*Eligibility criteria for all groups included informed consent.

Abbreviations: LTBI, latent tuberculosis infection; NTP, National Tuberculosis Program; TB, tuberculosis.

21. COPD, lung function and pulmonary embolism

PC-870-04 Incidence and risk factors of chronic obstructive pulmonary disease among smokers in Bangladesh

A Siddiquee,¹ M A H Chowdhury,¹ S Ahmed,¹ S Pervin,¹ K Hasan,¹ A Naheed,¹ D S Alam² ¹International Center for Diarrheal Disease Research, Bangladesh Dhaka, Bangladesh; ²Centre for Global Health Research, Li Ka Shing Knowledge Institute, St. Michael Hospital, Toronto, ON, Canada. e-mail: tanweer@icddr.org

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide; the brunt of which is in the low- and middle-income countries. The prevalence of COPD among Bangladeshi adults is 13.5%. Smoking is highly prevalent in Bangladesh, especially among males. There is scarcity of population based data on COPD incidence among smokers. The goal of this study is to estimate incidence of COPD and its risk factors among adult (40 years or above) ever smokers.

Design/Methods: We conducted a population based cohort study in urban Dhaka and rural Matlab where 652 adult smokers underwent spirometry, who had normal lung-function detected 2 years back in an ongoing COPD prevalence study. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Socio-economic and lifestyle variables included educational status, household income, occupation, exposure to biomass fuel burning, and smoking history. Risk factors of incident COPD cases were identified using multiple logistic regression model.

Results: COPD developed in 46 adult smokers, which corresponds to a 2-year cumulative incidence of 7.1%, giving an average annual incidence of 3.55%. Mean FEV1 and FVC among incident COPD cases were 1.80l (SD = 0.54) and 2.34L (SD = 0.51) respectively. Both FEV1 and FVC were significantly lower ($P = 0.000$ and $P = 0.008$ respectively) among the incident COPD cases. Incident COPD is significantly associated with age, occupation, income, respiratory symptoms and BMI on bivariate analysis. In the adjusted model, older age (≥ 60 y: OR 4.2, 95%CI 1.58-12.5) and presence of respiratory symptoms in last 12 months (OR 3.86, 95%CI 1.74-8.58) are independent risk factors for incident COPD among the adult ever smokers.

Conclusion: COPD incidence is very high among smokers in Bangladesh. Ever smokers at older age group and/or presence of respiratory symptoms should be priority individuals to reduce COPD incidence in Bangladesh.

PC-871-04 DNA damage and cellular abnormalities detected by micronucleus assay in patients with COPD, tuberculosis and lung cancer

A Gonçalves Da Silva,¹ M J Bresciani,¹ T E Karnopp,¹ A Ferreira Weber,¹ J H Ellwanger,¹ J A P Henriques,² A R Moura Valim,¹ L Possuelo¹ ¹University of Santa Cruz do Sul - UNISC, Santa Cruz Do Sul, Rio Grande do Sul, ²Federal University of Rio Grande do Sul - UFRGS, Porto Alegre, Rio Grande do Sul, Brazil. Fax: (+55) 145 137 171 855. e-mail: andreag@unisc.br

Background: The inflammation plays a central role in many lung diseases, including COPD, tuberculosis and lung cancer. Currently, studies have related inflammation with the increasing cancer incidence. The study of DNA damage at the chromosome level is very important because chromosomal mutation is an event of carcinogenesis.

Design/Methods: We investigated the DNA damage (peripheral blood lymphocytes) in patients with chronic obstructive pulmonary disease (COPD, $n = 28$), lung cancer (LC, $n = 18$) and tuberculosis (TB, $n = 22$) and control individuals ($n = 17$) by comet assay. The cytogenetic DNA damage was evaluated by buccal micronucleus cytome assay (BMCyt).

Results: A higher percentage of apoptotic cells was found in patients with respiratory disease compared to control subjects. Some significant differences were also observed among the case groups (COPD, TB and CP) and the control group. COPD patients had a higher percentage of apoptotic cells and necrosis compared to the LC patients and a higher percentage of apoptotic cells compared to the TB group. The TB group had a higher percentage of DNA damage compared to the COPD and LC groups and defects in cytokinesis and apoptotic cells compared to the COPD group. The TB group also had a higher percentage of apoptotic cells and necrosis compared to the LC group.

Conclusion: Our results indicated that patients with COPD, TB and LC had a low frequency of permanent

DNA damage. Patients with COPD presented cellular abnormalities that corresponded to death by apoptosis and necrosis, while patients with TB presented defects in cytokinesis and dysfunctions in DNA repair that resulted in the formation of micronuclei.

PC-873-04 Prevalence of COPD among subjects with symptoms or exposure to risk factors in the city of Telavi, Georgia

M Maglakelidze,^{1,2,3} N Maglakelidze,^{2,3}

T Maglakelidze,^{2,4} I Chkhaidze^{2,5} ¹The Black Sea Health Alliance, Tbilisi, ²Georgian Respiratory Association, Tbilisi, ³National Center for Disease Control and Public Health, Tbilisi, ⁴LTD "Diagnostic Center", Tbilisi, ⁵Tbilisi State Medical University, Tbilisi, Georgia. e-mail: maka_mag@hotmail.com

Background: Chronic Obstructive Pulmonary Disease (COPD), which is defined as chronic airflow limitation is one of the leading causes of mortality and morbidity. The major risk factors of COPD are smoking, outdoor and indoor pollution. The prevalence of COPD in Georgia is suspected to be high due to high smoking rates and air pollution. There is no exact definition for the diagnosis of COPD in the Georgian State Medical Standards list; the present definition is Other Chronic Obstructive Diseases of Lung, official prevalence rate of which is low - 0.097%

Design/Methods: A quantitative cross-sectional study was carried out in Telavi family medicine center, for determining the prevalence of COPD and relation of its risk factors in Telavi. The subjects over 35 years of age who had symptoms of prolonged cough, sputum production, or dyspnea, and/or a history of exposure to disease risk factors were included. COPD diagnosis was made through a questionnaire and spirometric examination using the criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Results: 101 patients were consecutively included in the study, in the period of February 15-April 15, 2010. The sex ratio M/F was 1.24. The mean age of study participants was 55 years. COPD was confirmed in 35.6%. The risk of COPD in men was 4.6. times higher than in women. Seven subjects (age range 35-39 years) were diagnosed with COPD. They did not report to be current or past smokers. There were no patients detected with very severe form of COPD. The results demonstrated neither, statistically significant association between the duration of cough and the severity of COPD, nor statistically significant association of smoking and the severity of COPD. A Chi-square test demonstrated that COPD was dependent on outdoor pollution and the dependency was statistically significant $P < 0.05$. Statistically significant dependency between COPD and indoor pollution was not found.

Conclusion: The prevalence of COPD among investigated population was 35.6%. The estimate prevalence rates for COPD in Telavi appeared to be 1.7 times higher than the official rates for Other Chronic Obstructive Diseases of Lung. The results of the study can serve as baseline data for broader studies on COPD, which should focus on the impact of various risk factors. Specific public

policy issues need to be re-examined from the angle of environmental contribution to the burden of COPD and definition of COPD has to be included in Georgian State Medical Standards list.

PC-874-04 Chronic obstructive pulmonary disease screening among elderly in an urban community of South India using the IPAG questionnaire

R C Chauhan,¹ A J Purty¹ ¹Pondicherry Institute of Medical Sciences, Puducherry, India. e-mail: rcchauhan21@gmail.com

Background and challenges to implementation: Under-diagnosis of chronic obstructive pulmonary disease (COPD) is common as this disease is often not recognised and diagnosed until it is moderately advanced. One of the barriers to the diagnosis of COPD is the difficulty with which spirometry is performed in the general practice/community setting. International Primary Care Airways Guidelines (IPAG) questionnaire is a feasible validated screening tool for COPD diagnosis in community setting.

Intervention or response: This community based observational study was conducted among 1037 elderly people in urban areas of Puducherry in India. Participants were recruited using multistage random sampling technique. IPAG questionnaire [Cut off Score – 17 (Positive predictive value: 92%)] was administered among all study subjects. We compared quantitative parameters between COPD and non-COPD subjects using the student *t*-test and χ^2 test was applied for qualitative variables.

Results and lessons learnt: Data from 1037 subjects (435 males) were analysed. The proportion of smokers among male was 16.5%. A positive IPAG questionnaire for possible COPD (≥ 17 points) was obtained in 342 (33.1%) subjects. Based on the answers to the questionnaire given by the subgroup of possible COPD subjects, 69 (22.2%) had no cough, 215 (62.9%) reported sputum production in the absence of a cold, 186 (54.4%) cough up phlegm (sputum) from their chest first thing in the morning, 162 (47.4%) had frequent or occasional wheezing and 113 (33 %) reported to have or had any allergies. Age and body weight found to be associated with positive IPAG questionnaire. Possible COPD was significantly higher among smokers (52.9%) as compared to non-smokers (31.7%) ($P < 0.01$).

Conclusions and key recommendations: Proportion of subjects with possible COPD was high in community. IPAG questionnaire was an easy to administered tool for screening of COPD and little expertise is sufficient for its administration. IPAG questionnaire could be used for screening and planning of health interventions in communities in developing countries.

PC-875-04 Silico-tuberculosis and associated risk factors in Iran

A Farazi,¹ M Jabbariasl² ¹Arak University of Medical Sciences, Arak, Iran. Fax: (+98) 861 313 4002. e-mail: farazialiasghar@yahoo.com

Background and challenges to implementation: Co-existence of silicosis and tuberculosis is known as silico-tuberculosis. This article review the burden of silicosis and tuberculosis in workers who exposed to silica and evaluate influencing factors that may increase the risk of silico-tuberculosis.

Intervention or response: An analytical cross-sectional study was performed in silica exposed workers in Markazi province of Iran during 2011-2012. Sampling method was un-randomized and considering all workers who at least 6 months exposed to silica. The study was done via questionnaire, clinical examination, spirometry, chest X-ray and tuberculosis investigations.

Results and lessons learnt: A total of 3121 workers were included in the study, the mean age of participants was 43.1 ± 12.4 years, and mean employment duration 14.9 ± 6.8 years. Prevalence of TB in silica-exposed workers without silicosis was 172 cases per 100 000 people and prevalence in silicosis cases was 917 cases per 100 000 people. Incidence of TB in silica-exposed workers without silicosis was 69 cases per 100 000 people and incidence in silicosis cases was 459 cases per 100 000 people. In the current study, frequency of LTBI/TB was significantly higher in subjects with silicosis workers compared to the non-silicosis group ($P=0.005$). Prevalence of TB in silica-exposed workers without silicosis was 5.2 fold and prevalence in silicosis workers was 27.8 fold higher than general population. Incidence of TB in silica-exposed workers without silicosis was 3.3 fold and incidence in silicosis cases was 21.8 fold higher than general population. The frequency of LTBI/TB was higher in age over thirty years old ($P=0.02$), in workers with employment duration over 10 years ($P=0.004$), in workers with exposure duration over 5 years ($P=0.03$) and smokers with over 5 pack-years ($P=0.01$).

Conclusions and key recommendations: Exposure to silica causes a renewed multiplication of bacilli in the healing TB lesions. Prevalence of pulmonary tuberculosis in silicosis is more common when compared to prevalence in general population, hence all should use prophylactic measures intensification of work place.

PC-876-04 Validation of the American Thoracic Society respiratory questionnaire for lung function assessment among an occupational group of textile workers

T Jamali,¹ D A Nafees¹ ¹Aga Khan University, Karachi, Pakistan. e-mail: tanzil.jamali@aku.edu

Background: The objective of this study was to determine the correlation of spirometric lung pattern with respiratory symptoms and to validate the American Thoracic Society (ATS-DLD-78A) respiratory questionnaire for lung function assessment among an occupational group of textile workers.

Design/Methods: This was a cross-sectional survey conducted in 2009-2010 which included 372 workers from 15 textile mills in Karachi. Data was collected through the ATS-DLD-78A respiratory questionnaire and lung function was assessed by using a portable spirometer.

Results: A general trend of decrease in lung function (predicted FVC, FEV1 and FEV1/FVC ratio) was observed among participants who had chronic respiratory symptoms. Predicted FEV1 was significantly reduced for chronic cough (aOR: 3.09, CI: 1.26, 7.56), chronic wheeze (aOR 1.98, CI: 1.05, 3.71) and shortness of breath grade 2 (aOR: 2.07, CI: 1.05, 4.07). The risk of decrements in lung function significantly increases with the addition of chronic symptoms on predicted FEV1; cough + wheeze (aOR: 2.08 CI: 1.05, 4.10), cough + shortness of breath grade 2 (aOR: 2.47, CI: 1.18, 5.18), phlegm + shortness of breath grade 2 (aOR: 2.59, CI: 1.23, 5.43) cough + wheeze + shortness of breath grade 2 (aOR: 4.64, CI: 1.97, 10.93) (aOR: 4.18, CI: 1.68, 10.37). We found low sensitivity and high specificity and negative predicted values for the respiratory symptoms.

Conclusion: A combination of chronic respiratory symptoms was best associated with decrements in lung function. These findings have relevance for developing evidence-based approaches for the respiratory health surveillance among textile workers.

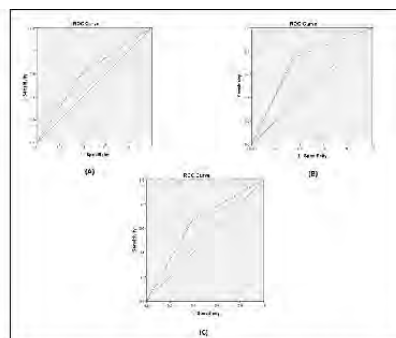


Figure: A) ROC for % predicted FVC with combined respiratory symptoms. Area under the curve 0.60, Test variable=Chronic cough+ chronic phlegm + chronic wheeze + shortness of breath grade 2. B) ROC for % predicted FEV1 with combined respiratory symptoms. Area under the curve 0.69, Test variable=Chronic cough+ chronic phlegm + chronic wheeze + shortness of breath grade 2. C) ROC for % predicted FEV1/FVC with combined respiratory symptoms. Area under the curve 0.63, Test variable=Chronic cough+ chronic phlegm + chronic wheeze + shortness of breath grade

PC-877-04 Prevalence of chronic obstructive pulmonary disease among patients previously treated for pulmonary tuberculosis in Manila: a multi-center study

C Gulay,¹ H Delfin,¹ J Benedicto,¹ L Fernandez,¹ R Pagcatipunan, Jr¹ ¹Philippine General Hospital, Manila, Philippines. e-mail: coleengulay@gmail.com

Background: Chronic obstructive pulmonary disease (COPD) has been a major cause of death worldwide, ranking as the fourth leading cause of death worldwide. In several epidemiologic studies, pulmonary tuberculosis (PTB) is currently an emerging potential risk factor in the pathogenesis and severity of COPD. This study aims to determine the prevalence of COPD among patients who were previously treated for PTB in various Directly

Observed Treatment Short-Course (DOTS) Centers in Manila.

Design/Methods: We performed a prospective cross-sectional study using purposive randomized sampling among patients managed in different DOTS centers in Manila. Participants were aged > 40 years and completed a questionnaire to assess their demographic profile, exposure to possible risk factors for COPD, presence of other confounding factors which may present with obstructive changes, and TB-treatment related variables. A diagnosis of COPD was based on the post bronchodilator FEV1/FVC < 70 as recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Pulmonary function tests among matched population without history of PTB were also gathered to compare prevalence of COPD among these patients against those with history of PTB.

Results: Among 224 participants who were previously treated for pulmonary tuberculosis, 20.47% met the criteria for COPD with an odds ratio of 1.10 (95%CI 0.68, 1.76). This is compared with 19.38% who met the criteria for COPD among 227 participants without history of PTB. This may imply that the risk for COPD is around 10% higher for patients previously treated with PTB. In this study, majority of the patients diagnosed with COPD belong to GOLD Stage III.

Conclusion: The prevalence of COPD in patients previously treated for PTB in this study is not statistically significant. Nevertheless, our data suggest that previous history of PTB posed a risk for development of obstructive airways disease that warrants screening to provide appropriate intervention and maximized therapy.

PC-878-04 Activity of blood phagocytes in sarcoidosis and tuberculosis: phagocytic activity of neutrophils as simple test for differentiation both diseases?

A Dubaniewicz¹ ¹Medical University of Gdansk, Gdansk, Poland. Fax: (+48) 583 491 513. e-mail: aduban@gumed.edu.pl

Background: Clinical and histopathological similarities between sarcoidosis (SA) and tuberculosis (TB) suggest a participation of *Mycobacterium tuberculosis* in the etiopathogenesis of SA. Because these resemblances may be cause of a dangerous misdiagnosis both diseases, there are searches for new biomarkers useful for the discrimination of sarcoidosis from tuberculosis. We recently revealed that genetically different (HLA and non-HLA, e.g. NRAMP1 and FCGR) patients with SA and TB induce dissimilar immune responses to the same mycobacterial heat shock proteins, which are implicated in forming of immune complexes (CIs). The complexemia in both diseases may be a result of an alteration in the abilities of monocytes and/or neutrophils to phagocytosis/clearance antigen(s)/CIs with following persistent antigenemia and granuloma formation.

Design/Methods: Therefore we evaluated phagocytic activity of blood monocytes and neutrophils in 25 SA

patients, 25 TB patients, and 20 healthy volunteers using the PHAGOTEST® kit by flow cytometry.

Results: We revealed that the total number of white blood cells was significantly higher in TB than in SA and healthy controls ($P = 0.003$, $P = 0.02$, respectively), whereas there was no differences between SA and controls. The total number of blood monocytes was higher in SA than in TB and controls ($P = 0.002$, $P = 0.002$, respectively) and also in TB compared to controls ($P = 0.04$). We revealed increased of phagocytic activity of monocytes in SA than healthy individuals ($P = 0.03$) and insignificantly than in TB, whereas there was no differences between TB and healthy controls. We also revealed higher total number of neutrophils in TB than in SA and controls ($P = 0.0004$, $P = 0.01$, respectively), whereas there was no differences between SA and healthy individuals. Phagocytic activity of neutrophils in TB was higher than in SA and controls ($P = 0.004$, $P = 0.01$, respectively), whereas there was no differences between SA and healthy controls.

Conclusion: Our results revealed increased phagocytic activity of monocytes in both disease, but in contrast to SA, increased phagocytic activity of neutrophils was detected in TB. Current study suggest different role of neutrophils in the etiopathogenesis of both diseases. Analysis of phagocytic activity of blood neutrophils may be useful for a differentiation of SA from TB. Funding: grant 5160/B/P01/2010/39.

PC-879-04 Determinants of pulmonary embolism in Kinshasa hospitals

A Bakebe Mbaku,¹ M Kashongwe Murhula,¹ M Tshiasuma,¹ C Mulenga,¹ S Bisuta Fueza,¹ B Kabengele,¹ Z Kashongwe Munogolo,¹ J M Kayembe Ntumba¹ ¹Kinshasa university hospital, Kinshasa, Democratic Republic of the Congo. e-mail: alainbakebe@yahoo.fr

Background: Pulmonary embolism (PE) is no longer a curiosity in our environment; this reality could be explained by the increasingly higher frequency of its predisposing factors.

Design/Methods: Multicentric cross-sectional study undertaken between January 2011 and April 2014. Patients aged 18 years or more admitted for acute dyspnea and / or acute chest pain suspected of respiratory origin were eligible. The diagnosis of PE was based on computed-tomographic pulmonary angiography or on a set of arguments involving clinical, echocardiographic, lower limb compression venous ultrasonographic features. The χ^2 test of Pearson and Wald with 95%CI were used in the statistical analysis. Significance was accepted at $P < 0.05$.

Results: 158 patients were included in our study. Male gender was predominant with a sex ratio of 1.2. The mean age of patients was 54.8 ± 14.8 years. The main risk factors including risk surgery ($P = 0.018$), immobilization ($P < 0.001$), obesity ($P < 0.001$), diabetes mellitus ($P < 0.001$) and heart disease ($P = 0.014$). Immobilization (OR: 8.33; $P < 0.001$) and obesity (OR:

8.06; $P < 0.001$) were found to be major determinants of the EP in multivariate logistic regression.

Conclusion: The EP is common in our environment. The emergence of certain factors related to the epidemiologic transition in black Africa might partly explain the increased prevalence of venous thromboembolic disease.

22. Smoking cessation

PC-880-04 A European Respiratory Society Consensus Document to help smokers with pulmonary disorders to quit

C Vardavas,¹ C Gratziou,² C Jimenez-Ruiz,³ J I De Granda⁴ ¹University of Crete, Rethymnon, ²Athens University, Athens, Greece; ³Sociedad Madrileña de Neumología y Cirugía Torácica, Madrid, ⁴Hopital 12 de Octubre, Madrid, Spain. e-mail: maeve.barry@ersnet.org

Background and challenges to implementation: It is known that tobacco smoking is the major etiological factor for the development of COPD and about 15-20% of all smokers will develop COPD. On the other hand, smoking cessation is the only therapeutic intervention that can avoid chronic progression of COPD. It's also known that smoking cessation reduces the annual decrease of FEV1, improves responses to bronchodilator drugs and inhaled corticosteroids, reduces the incidence of acute exacerbations and reduces bronchial infections. The ERS Consensus Document to help smokers with Pulmonary Disorders to quit is a qualitative review regarding smoking cessation in patients with COPD and other pulmonary disorders. It describes the epidemiological links between smoking and pulmonary disorders, the evidence for benefits of stopping smoking, how best to assess tobacco dependence and what interventions currently work best to help pulmonary patients quit. Finally, it describes characteristics and management of smokers who find it difficult to quit.

Intervention or response: Lung cancer, asthma and tuberculosis are disorders that are related with tobacco consumption. More than 85% of lung cancer is due to smoking and around 15% of lung cancer patients still smoke 6 months after diagnosis. Many benefits appear after smoking cessation in patients with lung cancer. The most relevant are as follows: reduction in surgical complications, improvement of responses to chemotherapy and radiotherapy and increase in survival time.

Results and lessons learnt: Smoking rate among asthma patients is similar to the general population and smoking contributes to deter the prognosis of this disorder and avoid the benefits of bronchodilators drugs and inhaled corticosteroids.

Conclusions and key recommendations: Assessments of smoking characteristics in patients with pulmonary disorders is a crucial intervention. Assessments should include: number of cigarettes smoked daily, number of years of smoking, CO index, measurement of blood cotinine levels, assessment of motivation and self-efficacy to quit and assessments of depression, tobacco depen-

dence and previous attempt to quit. Smoking cessation strategies for patients with pulmonary disorders should include: a combination of counseling and pharmacological treatment (NRT, bupropion and varenicline).

PC-881-04 Impact of smoking cessation intervention package on treatment outcome of tuberculosis patients in North India: a cluster randomized control trial

S Goel,¹ J Kathiresan,¹ A Garg,^{2,3} S Raj,⁴ R J Singh² ¹Post Graduate Institute of Medical Education and Research, Chandigarh, ²International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ³Health and Family Welfare, Chandigarh, ⁴Punjab University, Chandigarh, India. Fax: (+91) 172 2744 993. e-mail: sonugoel007@yahoo.co.in

Background: Smoking is an independent risk factor for the development of tuberculosis and also decreases the effectiveness of the tuberculosis treatment. However, cessation may yield substantial positive effects on TB treatment outcomes, relapse and future lung disease. The Union recently called for inclusion of brief smoking cessation ABC package in standard TB case management. The objective of the present study was to ascertain the effect of a comprehensive smoking cessation intervention package on treatment outcomes of pulmonary tuberculosis patients.

Methods: This cluster randomized control trial was conducted among all pulmonary tuberculosis patients over 15 years of age, enrolled for DOTS in two quarters (January till June 2013), in all 17 Designated Microscopy Centres (DMCs) of Chandigarh, located in north India. The clusters were defined at the Designated Microscopy Centre (DMC) level with 9 DMCs as intervention arm and 8 as control arm. Both the arms received the established standards of care for Pulmonary TB patients along with DOTS treatment. The intervention arm received the standardized smoking cessation intervention package in addition to control arm. 'ABC for TB' is a package that delivers the activities of Ask, give Brief advice and provide Cessation support. It can be delivered by any health care worker within as little as 2-5 minutes within existing programme. These services are delivered at the time of registration and during sputum re-examination visits. The two arms were followed up until the treatment completion.

Results: Total 686 tuberculosis patients were enrolled in the study. 12.6% ($n = 87$) were daily smoker and 46.3% ($n = 318$) were smokeless tobacco users. Cure rate (68.1% vs. 62.6%), transfer out rate (4.7% vs. 3.6%) and defaulter rates (2.6% vs. 1%) was higher in intervention group than in control group but was not statistically significant. Treatment failure rate was statistically significantly higher in intervention group (4.9%) as compared to control group (1.7%). Patients who were willing to quit were significantly more in intervention group (84.8%) than control group (40.5%).

Conclusions: Participants who received comprehensive smoking cessation intervention package had a better outcome than who received the usual T.B care. The

comprehensive smoking cessation package should be integrated within existing Revised National Tuberculosis Control Programme (RNTCP) of country.

PC-882-04 In-school cessation in low-income schools in Mumbai

A Pilankar,¹ D Chadha¹ ¹Salaam Bombay Foundation, Mumbai, India. e-mail: ajay@salaambombay.org

Background and challenges to implementation: 14.6% of youth (age 13-15 years) use tobacco in India. Despite the high rate of tobacco use among children and youth, there are no cessation programmes available for youth and the costs of nicotine replacement therapies are prohibitively high. To curb the tobacco epidemic among youth, cessations programmes are urgently needed.

Intervention or response: Salaam Bombay Foundation (SBF) began an in-school cessation programme in 2012 in public schools in Mumbai for students in grades 5 to 10. The objectives of the cessation programme are to increase quit attempts, motivate users to quit, and prevent the transition from betel nut use to smokeless tobacco use. The SBF cessation programme provides an orientation for all students, and a 6-month counseling programme for students who register. Registered students participate in 6 group sessions designed to sensitize students to tobacco's harmful health effects, motivate them to quit, and coach them to build refusal skills and resist peer pressure.

Results and lessons learnt: Approximately 4000 students have been oriented to the cessation programme. 312 (7.8%) students have registered. Most of the registered students report betel nut consumption ($n=241$, 77.2%), tobacco consumption ($n=15$, 4.8%) or both ($n=56$, 17.9%). Following six counseling sessions (6 months after registration), students have ceased betel nut use ($n=210$, 87.1%), tobacco use ($n=11$, 73.3%), or both ($n=41$, 73.2%).

Conclusions and key recommendations: Cessation programmes for children and youth are needed in countries where youth tobacco use is high. While MPOWER measures advocate for cessation efforts in primary healthcare services and through free telephone quit lines, in-school cessation programmes should be adopted as well. School-based cessation programmes can be effective and should be designed specifically for child and youth users with an emphasis on: Role-playing to build refusal skills and address peer pressure Activity-based sessions to keep students engaged Orientation for school administrators and teachers.

PC-883-04 Smoking cessation outcomes among in-patients in a tertiary care hospital: learning from LifeFirst Programme in India

P Todankar,¹ V Thawal,¹ H Gupte,¹ L Choudhuri¹

¹RESEARCH, Narotam Sekhsaria Foundation, Mumbai, India. e-mail: priyamvada.todankar@gmail.com

Background: It is well documented that in India tobacco usage kills about 1 million people each year which is

more than TB, HIV/AIDS and malaria combined. It is estimated that if the trends continue then tobacco will account for 13% of all deaths in India by 2020. Taking into consideration the gravity of the issue, Narotam Sekhsaria Foundation (NSF), a leading grant making organisation in India is playing a pivotal role in devising and testing tobacco dependence treatment models in various healthcare and non healthcare settings under its' flagship programme 'LifeFirst'.

Design/Methods: Inpatient phase is seen as a vital opportunity to encourage and prepare patients to enroll in tobacco cessation programme. One of the models of LifeFirst is implemented in a tertiary care hospital in Mumbai for the inpatients. Training of resident doctors, nurses and other para-medical staff was conducted by NSF experts trained at Mayo clinic (USA). It emphasized on screening the admitted patients for tobacco use, providing brief advice and referral to specialist services. The other part of treatment protocol includes understanding patient inclination towards cessation; enrolling him/her in LifeFirst programme and providing detail follow up counseling over a span of 6 months through 6 follow up sessions.

Results: The discussion here includes smoking cessation among the inpatients reached till date through this model. Total numbers of inpatients who reported any form of tobacco use was 1443 cases. Of these, 397 (28%) were classified as smokers. When posed with the question on intention to join LifeFirst, 175 (45%) have stated that they are keen however only 109 (27%) joined. For these 109 cases, efforts were made to reach them with 6 input follow up sessions as per the treatment protocol. After 6 months completion, it is observed that 40% of them have received all 6 sessions and 60% have received less than that due to patient related issues. A comparative analysis of those who received all 6 sessions as against those who received less than 6 sessions indicates that the 7 day PPA at 6 months among those input completion cases is 47% whereas among the comparative group it is 28%. In both the groups, no remarkable difference was observed in terms of gender, marital status, age of initiation of tobacco use. Most of them were admitted in the cardiology department. These observed analyses of service data will guide to study the variation in the outcome in a more scientific manner.

PC-884-04 National survey of smoking cessation services in Iran's primary health care system

Z Hesami,¹ M Aryanpur,^{1,2} M R Masjedi² ¹National Research Institute Tuberculosis and Lung Diseases, Tobacco Prevention and Control Research Center, Shahid Beheshti University of Medical Sciences, Tehran, ²Iranian Anti Tobacco Association, Tehran, Iran. Fax: (+98) 2120 10484. e-mail: zahra_hessami@yahoo.com

Background: Delivery of smoking cessation supports via primary health care settings could be an effective way to increase people access to cessation services. This study was aimed at evaluating structural characteristics of

smoking cessation services established within the Iranian Primary Health care system.

Design/Methods: In order to obtain structural information about smoking cessation services, firstly a phone call was made with coordinating authorities of tobacco control programs in each university which are under supervision of Ministry of Health. Secondly, after describing the objectives of project they were asked to fill the related questionnaire. The questionnaire was available at MOH website and follow-up for its completion was done via telephone call.

Results: Smoking cessation centers started their activities in 2007 and their number increased between 2008 and 2011. In all primary health centers, smoking cessation services are provided free of charge. In sixty percents of centers individual therapy was used, a combination therapy (including pharmacotherapy) is highly preferred. Nicotine patch was the most common drug which is used (62 %) in smoking cessation clinics. General physicians are the main providers of smoking cessation programs in health care centers (87%). The number of smoking cessation centers in primary health care system decreased during years of 2011 (89 centers) and 2012 (79 centers) compare with 158 centers in 2010. There isn't national quit line in Iran.

Conclusion: This study shows smoking cessation programs provided in primary health care system in Iran. The present study gathered useful and updated information on structural of smoking cessation services in Iran's primary health care system.

PC-886-04 Cross-sectional survey on quitting attempts among adolescent smokers in Dharan, Eastern Nepal

P M S Pradhan¹ ¹Patan Academy of Health Sciences, Lalitpur, Nepal. e-mail: pramil.pradhan@gmail.com

Background: Tobacco dependence is known to be a chronic condition and only few of those who initiate quitting become successful. Adolescent smoking is in rising trend in Nepal. They often want to stop smoking and frequently attempt smoking cessation but are unable to maintain long term abstinence mainly because they are addicted to tobacco and experience withdrawal symptoms just like adults. This study aimed to explore the quitting attempts among adolescent smokers in Dharan Municipality of Eastern Nepal

Design/Methods: A cross sectional study was conducted using pre tested self administered questionnaire adapted from Global Youth Tobacco Survey to assess current smokers and quitting attempts among the representative sample of 1312 adolescent students in middle (14-15years) and late adolescence (16-19 years) selected by stratified random sampling from July 2011 to June 2012. Among them 182 were current smokers. Descriptive statistics were used to explore the reasons behind quitting, duration and willingness to quit in the future.

Results: The prevalence of current smoking was 13.7%. Among the current smokers, 66.5% had attempted to quit in the past because they believed smoking was

harmful to health (35.5%), their parents instructed them to quit (21.5%) and they did not want to continue smoking (10.7%). The median duration of quitting was 150 days (Inter-quartile range 60 to 315 days). Nearly 8% of the current smokers were unwilling to quit smoking in the future because they thought it is already a habit (60%) and they could not succeed to quit (20%). **Conclusion:** Even after multiple quitting attempts at smoking during adolescence, relapse often occurs. Tobacco focused interventions to support abstinence are of potential value at this stage where the adolescents are most vulnerable to habituate smoking.

PC-887-04 Effective method for quitting tobacco

A Tenna¹ ¹ADIC Alcohol and Drug Information Centre, Colombo 05, Sri Lanka. Fax: (+94) 112 508 484. e-mail: tennaamaranath@gmail.com

Background and challenges to implementation: In Sri Lanka, Tobacco prevalence is in decline trend. Cigarette consumption has reduced by 7% in 2014 compared to 2013. However, the usage is high in certain groups compared to the general public (ADIC spot survey, 2014). Through this survey, it was identified that officers in armed forces have a high prevalence rate of tobacco use (63%). Therefore, an intervention was implemented in Air Force and Navy camps in order to help smokers to quit smoking. **Objective:** To reduce tobacco consumption among soldiers in selected Air Force and Navy camps, Sri Lanka

Intervention or response: The intervention was conducted with 712 officers in 2014. Majority of the tobacco users were daily users ($n=236$, 53%). As the first step, a discussion was conducted with Public Health Officers (PHI) attached to the medical unit of the camps to introduce the programme. Respective PHIs organized awareness programme in their camps. ADIC conducted a 3-hour awareness programme to develop enthusiasm among soldiers to quit smoking. The strategy used was to calculate expenditure on tobacco and explain how they have become victims of tobacco industry. While increasing the enthusiasm to quit smoking, ADIC had introduced 6 steps method for tobacco quitting. Follow-up calls were given within 4 weeks.

Results and lessons learnt: 150 tobacco users were selected to evaluate the project impact. The evaluation was carried out in two stages. Firstly, the post test conducted at the end of the awareness programme revealed that 72(48%) took a decision to stop smoking and 68 (45.33%) decided to reduce smoking, 10 (6.66%) didn't respond. Second stage evaluation was conducted over the telephone conversations within a month after the awareness programme. 138 responded in total and 59 out of 72 smokers who decided to stop actually stopped smoking while out of the 68 who decided to reduce, 51 reduced, 12 decided quit and 17 have given up their attempt to reduce.

Conclusions and key recommendations: Most of the smokers want to be free from smoking. What is required

is an intervention that doesn't portray quitting as a difficult task rather an intervention that raises their enthusiasm to quit.

PC-888-04 Developing and evaluating a behavioural support intervention for smokeless tobacco cessation in Pakistan and the UK

O Dogar,¹ C Jackson,¹ R Bibi,¹ H Thomson,² I Kellar,³ K Siddiqi¹ ¹University of York, York, ²Leeds City Council, Leeds, ³University of Leeds, Leeds, UK. e-mail: ofd500@york.ac.uk

Background: Around 300 million people worldwide consume smokeless tobacco (SLT). Considered to be a part of the culture, its use is particularly common in people of South Asian-origin. A recent Cochrane review suggests that behavioural support interventions (BSIs) are likely to be effective in SLT cessation. However, studies in this review were mainly conducted in the US and European populations who, compared to South Asians, use less addictive and less hazardous products (e.g. moist snuff). Moreover, its consumption among South Asians has strong socio-cultural dimensions, which need to be considered in BSIs. We aim to evaluate the acceptability, feasibility and fidelity of a new BSI for South Asians trying to quit using SLT.

Design/Methods: This is a two-country, multi-methods pilot study, using qualitative and quantitative methods to develop a solid theoretical framework for development of a SLT cessation intervention that is culturally appropriate for use with the South-Asian population. The BSI was developed, tested and refined in three iterative phases: Development phase (6 months): Two expert panel workshops were conducted to, first, select the behavioural determinants of SLT use and related behaviour change techniques (BCTs) based on their importance and relevance and second, to inform the structure and key messages for the intervention. Feasibility assessment phase (8 months): The BSI was tested at five sites in the UK and Pakistan, delivered by trained cessation advisors to 32 SLT users. All BSI sessions (pre-quit, quit and post-quit) will be audiotaped and analysed for fidelity, 16 participants and four advisors will be interviewed in depth to assess the feasibility and acceptability. All study participants will be tested for SLT use status via urine/salivary cotinine testing at 6 months. Refinement phase (4 months): The BSI will be refined in light of the results from feasibility testing.

Results: Findings from the qualitative interviews, the audio-taped sessions' and participant SLT use status at 6 months will inform any further modifications needed in the content, structure or format of the BSI.

Conclusion: The refined BSI will be the first behavioural intervention of its kind developed specifically for SLT users of the South Asian-origin, with a comprehensive methodology involving the use of BCTs proven effective for tobacco cessation, ready for effectiveness testing in a randomised controlled trial.

23. Social media campaigns

PC-889-04 Using a social media tool to enhance formal media in exposing tobacco industries interference in Bangladesh

M Mehedi,¹ I Rasul¹ ¹PROGGA Knowledge for Progress, Dhaka, Bangladesh. e-mail: mehedi198598@gmail.com

Background and challenges to implementation: 23 million Bangladeshi people are actively using social media in a regular basis. This has become a popular mode of media linking people in and out of the country. The formal media is not much aware how to use this technology as a support for exposing tobacco industry interference. Recently PROGGA, which runs a network consists of 300 journalists all around Bangladesh launched a social media tool (www.facebook.com/tobaccoindustrywatch.bd) to expose tobacco industry interference at present and share the stories for all stakeholders including the journalist who are engaged in tobacco control. As this is a new technology the traditional journalists are not much used to using this tool. This is a challenge to implement this type of tool at this moment.

Intervention or response: The journalists were given training on social media tools usages in their day-to-day reporting in respective media houses. They were also trained to keep them updated using different types of social media tools.

Results and lessons learnt: News, stories, pictures, video and audio clippings, which reflects tobacco industry's interference were collected from different sources and were exposed and disseminated in the above mentioned social media tool and other electronic outlets. The journalists of the network contacted PROGGA to know more about this news stories and did further investigation for in-depth reporting on this issue. They published these stories in formal media and repeatedly exposed the company's ill tactics. Thus the tobacco industry had to stop many of the campaign/promoting activities they were running unlawfully. Thus how PROGGA exposed the tobacco industry's ugly faces to the policy makers and to the public showing concern for public health.

Conclusions and key recommendations: Exposing industry interference by social media hindered their business, which brings success to public health by preventing more people from tobacco usage. Usage of social media to combat industry interference should be highlighted by training more journalist and try to use this technique in their day to reporting activities.

PC-891-04 Education, communication and public awareness about tobacco control: findings from the ITC Brazil survey

C Perez,¹ F Mendes,² T Cavalcante² ¹Brazil Cancer Foundation, Rio De Janeiro, RJ, ²National Cancer Institute of Brazil, Rio De Janeiro, RJ, Brazil. e-mail: cperez@inca.gov.br

Background: Article 12 of the FCTC requires Parties to promote and strengthen public awareness of tobacco

control issues by providing broad access to public awareness programs on the health risks of tobacco consumption and exposure to tobacco smoke, and about the benefits of cessation. The International Tobacco Control Policy Evaluation Survey Brazil (ITC) measured changes in smokers' knowledge of specific health risks of smoking and perceptions of harm.

Design/Methods: The ITC Brazil Survey is a longitudinal cohort survey and was conducted in Brazil with 1,200 adult smokers and 600 adult non-smokers living in three cities. Telephone-administered surveys were conducted using an area stratified random sampling strategy, yielding a representative sample of the four largest cities in Brazil (Rio de Janeiro, Porto Alegre, and Sao Paulo). The Waves included questions a variety of tobacco control measures, including education, communication, and public awareness related to smoking.

Results: The ITC Brazil Survey asked respondents whether they had noticed any advertising or information about the dangers of smoking, or encouraged quitting. At Wave 1, 37% of smokers and 34% of non-smokers in the combined sample "often" or "very often" noticed information about the dangers of smoking. These percentages decreased to 25% of smokers and 21% of nonsmokers at Wave 2. At Waves 1 and 2, smokers were asked to report on various reasons that led them to think about quitting smoking in the last 6 months. There was a decrease in all reasons to quit between Wave 1 and Wave 2. Significantly, fewer smokers at Wave 2 stated that advertisements or information about the health risks of smoking "somewhat" or "very much" led them to think about quitting.

Conclusions: The findings suggest that noticing advertisements related to the dangers of smoking, or encouraging quitting, decreased between Waves 1 and 2. Only a quarter of smokers surveyed frequently noticed anti-smoking information at Wave 2. Similarly, there were decreases at Wave 2 in the percentage of smokers who thought about the harm smoking might be doing to them or to others. These decreases are of concern and suggest that anti-smoking campaigns and continued strengthening of educational activities are needed to increase the visibility of anti-smoking information, which is aimed especially to prevent smoking initiation and to encourage quitting.

PC-892-04 Media intervention as a tool to oppose tobacco industry interference

B Sharma¹ ¹Freelance, Indore, India. e-mail: silkdrops@rediffmail.com

Background and challenges to implementation: In India one of the member of parliamentary committee to review tobacco control in India said that there are no Indian studies to prove link between tobacco and cancer. Later on it was found out that the statement was given by committee member who had bidi manufacturing unit. As India is signatory to Framework Convention on Tobacco Control (FCTC) and article 5.3 of FCTC prohibits tobacco industry interference, the comment by a

committee member was taken seriously by Indian media and lot of media intervention was done in the matter.

Intervention or response: Media response regarding the comment of parliamentary committee member was observed in Dainik Bhaskar newspaper which is one of the leading newspaper in India. News was analysed for a period of 15 days.

Results and lessons learnt: Front page news was published with catching headlines like "smoking 60 cigarettes a day with no cancer, no death". The headline was very effective in generating public interest and putting pressure on government. Newspaper also called all the 15 members of the committee and asked them about their views on the matter, their views published on front page. Statement of opposition leaders and ex Health Minister in favour of tobacco control also published. A special viewpoint of newspaper editorial in support of tobacco control was also published. Newspaper highlighted the link between parliamentary committee members and tobacco industry and direct conflict of interest was exposed. The newspaper also exposed the fact that as government has to implement pictorial warning on 85 % of tobacco package and in order to prevent that the committee members were trying to postpone the implementation of pictorial warning. Emotional stories of tobacco victims were published. Government of India had to intervene in the matter and Prime Minister Said that there should be no conflict of interest involved in taking decisions related to tobacco control.

Conclusions and key recommendations: Media stories when drafted in a good manner and published regularly with good space can play an important role in exposing tobacco industry interference.

PC-893-04 Media advocacy for the implementation of regulating smoking in films

B Mathew¹ ¹Voluntary Health Association of India, Delhi, India. e-mail: binoymathew84@gmail.com

Background and challenges to implementation: India, the world's largest producer of movies produces more than 1000 movies a year in several languages. Bollywood represents the Indian Hindi movie industry and the worldwide viewership for their movies is estimated to be about 3 million. Bollywood movie stars in India are public figures, have large fan followings and exercise tremendous influence on the behavioural attitudes of adolescents. One of the major influences on the uptake of teen tobacco use is the glamorization of tobacco use in movies and on television. Movies are seen as very influential for kids and teens.

Intervention or response: Using earned media to create pressure on policymakers and to put indirect pressure on the Government to ensure implementation of the rules notified by the Government of India which firmly intended to regulate the depiction of tobacco use in Films and Television with effect from the prescribed date of implementation. The strategy was to ensure that news items or stories come out to attract the attention of the

government and the public. I increased consumer awareness about the issue of smoking scenes in films through a sustained strategy of media engagement. We increased our interactions with the media, both on a one-to-one basis.

Results and lessons learnt: In order to sustain the media's engagement with the issue, over the period of time, about 8 to 10 press releases were shared with the journalists and this strategy of media advocacy resulted in nearly 40 – 45 stories in National and Vernacular Media during May to December 2012.

Conclusions and key recommendations: Extensive media coverage pan India (spanning national, regional and local media), Ensured that news items or stories on prohibition of smoking in films are published/aired regularly to attract the attention of the government and the public. From November 2012 onwards, the new films screened at movie halls started showing the disclaimers" of 30 seconds each on the ill-effects of tobacco use with strong graphic pictures of cancer affected mouth, pictures on how smoking causes heart attacks, effects of second hand smoke etc both in English & Hindi that appeared in the beginning and during the interval of the movie.

PC-894-04 #AnswerSunita: a social media advocacy campaign to protect new pack warning notification in India

P Puri,¹ S Hamill,¹ D Svenson,¹ P Chaturvedi,² N Murukutla,¹ S Mullin,¹ V Mallik,¹ T Johnston¹ ¹World Lung foundation, New York, NY, USA; ²TATA Memorial Hospital, Mumbai, India. e-mail: ppuri@worldlungfoundation.org

Background: In August 2014, then Health Minister of India launched a national tobacco control testimonial campaign "Sunita" who after being diagnosed with tobacco-related oral cancer at a young age of 27 years underwent major surgery and then agreed to tell her story in a PSA to raise awareness about the harms of tobacco. Two months subsequent to campaign launch, new larger and stronger pack warnings were notified to be implemented from 1st April'15. However, the move was delayed after tobacco industry interference. Ironically, Sunita died on the same day of implementation, leaving a letter with dying request of larger graphic Pack Warnings to PM Modi. WLF and partners launched #AnswerSunita, a social media advocacy campaign aimed at highlighting the cost

Intervention or response: The key message of the campaign was "PM Modi: #AnswerSunita's dying request and pick children's health over tobacco industry profits by passing larger graphic pack warnings." The ongoing effort was intended to be intense but short lived, working in synergy with advocacy efforts from other partners. The campaign comprised of four main pieces – an online #AnswerSunita microsite with "death clock" and "profit clock", social media tools like Thunderclap (an "online flash mob" application), Facebook and Twitter, traditional media PR and daily social media messages.

Results: The campaign generated more than 200 news stories in three days and helped build pressure on the government. The campaign reached over 275 000 people through social media, with many signing up to a ThunderClap campaign to simultaneously tweet Prime Minister Narendra Modi calling for larger graphic warnings. Monetization of the media coverage is underway.

Conclusions: This paper demonstrates how social media tools can be used to target messages to policy makers in India. The #AnswerSunita campaign served as a "framing" tool, which allowed advocates to portray the human face of the issue and the health costs. The campaign underscores how social media can hold significant promise for tobacco control advocacy.

PC-895-04 Media coverage of tobacco control activities in Mizoram, India, 2011-2014

J R Ralte,¹ T Lalbiaksanga,¹ L Rokhum,¹ H Renthlei,² L Lalnuntluangi,³ Z Chhakchhuak,³ R J Singh⁴ ¹Mizoram State Tobacco Control Society, Aizawl, ²Mizoram University, Department of Management, Aizawl, ³Health & Family Welfare, Govt. of Mizoram, ⁴International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: tluangtlei@gmail.com

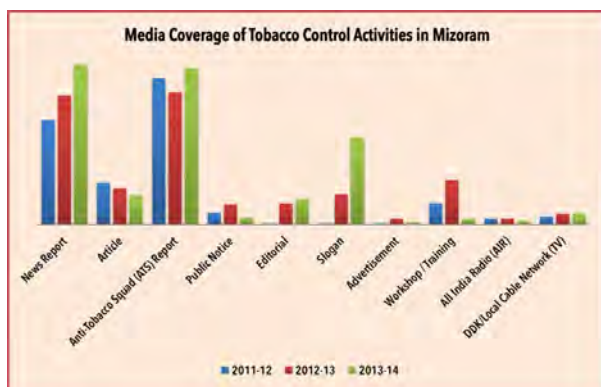
Background: Mizoram, a tiny Northeast Indian state has the highest prevalence of adult tobacco use in India - 67% (GATS 2009). Mizoram State Tobacco Control Society (MSTCS) has undertaken the task of implementing tobacco control activities in the state. MSTCS has worked in close partnership with the Mizoram Journalists' Association (MJA) and as a result has garnered strong support from the media. Since unpaid media coverage is a good indicator of public education and awareness regarding a particular issue, improving media coverage of tobacco control activities in both print and digital media is a positive development towards reducing tobacco use prevalence. This study attempts to assess the level of media coverage received by tobacco control activities in the state from 2011 to 2014.

Design/Methods: A detailed analysis of tobacco related news articles in print media (8 major newspapers) and digital media (television & radio) was conducted for the period 2011 - 2014.

Results: A steady increase in coverage of tobacco related news and anti-tobacco squad (ATS) has been observed. Over the study period, 31% ($n = 339$) of all media coverage is news report of tobacco control activities in print media; 34% ($n = 375$) is ATS related. 9% ($n = 102$) are slogans and 8% ($n = 92$) are articles/essays. 6% ($n = 61$) are related to trainings and workshops. Other print media items are Public notices - 3% ($n = 33$), Editorials - 3.7% ($n = 41$), advertisements (anti-tobacco messages) - 0.7% ($n = 8$). Digital media coverage is relatively lesser - 1.1% ($n = 13$) for All India Radio and 2.2% ($n = 25$) for Doordarshan (national television). The Figure depicts the increasing trend in media coverage.

Conclusion: Due to close partnership and collaboration with media personnel and MJA, MSTCS has made great strides in making tobacco control visible and a part of

daily life for Mizos through unpaid media coverage. This will be instrumental in conditioning the social environment in relation to smoking and aid in reducing the overall prevalence of tobacco use in the future. Future efforts should focus on increasing digital media coverage and more articles on harmful effects of tobacco in print media.



PC-897-04 Social media workshop for tobacco control

C Garcia^{1,2} ¹FTC Alliance, Philippines, Quezon City, Philippines; ²World Lung Foundation, New York, NY, USA. Fax: (+632) 441 4383. e-mail: kaloi.garcia@gmail.com

Background and challenges to implementation: In this day and age, the potential of social media cannot be taken for granted. With the Youth as the main users of Social Media, tobacco control advocates should know how to maximize the necessary tools to reach out to the Youth, which are also the main target of the tobacco industry. This training workshop aims to arm selected Tobacco Control advocates with appropriate knowledge on the use of Social Media by increasing their capacity in public engagement to promote tobacco control issues using digital social media tools. Health Promotion Officers from different Regional Department of Health offices, Tobacco Control Focal Points and Local Legislators coming from 16 Regions of the Philippines attended the workshop.

Intervention or response: The 8-step Communication Planning template of the World Lung Foundation was used in this workshop. To wit: Step 1: Define the problem Step 2: Identify target audience Step 3: Develop campaign goals Step 4: Create key messages Step 5: Partnerships & resources Step 6: Campaign materials Step 7: Implementing the campaign Step 8: Evaluate the campaign In addition, a SWOT (Strength-Weakness-Opportunities-Threats) Analysis using World Cafe methodology was incorporated in the workshop to probe deeper in defining the tobacco problem in the Philippines. Establishment of a pool of social media campaigners in expanding the tobacco control movement's sphere of influence, create demand for stronger smoke-free policies, and help develop a digital communication plan amongst advocates of the Regional and Provincial

Tobacco Control Networks are among the results of this Social Media Workshop for Tobacco Control.

Results and lessons learnt: Six Communication Plans were developed to address the problems identified in the SWOT Analysis. More hands-on time should have been given to participants to enable them to experience the actual procedures in posting contents using Facebook, Twitter and other social media platforms. Having a contest within the workshop pushed the participants to engage and ask support within their own network of friends in their social media circles. With the pool of new social media warriors, online campaigns can easily be launched and get national and local support.

Conclusions and key recommendations: More and more tobacco control advocates all over the world should be given this kind of training to be effective and stay relevant in maximizing the use of social media in tobacco control.

24. Engagement of CSOs, communities and patients in TB control and management

PC-898-04 Outcomes of private practitioners' engagement in tuberculosis case notification in Afghanistan: a document review

H Akhgar,¹ H Manochehr,¹ M Rasoli,¹ G Qader² ¹Ministry of Public Health, Kabul, ²Management Sciences for Health, Kabul, Afghanistan. e-mail: ntp.mhakhgar@gmail.com

Background and challenges to implementation: The private health sector progressed significantly in Afghanistan. According to an assessment private sector is the first contact for 65% of Afghans. Also, large number of persons presumptive to have TB attending these facilities that usually go unprofessional identification, diagnosis and treatment that usually resulted in delayed diagnosis and treatment initiation of TB. Addressing these challenges, NTP conducted national situation analysis (NSA) for public private (PPM) DOTS strategy, policy, and practical guidelines drafted, to establish a framework for TB services by private health provider, indicating the actions required for implementation and successful achievement of the strategy. We assessed the outcomes of implementation of PPM-DOTS strategy on TB case notification and treatment in three provinces of Afghanistan.

Intervention or response: The team used standard TB program's recording and reporting forms as data collection tools. Between January to December 2014, a total of 140 private practitioners oriented on TB DOTS, conducted regular quarterly review workshops aiming at monitoring DOTS implementation through private practitioners.

Results and lessons learnt: The data for Jan-Dec 2014 shows that in 4806 presumptive TB cases referred by those engaged in PPM, of them 2034 cases diagnosed as TB all forms that made 6% of total diagnosed TB cases in the country and 712 cases as bacteriological confirmed

TB. Also, 819 cases diagnosed as sputum smear negative TB cases and 503 extra pulmonary TB cases.

Conclusions and key recommendations: The above findings shows that engagement of private practitioners contributed to significant improvement in TB case notification in intervention provinces, improved referrals and strengthened coordination mechanism between public and private health facilities, also, a sustainable partnership for TB control established with the private practitioners. Thus, we strongly recommend scale up of PPM DOTS to other provinces and similar settings elsewhere.

PC-899-04 A community-based multi-department linked collaborative tuberculosis control model in China

H Su,¹ I Tang¹ ¹Minhang District Center for Disease Control and Prevention, Shanghai, China. Fax: (+86) 215 488 5229. e-mail: suhualin@sina.com

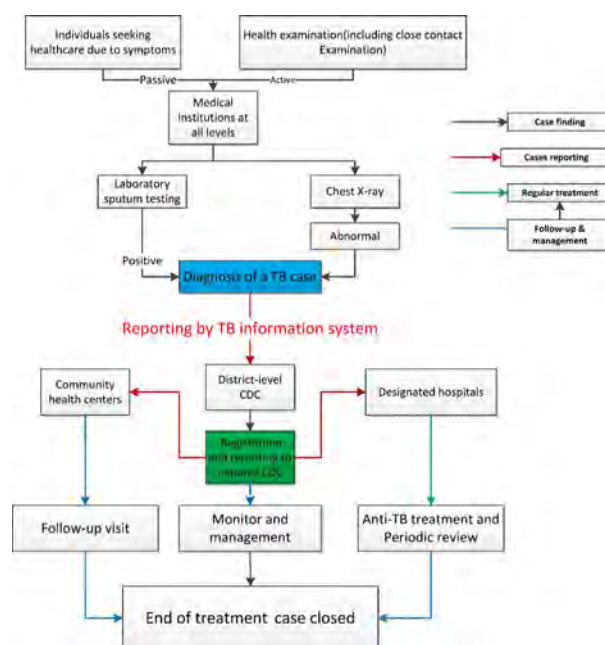
Background and challenges to implementation: China has the world's second largest tuberculosis epidemic (after India). After 2004, the government increased its commitment and leadership to tackle public health problems and, among other efforts, increased public health funding, revised laws that concerned the control of infectious diseases. Before 2000, specialized TB hospitals in Shanghai were in charge of the diagnosis and treatment of TB. With the development of society of China, the system faced with many challenges. One group of special concern is work migrants, most often poor men, who leave the countryside to join the wage economy in towns and cities all over China. The Chinese experience has shown that investment in community-based intervention control programs of TB was needed, and indeed essential, to improve the adherence to anti-TB treatment, especially for migrants.

Intervention or response: A community-based multi-department linked collaborative tuberculosis control was established in the Minhang District. Under the system, district CDC are in charge of planning, surveillance, management, monitoring, assessment, health education and faculty training of TB control and prevention; the TB designated hospitals are responsible for the reporting, diagnosis, treatment of TB patients; the community health centers are the venues for delivery of medications, observed treatment, contact tracing and health education of TB patients. The core characteristics of the system are multi-department linkage and decentralization of the facilities related to the TB control. All TB suspects are compulsorily referred to designated hospitals for diagnosis and treatment. Once a patient is diagnosed as TB, community health centers will perform the management and follow-up for the patients. The CDC will train the staff, monitor DOTs implementation and conduct assessment for TB program regularly.

Results and lessons learnt: Since the program was initiated in 2003, referral arrive rate increased from 64.91% to 95% in 2014. The coverage of monitoring for the migrants increased from 54.98% to 98% in 2014.

The cure rate for smear positive migrants increased from 11.36% in 2003 to 84.49% 2013, with no significant difference with local residents.

Conclusions and key recommendations: The community-based multi-department collaborative tuberculosis control model has a positive impact on TB control and prevention.



PC-900-04 Using community health volunteers to reach TB patients living in remote areas: the islands of South Nias Regency, Indonesia

E Siahaan,¹ J Ake,¹ S Ruschak¹ ¹Yayasan Menara Agung Pengharapan Internasional, Medan, Indonesia. Fax: (+62) 787 7636. e-mail: esiahaan@map.org

Background and challenges to implementation: South Nias Regency is one of the most under-developed areas in Sumatera Province, Indonesia. It contains over 100 islands, many of which are inhabited by indigenous people. TB prevalence in the Regency is higher than the revised national estimate, but due to the lack of human resources and the high transportation costs between these remote islands, many TB patients do not access care.

Intervention or response: Indigenous community volunteers were recruited and trained to screen for symptoms of TB. Individuals suspected of having TB were then referred to a health facility for smear microscopy. Community volunteers facilitated transportation to ensure testing occurred. When a patient was detected, the volunteers helped to initiate and follow up treatment on the remote islands. In addition to these community-based activities, laboratory technicians were trained and monitored to improve the quality of diagnostic services offered through government health facilities.

Results and lessons learnt: In a span of just 9 months, 1536 community volunteers screened over 50 000 people

for symptoms of TB across 112 villages. These activities resulted in the detection of 579 suspected TB patients who were referred for testing. Over 225 smear-positive TB patients were diagnosed and 44 of these newly detected patients were among children aged less than 14 years. These active case finding activities resulted in +86% increase in new smear-positive case notifications compared with the same quarters in the prior year, indicating that the TB patients detected among people living on remote islands would likely not have been treated in the absence of the project.

Conclusions and key recommendations: This project demonstrates that community health volunteers can be a highly effective solution for expanding TB care services into remote and underserved populations in conjunction with strengthening existing government laboratory services. In light of the significant upward revision of Indonesia's prevalence estimate and subsequent decline in its case detection rate, initiatives which are able to expand services and demonstrate increases in anti-TB treatment uptake should be prioritized for scale-up.

PC-901-04 Does timing of household visits for active tuberculosis case finding affect outcomes in a community-driven TB control program in India?

N Singh,¹ B Thapa,¹ D R Mishra,¹ A Das,¹ S Chadha,¹ S Mohanty,¹ J Tonsing¹ ¹International ⁴Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: bthapa@theunion.org

Background: A civil societies are engaged in community driven Tuberculosis (TB) care and control programme in northern Himalayan state Uttarakhand since April 2103. Every month, 13 000 households are visited by community volunteers to disseminate TB related messages, find presumptive TB patients (PTBP) and link to the diagnosis and treatment services. Regular transportation is an issue and activity is conducted during the afternoon hence reaching all individuals in a household is a challenge. The study aims to determine whether the intervention conducted in the morning will lead to higher reach of household individuals, dissemination of TB related messages, identification of PTBP and TB diagnosis.

Design/Methods: The intervention was carried in 2 marginalized villages –15 kilometres from nearest microscopy centres-in Haridwar Districts of Uttarakhand. The number of households were 900 (Bhogpur) and 1100 (Shapura). The household visits were made by community volunteers between 7 –11 am (morning) in Bhogpur and between 11 am-4 pm (afternoon) in Shapura. The intervention included; dissemination of TB related messages (symptoms, free diagnosis and treatment services), distribution of information, education and communication (IEC) materials, identification of presumptive TB patients (PTBP) through screening of household individuals for cough or 2 or more than 2 weeks and linking to diagnosis and treatment services.

Results: Community volunteers visited 887 (98%) and 880 (80%) households in the morning and afternoon,

respectively. Of those visited, 60% (3316/5566) and 55% (2569/4701) individuals were directly reached during the intervention with 5% increase ($P < 0.001$) and an additional 747 individuals were reached in the morning. Interestingly the morning and afternoon interventions reached more children (70% and 67%), and females (56% and 62%), respectively. Proportion of PTBP identified in the morning was 1.4% (45/3316) in comparison to 2.5% (65/2569) identified in the afternoon ($P > 0.05$). Of those, 2 (7.4%) and 3 (4.5%) TB patients were diagnosed and initiated on treatment, respectively ($P > 0.05$).

Conclusion: 747 individuals were additionally reached through household visits conducted in the morning. Household visits in the morning could reach more individuals in a community driven TB control programme in geographically constrained villages of Uttarakhand.

PC-902-04 Local participation for TB control by using a community-based organization model in migrant populations

R Chantichai,¹ C Thamsuwan,¹ T Samart² ¹World Vision Thailand, Bangkok, ²World Vision Thailand, Ranong, Thailand. Fax: (+662) 229 211. e-mail: ruangtong.ann@gmail.com

Background: Since 2007, the World Vision Foundation of Thailand (WVFT) has received the trust and budget support from the Global Fund - Round 6 as the Principal Recipient for the project entitled "TB Reduction among Non-Thai Migrants" (TB-RAM). WVFT received additional funding as a Sub-Recipient to DDC, MOPH as part of the project entitled "Universal access to quality TB control & care and empowering communities in Thailand". Both projects ended as of Sep14, but there is continuing implementation to develop the cadre of migrant workers (MW) to function as migrant health volunteers (MHV) for referral community members who have symptoms of TB for diagnosis. These MHV then administer DOT for those persons diagnosed with TB.

Intervention: Project implementation in 5 border provinces are Phuket, Phang Nga, Chumporn, Ranong, and Tak. Start from recruitment of MHV who then formed groups of MW to establish CBO, with WVFT as the coordination focal point and mentor in defining the nine sections of the program as follows: (1) Community Participation; (2) Conduct the activities in community such as revolving funds to assist TB and HIV cases, occupational development, etc.; (3) Form task forces for ad hoc activities; (4) Recruit general membership; (5) Conduct finance & accounting & auditing; and (6) Perform miscellaneous tasks. Members of the program share information on activities with stakeholders on a regular basis at various local forums. Implementers use these program meetings to provide educational information on TB and other prevalent diseases, and information on rights of MW related to health promotion. There is capacity building of the network of MHV, and an

emphasis on TB case-finding at the earliest stage of illness for immediate referral for proper therapy.

Results: The program conducted training for over 5000 MHVs. A total of 56 CBOs have been established with nearly 2000 members. There is a set of SOP for coordination of case referral for those suspected of having TB based on case-finding activities of the MHV.

Conclusions: The creation of this CBO is continuing beyond the end of the external Project funding. The MHV continue to provide TB education, screening and referral for their communities. Thus, this is an example of a locally-sustainable CBO for TB control which can be expanded to address other infectious and non-communicable diseases that affect these expanding communities of MW in Thailand.

PC-903-04 Integrating HIV and malaria into TB outreach: lessons learnt from TB elimination campaigns conducted in 2014 in Imo State, Nigeria

A F Omoniyi,¹ G Akang,² A Awe,¹ C Orji,³ G Madu,³ M Gidado,⁴ J Kuye,² E Oyama¹ ¹World Health Organization Country Office, Abuja, ² National Tuberculosis and Leprosy Control Programme, Abuja, ³Imo State TBL Control Programme, Owerri, ⁴KNCV Tuberculosis Foundation, Abuja, Nigeria. e-mail: omoniyifadare@yahoo.com

Background and challenges to implementation: Imo state with population of 3.9million ranked high among the 6 high TB-HIV burden states in Nigeria. The state notified 8% of the estimated TB cases in 2013. The programme in collaboration with the HIV and malaria programme in 2014 conducted an outreach in one of the LGAs with the lowest case finding in the state. The aim of this study is to assess what worked, challenges and lessons learnt in the integration of HIV and Malaria into TB outreach.

Intervention or response: Desk review was done to identify LGA and community with high TB burden, which led to the selection of the Amakohia/Akauma community in Owerri North LGA. PHC Health workers and community workers were trained; microscopes, anti-TB drugs, HIV and malaria rapid test kits, posters in local language and other tools were provided. Community workers went around the community for one week inviting community members with TB signs and symptoms to the PHC. TB diagnosis performed with sputum AFB using front-loading system, presumptive TB cases were routinely screened for HIV and malaria. Diagnosed TB cases were started on anti-TB drugs, those with malaria positive results were giving anti-malaria drugs. HIV positive clients were linked to the nearest HIV treatment center. GeneXpert test was done for chronically ill patients with AFB negative results.

Results and lessons learnt: 308 TB suspects (125 males & 183 females) were seen during the one week TB elimination campaign, 60% whom were females. 5% (15) of the TB suspects were diagnosed with TB. 14(93%) of the diagnosed TB cases were bacteriologically positive. 82% (253) of the TB suspects were tested for HIV, 2% (5) were HIV positive. 14.4% (2) of the TB patients was found to be HIV positive. All the TB-HIV

co-infected patients were started on CPT. 70% (217) of the presumptive TB cases were tested for Malaria; 17% (36) of whom were positive and treated for malaria.

Conclusions and key recommendations: TB outreaches provide opportunity for HIV and malaria programmes to reach members of the community with their services at the same time in a cost effective manner using the same structure. The integration also ensure access of TB cases to HIV and Malaria services. Most of the presumptive TB cases with history of fever could also be having malaria as shown by 17% malaria positivity rate among presumptive TB cases. Collaboration with malaria programme should also be strengthened in addition to that with HIV programme.

PC-904-04 Increasing access to TB diagnostic services through remote smearing stations in Zamboanga City, Philippines

R Agbulos,¹ J Bue,¹ T Yu,² S Dela Cruz,² S Masulit,² A Lagos³ ¹Systems for Improving Zamboanga City Health Office, Zamboanga, ²Philippine Business for Social Progress, Manila, ³Management Sciences for Health - SIAPS, Quezon, Philippines. e-mail: virgilbelen@gmail.com

Background and challenges to implementation: Microscopy services are available in all 16 health districts, 10 hospitals, and 31 private clinics in Zamboanga City (population: 907 725) in southern Philippines. However, these are mainly in the urban center, out of reach of people living in island and remote barangays (villages). TB diagnostic services are inaccessible due to distance, limited availability and high cost of transportation, poor road infrastructure, and high cost of staying in the city. This contributed to missed opportunities for TB diagnosis and subsequent treatment.

Intervention or response: In 2008, USAID/Philippines supported the establishment of 12 remote smearing stations (RSS) in access-poor villages. The RSS made use of the barangay health station or any appropriate pre-existing structure which was designated as smear preparation area, and engaged barangay health workers (BHWs) as informal laboratory workers (ILWs) after completing a rigorous three-day training. Quality assurance and infection control practices ensured quality smears and safe handling of specimens. The RSS initiative applied a systems approach consisting of (i) a situational analysis to determine the need for, feasibility, and acceptability of RSS in an area; (ii) advocacy to secure the barangay government's commitment to provide logistical and community support; (iii) training of ILWs in sputum smear preparation, infection control, and recording and reporting using a modified training curriculum designed specifically for ILWs; and (iv) strengthening the system for RSS operations, including a system for the referral and transport of slides with smeared sputum, local financial support, supply management, recording and reporting, quality assurance, supervision, and monitoring and evaluation.

Results and lessons learnt: The RSS brought diagnostic services considerably closer and made access more

convenient for patients and health workers in remote areas. This led to increased detection of new smear-positive cases among residents living in remote areas. In 2008, the RSS contributed 3% (33/1095) to the city's total smear-positive cases, and nearly half or 46% (417/901) in 2014.

Conclusions and key recommendations: The RSS brings quality-assured diagnostic services to underserved TB clients in remote and inaccessible areas where microscopy services are unavailable, thus addressing equity issues.

PC-905-04 Piloting Photovoice as a participatory research methodology in a cookstove adoption study in Malawi

J Ardrey,¹ N Desmond,¹ R Tolhurst,¹ K Mortimer¹

¹Liverpool School of Tropical Medicine, Liverpool, UK. e-mail: jane.ardrey@lstm.ac.uk

Background: Many rural Malawians cook on open fires and are exposed to high levels of air pollution from burning biomass fuels (crop residues, wood, charcoal). The WHO Global Health Observatory Report 2014 estimates that household air pollution (mainly from cooking) resulted in 4.3 million deaths worldwide in 2012. The Wellcome Trust has a specific challenge of 'connecting environment, health and nutrition' and supports research that bridges these themes. The Cooking and Pneumonia Study (CAPS) is a Wellcome Trust, MRC and UKAid funded village-level ($n=150$) randomised controlled trial underway in Malawi (www.capstudy.org). The CAPS intervention is an efficient burning advanced cookstove that may reduce exposure to household air pollution.

Intervention: The primary aim of CAPS is to study the impact of the intervention on pneumonia in the under 5s. It also provides a unique opportunity to gain understanding about the social and cultural factors that may facilitate sustained use of improved cookstoves. In January 2015 the use of Photovoice as a participatory research methodology was piloted at the CAPS Chikhwawa site. Photovoice is a photographic technique that allows communities and particularly women to share knowledge about their perspectives and priorities in areas such as food, cooking and household labour. For this Wellcome Trust-funded pilot study 4 households (6 individuals) were trained to use a basic digital camera and asked to collect images related to food and drink. After 24-48 hours the cameras were collected and the images processed. Each household was then interviewed about why they took the images and this process was captured on film. These interviews were conducted by CAPS fieldworkers who were given guidance about the methodology and provided with a topic guide.

Results: The pilot Photovoice work generated over 400 images and a 1 hour film that are revelatory of community concerns about food and cooking and can be thematically analysed. The participants were able to use the technology after training (only 1 participant had used a camera before), to produce clear and relevant images and to explain their selection. The collection of

interview data through film was useful for capturing discussion and was acceptable to participants and field staff.

Conclusion: Photovoice is a feasible participatory research methodology that can play a valuable role in qualitative studies of improved cookstove adoption in challenging developing country settings.

25. HIV and lung health: something for everyone

PC-906-04 Spirometric restrictive pattern in HIV-infected subjects: a cross-sectional comparative study

P-Y Walter,¹ E W Pefura-Yone,^{1,2} V Poka,¹

A D Balkissou,^{1,2} A P Kengne³ ¹Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, ²Yaounde Jamot Hospital, Yaounde, Cameroon; ³Medical Research Council, Cape Town, South Africa. e-mail: pefura2002@yahoo.fr

Background: Restrictive spirometric pattern is a risk factor for all-cause and cause-specific mortality. We are not aware of studies evaluating restrictive syndrome in HIV-infected individuals. Accordingly, we conducted a cross-sectional study to determine the prevalence of spirometric restrictive pattern according to HIV infection status, and investigated the determinants of restrictive pattern in HIV-positive individuals in Yaounde.

Methods: A group of HIV-positive subjects, and age and sex matched HIV-negative controls group were enrolled. HIV-positive subjects were recruited in the approved center for HIV treatment of Yaounde Jamot Hospital between November 2012 and April 2013, and controls were recruited through multilevel stratified random sampling in general population in Yaounde, Cameroon between December 2013 and April 2014. Spirometric restrictive pattern was defined by a forced expiratory volume in 1s/forced vital capacity (FEV1/FVC) ratio $\geq$ lower limit of normal (LLN) and FVC $<$ LLN (LLN-restrictive pattern) or by FEV1/FVC ratio $\geq$ LLN and FVC $<$ 80% (fixed cut-off -restrictive pattern). Logistic regression models were used to investigate the determinants of restrictive pattern.

Results: Final sample comprises 430 HIV-positive subjects (68.4% women) and 444 HIV-negative subjects (68.9% women). The mean % predicted FEV1 was lower in the HIV-positive group compared to HIV-negative group (90.12% vs. 95.01%, $P < 0.001$). The mean % predicted FVC was also lower in HIV-positive subjects (88.51% vs. 95.44%, $P < 0.001$). The prevalence of LLN-restrictive pattern was 37.7% among HIV-positive subjects and 23.2% in HIV-negative patients ($P < 0.001$). Similarly, the prevalence of restrictive pattern based on the fixed cut-off was higher in HIV-positive subjects (28.8%) compared to HIV-negative subjects (18.5%), $P < 0.001$. In multivariable analysis including age, sex, education level, smoking, exposure to biomass and body mass index, HIV infection remained associated

to restrictive pattern regardless of definition used. In further multivariable analysis in the HIV-positive group, independent determinants of LLN-restrictive pattern were low formal education [odds ratio (95%CI):1.66 (1.08–2.57), $P = 0.022$] and smoking [1.97(1.08–3.59), $P = 0.027$]. Independent determinants of fixed cut-off-restrictive pattern in HIV patients were the low formal education [2.25(1.40–3.62), $P = 0.001$] and chronic respiratory symptoms [(2.00(1.26–3.15), $P = 0.003$].

Conclusion: HIV infection is associated to high prevalence of spirometric pulmonary restriction. The determinants of restrictive pattern should allow early identification of HIV-positive subjects necessitating specific interventions.

PC-907-04 Impact of HIV-coinfection on the clinical presentation of childhood tuberculosis in Ghanaian children

A Enimil,^{1,2} F Gallani,³ A Sarfo,² D Bosumtwe,² T Opoku,² A Badu-Peprah,^{1,2} S Antwi,^{1,2} A Kwara^{3,4} ¹Kwame Nkrumah University of Science and Technology, Kumasi, ²Komfo Anokye Teaching Hospital, Kumasi, Ghana; ³Miriam Hospital, Providence, RI, ⁴Warren Alpert Medical School of Brown University, Providence, RI, USA. e-mail: tonash@gmail.com

Background: Childhood Tuberculosis (TB) remains a major cause of morbidity and mortality globally. HIV-infected children are at a higher risk of developing active TB and TB-related death. To understand the effect of HIV disease on the clinical manifestations of TB in children, we compared presenting symptoms and signs of TB in the children with and without HIV coinfection.

Design/Methods: Children aged 3 months to 14 years old with clinical diagnosis of TB with or without HIV were enrolled into a prospective pharmacokinetic study of first-line anti-TB drugs at Komfo Anokye Teaching Hospital, Kumasi, Ghana. Baseline medical history and examination were documented by the attending clinician, entered into Microsoft access and analyzed in R statistical software. Descriptive statistics were used to summarize the patient characteristics. χ^2 test was used to compare dichotomized clinical variables. Continuous variables between the two groups were compared using Student's *t*-test or Mann-Whitney U test (if data distribution was skewed).

Results: Of the 144 children, 52 (36.1%) had TB alone, 82 (56.9%) were females and 117 (81.2%) had pulmonary TB. There was no difference in median age, age distribution or sex distribution between the two groups. Pulmonary TB was diagnosed in 88 (95.7%) of 92 children with TB and HIV coinfection and in 29 (55.8%) of 52 of children with TB alone ($P < 0.00$). The TB diagnosis in children with TB alone vs. TB-HIV coinfection was clinical in 71.7% vs. 67.4%, radiographic in 23.1% vs. 28.3% or smear-positive in 5.8% vs. 4.3%, respectively. There was no significant difference in the proportion of children presenting with cough, weight loss, diarrhea, headaches, lymph nodes enlargement, and shortness of breath, vomiting and fever among the groups ($P > 0.05$). Skin rashes ($P < 0.023$), oral

thrush ($P < 0.05$), pallor ($P < 0.03$), and failure to thrive ($P < 0.002$) were significantly more common in children with TB-HIV coinfection. Median (IQR) of weight in Kg was significantly lower ($P < 0.023$) in TB with HIV. The frequency of Ghon focus, adult-type infiltrate, cavitation, lymphadenopathy, pleural effusion, or pericardial effusion on chest radiographic examination were not different by HIV status ($P > 0.05$).

Conclusion: Overall, the clinical manifestations appeared similar between the groups. However, the presence of skin rashes, failure to thrive, pallor or oral thrush should prompt evaluation for HIV coinfection to enable early initiation of cotrimoxazole and concurrent antiretroviral therapy.

PC-908-04 Baseline anaemia among HIV-infected and non-infected patients initiating treatment for rifampicin-resistant tuberculosis in Khayelitsha, South Africa

J Hughes,¹ E Mohr,¹ V Cox,¹ L Wilkinson,¹ G Van Cutsem,² H Cox³ ¹Médecins Sans Frontières (MSF), Khayelitsha, ²MSF, Cape Town, ³University of Cape Town, Cape Town, South Africa. e-mail: mohrek27@gmail.com

Background: Anaemia is commonly reported among patients with rifampicin-resistant tuberculosis (RR-TB) and human immunodeficiency virus (HIV) as a result of the disease or drugs used for treatment (zidovudine, isoniazid, linezolid). Since tenofovir is contraindicated with aminoglycosides, baseline anaemia may limit potential drug choices for either condition and may necessitate additional interventions or regimen modifications. We investigated the frequency of baseline anaemia in a setting of high RR-TB-HIV co-infection in Khayelitsha.

Methods: We conducted a retrospective cohort study of patients initiating RR-TB treatment in 2013. Frequencies of HIV infected and uninfected RR-TB patients with baseline anaemia were calculated.

Results: Among 197 patients starting standardised RR-TB treatment, 139 (71%) were HIV-infected and 83 (60%) of these were on antiretroviral therapy (ART) at the time of RR-TB treatment start. Although ART regimen data was unavailable, >90% of HIV-infected patients in Khayelitsha are initiated on tenofovir-based regimens. Baseline haemoglobin (Hb) measurements were available for 48 (83%) HIV-uninfected patients, 63 (76%) HIV-infected patients on ART and 47 (84%) not on ART. Anaemia was graded according to documents for the division of AIDS. Overall, 31/158 (20%) patients had at least moderate baseline anaemia; 8/48 (17%) vs. 23/110 (21%) HIV uninfected and infected, $P = 0.5$ (Table).

Conclusion: One fifth of patients initiating RR-TB treatment had at least moderate baseline anaemia; there was no significant association with HIV infection. Concurrent use of haemotoxic drugs in co-infected patients could contribute to worsening anaemia. Due to limited treatment options and poor outcomes associated with RR-TB, linezolid and isoniazid may still need to be

used in anaemic patients. In these cases zidovudine should be avoided and routine monitoring of Hb is recommended throughout treatment. Countries with high burdens of RR-TB and HIV co-infection, using zidovudine in first line ART regimens, should consider substitution with tenofovir. This will aid in reducing the risk of baseline anaemia and drug interactions during RR-TB treatment.

Table

	HIV infected on ART <i>n</i> (%)	HIV infected not on ART <i>n</i> (%)	HIV- uninfected <i>n</i> (%)	<i>P</i> value
No anaemia	34 (54%)	27 (57%)	33 (69%)	0.2
Mild anaemia	16 (25%)	10 (21%)	7 (15%)	0.5
Moderate anaemia	5 (8%)	4 (9%)	3 (6%)	0.9
Severe anaemia	6 (10%)	4 (9%)	5 (10%)	0.9
Potentially life- threatening anaemia	2 (3%)	2 (4%)	0	0.4
Total	63	47	48	

PC-909-04 Including traditional health practitioners in community-based public private partnership to provide HIV and TB services in KwaZulu-Natal

N Gqaleni,¹ W Mbokazi,¹ B Buthelezi,² S Radebe,³ M Shabangu,⁴ N Buthelezi,⁵ V Ngobese,⁵ G Nene⁶

¹Durban University of Technology, Durban, ²KwaZulu-Natal Department of Health, Ulundi, ³KwaZulu-Natal Department of Health, Newcastle, ⁴KwaZulu-Natal Traditional Health Practitioners, Paulietersburg, ⁵KwaZulu-Natal Traditional Health Practitioners, Newcastle, ⁶KwaZulu-Natal Traditional Health Practitioners, Vryheid, South Africa. Fax: (+27) 8657 70748. e-mail: nceba5850@gmail.com

Background and challenges to implementation: Traditional Health Practitioners (THPs) constitute an extensive network potentially capable of expanding and simplifying access to comprehensive TB-HIV prevention, care, treatment and support through various entry points. Through the USAID TB Program funding, the Durban University of Technology has conducted a project on the engagement of THPs in improving access to HIV and TB services.

Intervention or response: A pictorial HIV-TB Screening Tool and a Referral Form were developed for use by the THPs when referring their clients to health facilities. Operating in two district of Amajuba and Zululand, 800 THPs were trained in their wards, linked with their war-rooms, clinics, and community health care workers. Training among others included referral, TB screening and infection control, and HIV Counselling and Testing (HCT).

Results and lessons learnt: A recent National Workshop on THPs has endorsed the project including the referral systems developed. The KwaZulu-Natal Department of Health has incorporated the project's referral system into its Referral Policy. During October 2013 to March 2015,

800 trained THPs consulted with 22 879 clients, screened 1271 for TB-HIV and referred 818 suspects for TB-HIV related symptoms. Using radio, community dialogues and health talks we were able to reach 700 788 people. Twenty percent (160) THPs voluntarily undertook HCT. As part of promoting infection control 7630 N95 masks, were handed to THPs

Conclusions and key recommendations: We have demonstrated the potential role that can be played by THPs in enhancing community based TB prevention, care, and support programs which may now be scaled up.

PC-910-04 Longitudinal assessment of health-related quality of life of HIV-infected patients treated for TB and HIV in South Africa

T Mthiyane,¹ C Connolly,² Y Balakrishna,² A Pym,³

T Reddy,² R Rustomjee¹ ¹Medical Research Council, Cape Town, ²Medical Research Council, Durban, ³KwaZulu Natal Research Institute for Tuberculosis and HIV, Durban, South Africa. e-mail: thulimthiyane24@gmail.com

Background: Measuring Health Related Quality of Life (HRQOL) of human immunodeficiency virus (HIV) infected patients diagnosed with tuberculosis (TB) and receiving combined treatment has been rarely conducted in public health facilities in South Africa.

Design/Methods: This clinical trial enrolled TB and HIV coinfecting and only HIV infected participants before treatment commencement. Patients with CD4 count >200 were randomized to ARV therapy or no ARV therapy. HRQOL was measured at baseline, 3, 6 and 12 months. Participants were divided into four arms; Arm 1 – TB-HIV on TB and ARV therapy, CD4 >200; Arm 2 – TB-HIV on TB therapy only, CD4 >200; Arm 3 – TB-HIV on TB and ARV therapy, CD4 <200; Arm 4 – non-TB-HIV on ARV therapy, CD4 <200. Using the Functional Assessment of HIV Infection (FAHI) instrument we calculated composite physical, functional, emotional and mental health scores for participants that completed at least three months of treatment, compared scores between arms at month 0, 3, 6 and 12. The paired *t*-test was used to test for change in total score between each time point and baseline. GEE models which take into account correlated observations were used to model the total score as a function of time.

Results: Of 78 participants 76 (97.4%) participants completed all 5 domains of HRQOL (physical, emotional, functional, social and cognitive). There was a significant change in total score between month 0, 3, 6 and 12 (all $P < 0.0001$) and a significant increase in the total score over time ($P < 0.001$). There was no significant difference between the total score in arm 1 and arm 3 ($P = 0.719$) or between arm 2 and arm 4 ($P = 0.860$). Adjusting for baseline total score, baseline CD4 count had a significant effect on the total score ($P = 0.002$) and the rate of change in total score over time (interaction effect - $P < 0.001$).

Conclusion: Low CD4 count at enrolment was associated with poorer HRQOL at baseline and a higher rate of change in HRQOL over time. There was a general

improvement in quality of life of all patients, irrespective of CD4 count, in all domains except cognitive domain. This study should be conducted in a larger cohort using closer time points to verify these results.

PC-911-04 Characteristics and outcomes of HIV-infected, ART-naïve children diagnosed with TB disease in Mbeya, Tanzania

J Bacha,¹ J Benjamin,¹ L Campbell,¹ P Clowes,² C Mangu,² A Dinardo,³ K Ngo,³ A Mandalakas³ ¹Baylor College of Medicine Children's Foundation - Tanzania, Mbeya, ²National Institute of Medical Research - Mbeya Medical Research Centre, Mbeya, Tanzania; ³Baylor College of Medicine, Houston, TX, USA. USA, e-mail: bacha@bcm.edu

Background: HIV-infected children have increased risks for TB exposure, infection and disease, as well as poor response to treatment compared to their HIV-uninfected peers. Treatment is often complicated by delays in TB diagnosis, initiation of anti-TB treatment (ATT), and initiation of antiretroviral therapy (ART). In ART-naïve HIV-infected children with TB, guidelines favour earlier vs. delayed ART initiation following initiation of ATT. However, the optimal timing of ART initiation is unknown and limited data exist describing outcomes of this paediatric population.

Design/Methods: Retrospective chart review between March 2013 and December 2014 of patients at the Baylor Tanzania Center of Excellence (COE) in Mbeya, Tanzania. Inclusion criteria: HIV-infected children diagnosed with TB disease with no prior exposure to ART ("ART naïve"). Baseline, 6- and 12-month outcome data were captured using a standardized data collection tool and unique data base.

Results: Baseline data: 39 ART naïve patients were diagnosed with TB. 44% female (17/39); median age 6.1 years (0.7-17.8 yr). 97% (38/39) initiated ATT. Type of TB: 85% PTB (33/39), 10% EPTB (4/39), 5% LNTB (2/39). Diagnostic certainty: 23% confirmed (9/39), 56% probable (22/39), possible 21% (8/39) TB. 46% (18/39) were inpatients at time of diagnosis. All patients were treated with RHZE and none reported prior ATT. The Table compares the immunologic and nutritional characteristics of the cohort. Outcome data: 44% (17/39) completed ATT, 5% (2/39) cured, 21% (8/39) with ongoing ATT, 8% (3/39) transferred out, 8% (3/39) lost to follow up, and 16% (6/39) died. Median time to death after ATT initiation was 14.5 days (3-26d). A total of 87% (34/39) initiated ART, with median time from ATT to ART of 15 days (6-55days).

Conclusion: Our cohort of ART-naïve, HIV-infected children with TB disease exhibited TB disease associated with severe immunosuppression, malnutrition, and inpatient admission, as well as high rates of early mortality and LTFU, highlighting the importance of early disease recognition and treatment. However, early initiation of ATT and ART were associated with good immunologic and nutritional outcomes at 6 and 12 months, supporting the recommendation of early ART initiation following ATT in ART-naïve children.

Table Immunologic and Nutritional Characteristics of ART Naïve HIV-infected Children with TB Disease

	Baseline (n=39)	6 Month Outcomes (n=20)	12 Month Outcomes (n=12)
WHO Immuno-suppression	n=32 with CD4 data	n= 17 w/CD4	n=9 w/CD4
Severe	31% (10/32)	18% (3/17)	0% (0/9)
Advanced	22% (7/32)	12% (2/17)	11% (1/9)
Mild	22% (7/32)	35% (6/17)	44% (4/9)
Not significant	25% (8/32)	35% (6/17)	55% (5/9)
WHO Staging			
Stage 4	72% (28/39)	0 % (0/20)	0 % (0/12)
Stage 3	28% (11/39)	0 % (0/20)	0 % (0/12)
Stage 2	0% (0/39)	0 % (0/20)	0 % (0/12)
Stage 1	0% (0/39)	100% (20/20)	100% (12/12)
Median CD4 rise absolute (CD4 %)	N/A	187 (7%)	60 (4%)
Nutrition Status			
Severe malnutrition	64% (25/39)	0 % (0/20)	0 % (0/12)
Moderate malnutrition	10% (4/39)	0 % (0/20)	0 % (0/12)
Normal nutrition	26% (10/39)	100% (20/20)	100% (12/12)
Anthropometrics (median, range)		Change:	Change:
WHZ score	-1.61 (-5.55 to 1.36)	+1.29	+1.40
BMI	15.0 (10.7 to 23.7)	+1.75	+2.12
Weight-for-age Z-score	-3.73 (-6.60 to 0.36)	+1.03	+1.31

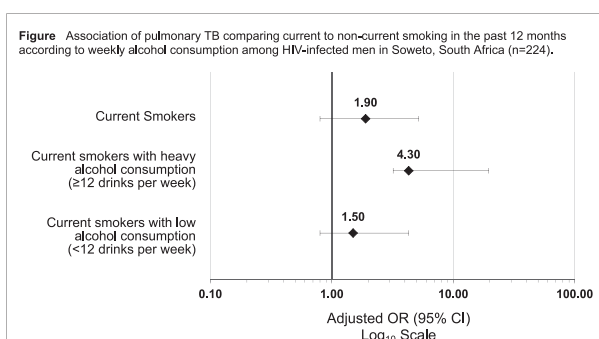
PC-912-04 Smoking and tuberculosis among HIV-infected men in Soweto, South Africa: a case-control study

L Bronner,^{1,2} N Martinson,^{2,3} R Moloney,¹ R Msandiwa,³ M Mashabela,³ J Golub^{1,2} ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²Johns Hopkins School of Medicine, Baltimore, MD, USA; ³Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa. e-mail: lizabronner@gmail.com

Background: Although there is ample evidence that smoking increases the risk of tuberculosis (TB), the magnitude of impact on TB risk among HIV-infected persons is poorly described. Given that a high proportion of patients with TB are co-infected with HIV in South Africa, this study investigates the association between smoking and pulmonary TB (PTB) among HIV-infected men in South Africa.

Design: We conducted an unmatched case-control study of HIV-infected men in Soweto, South Africa. Eligible subjects were antiretroviral therapy naïve with confirmed HIV. Cases had laboratory-confirmed PTB and controls had no evidence of active TB. Participants were interviewed to collect data on socio-demographics, TB disease, detailed smoking history, and alcohol usage. We defined current smoking as self-reported smoking within 12 months prior to PTB diagnosis. We defined heavy alcohol consumption as consuming ≥ 12 drinks per week. χ^2 and non-parametric Wilcoxon tests were used in bivariate analyses followed by multivariable logistic regression.

Results: We enrolled 284 HIV-infected men; 146 cases with PTB and 138 controls. Median age, CD4 count and BMI of the cases and controls were both 38 years, 60 and 84 cells/mm³, 23 and 24 kg/m², respectively. Forty-three percent were current smokers; 48% among cases and 39% among controls ($P = 0.15$). Heavy alcohol consumption did not differ significantly between cases and controls (75% vs. 69%), but among participants who consumed the equivalent of ≥ 12 alcoholic drinks/week, those who were also current smokers were more likely to be cases with PTB (69% vs. 42%, $P = 0.04$). In adjusted analyses, smokers had twice the odds of PTB (aOR 1.9; 95%CI: 1.1-3.4), while smokers who consumed ≥ 12 alcoholic drinks/week were 4.3 times more likely to develop PTB (95%CI: 1.2-15.3) (Figure).



Conclusions: HIV-infected male smokers are at greater odds of developing PTB than non-smokers, and heavy alcohol consumption significantly increases this likelihood. Our data suggests the deleterious effects of smoking in HIV-infected men with PTB are exacerbated by heavy alcohol consumption. This relationship, we posit, is likely due to a complex interaction of environmental and social conditions, and immunological responses. Our findings support calls for smoking and alcohol cessation and prevention efforts to be scaled up among HIV-infected patients in epidemic settings as part of efforts to control PTB.

PC-913-04 High prevalence of depression and hazardous/harmful alcohol use among TB-HIV patients initiating ART in Lesotho

E Hayes-Larson,^{1,2} Y Hirsch-Moverman,¹ S Saito,^{1,2} B Pitt,¹ L Maama-Maime,³ K Frederix,¹ A Howard^{1,2}

¹Columbia University, ICAP, Mailman School of Public Health, New York, NY, ²Columbia University, New York, New York, USA; ³National Tuberculosis Control Programme, Lesotho Ministry of Health, Maseru, Lesotho. e-mail: elh2167@cumc.columbia.edu

Background: Mental health issues have not been well characterized in TB-HIV co-infected patients in resource-limited settings. We sought to describe the prevalence and correlates of depression and hazardous/harmful (H/H) alcohol use among TB-HIV patients initiating ART within 8 weeks of TB treatment initiation who enrolled in the Start TB patients on ART and Retain on Treatment (START) Study.

Design/Methods: START is an ongoing cluster-randomized trial in 12 health facilities in Lesotho, evaluating the effectiveness, cost-effectiveness and acceptability of a combination intervention package vs. standard of care to improve early ART initiation, retention and TB treatment success in TB-HIV patients. Consenting adults with TB-HIV initiating ART within 8 weeks of TB treatment initiation were enrolled in a measurement cohort (MC). Data from MC interviewer-administered baseline questionnaires (collected 4/2013-3/2015) were analyzed to describe prevalence of depression (PHQ-9, with cutoffs for mild, moderate and severe of 5, 10, and 15, respectively) and H/H alcohol use (AUDIT score ≥ 8). Correlates of moderate/severe depression and H/H alcohol use were assessed with unadjusted generalized linear mixed models with a random effect for study site.

Results: Among 363 participants with available data, the median age was 35 y, 56% were male, and 54% were married/living with a partner. Overall, 42% reported symptoms consistent with mild depression, 29% reported moderate/severe depression, and 29% reported H/H alcohol use. Moderate/severe depression and H/H alcohol use were not associated; 7% of participants reported both conditions. Statistically significant correlates of moderate/severe depression included no education, more frequently needing or wanting help or being stressed by family/friends, and low health literacy (Table). Participants who had disclosed their HIV status or planned to disclose their TB diagnosis had lower odds of reporting moderate/severe depression. Significant correlates of H/H alcohol use included male sex and greater perceived TB stigma. Socially desirable response tendencies were associated with reduced odds of reporting both conditions.

Conclusion: Prevalence of moderate/severe depression and H/H alcohol use were high in this sample, and were correlated with different demographic, psychosocial, and TB-HIV-related factors. Interventions to prevent and treat H/H alcohol use and depression are urgently needed for TB-HIV patients in these settings.

Table. Participant characteristics and unadjusted associations with moderate/severe depression and hazardous/harmful (H/H) alcohol use among START MC participants

	Overall n (%) or median (IQR) N=363	Unadjusted odds ratios (95% CI) Moderate/severe vs. no/mild depression N=342	H/H alcohol use vs. no H/H alcohol use N=354
Demographic variables			
Age, y	35 (30-44)	1.01 (0.99-1.04)	0.98 (0.96-1.01)
Male	205 (56.5%)	1.04 (0.60-1.78)	7.74 (3.78-15.87)
Education			
None	26 (7.2%)	3.50 (1.41-8.71)	1.38 (0.50-3.87)
Primary	226 (62.3%)	1.51 (0.86-2.65)	0.96 (0.49-1.88)
Secondary or higher	111 (30.6%)	REF	REF
Psychosocial and TB/HIV-related variables			
Social support (1=Rarely, 2=Sometimes, 3=Often)			
Needed/wanted help for something serious	2 (1-3)	1.65 (1.25-2.19)	1.10 (0.83-1.46)
Stressed out by friends or family	1 (1-2)	1.71 (1.26-2.32)	1.03 (0.70-1.52)
Low health literacy	97 (27.5%)	2.80 (1.64-4.79)	1.34 (0.67-2.70)
Disclosed HIV status	345 (95.6%)	0.28 (0.09-0.93)	0.69 (0.21-2.25)
Plan to disclose TB status	328 (93.7%)	0.38 (0.15-0.93)	1.05 (0.37-2.98)
Perceived TB stigma (15 [lowest] to 60 [highest])	41 (38-45)	1.03 (1.00-1.07)	1.04 (1.00-1.07)
Socially desirable response tendency (0 [lowest] to 52 [highest])	38 (35-45)	0.94 (0.91-0.98)	0.95 (0.91-0.99)

ABSTRACT PRESENTATIONS SATURDAY 5 DECEMBER 2015

e-POSTER SESSIONS

06. Preventing infection and transmission of TB in health facilities and the community

EP-144-05 Transmission of multidrug-resistant tuberculosis among household contacts previously cured of tuberculosis in Delhi, India

R Singla,¹ N Singla,¹ J Caminero Luna,² D Behera,³, A Kumar,¹ J Arora,¹ M Varma Basil,⁴ R Sarin^{1,5} ¹National Institute of Tuberculosis & Respiratory Diseases, New Delhi, India; ²University General Hospital of Gran Canaria 'Dr. Negrin', Las Palmas de Gran Canaria, Spain; ³Post Graduate Institute of Medical Education and Research, Chandigarh, ⁴Vallabh Bhai Patel Chest Institute, New Delhi, ⁵National Institute of Tuberculosis & Respiratory Diseases, New Delhi, India. Fax: (+91) 1 126 517 834. e-mail: drrupaksingla@yahoo.com

Background: There are some reports of transmission of multi-drug resistant tuberculosis (MDR-TB) among household contacts (HHCs) of MDR-TB patients. However, transmission of MDR-TB among previously tuberculosis (TB) successfully treated HHCs of MDR-TB patients has not been described earlier.

Methods: HHCs of MDR-TB patients, enrolled between September 2011 and August 2012 under national programme, in a tertiary referral institute in Delhi, India, were prospectively followed up for 2 years. Previously TB successfully treated HHCs, who developed TB now, were evaluated. The transmission dynamics was studied by spoligotyping and mycobacterial interspersed repetitive units (MIRU) typing of cultures of index patients and their corresponding HHCs, whenever possible.

Results: Among 839 HHCs of 299 MDR-TB patients followed up in the study, nine HHCs, who had previously been TB successfully treated with first line drugs, were found to have developed TB now. Age of nine contacts ranged from 14- 65 years, median age being 23 years with Inter Quartile Range (IQR) 18-31 years. All were found to have MDR-TB. All nine HHCs were HIV negative. Two of nine HHCs had Beijing strain and two had spoligotyping results of unknown strains. In these four HHCs, including those with unknown strains, the spoligotyping and MIRU typing of the HHCs matched with their corresponding index confirming the possibility of transmission of MDR-TB from the index to the respective HHCs in the house hold in these cases. In rest five HHCs the, index and HHC pair could not be matched as the culture of index cases were not viable at the time when the contact developed TB. Time gap

between diagnosis of their respective index cases and development of MDR-TB in all HHCs ranged from 2-16 months, median duration being 10.5 months with IQR 3-11 months. Among two HHCs with Beijing strains time gap was just 3 months each.

Conclusions: There is high probability of transmission of MDR-TB from the index cases to the HHCs in the house. This occurs even if the HHCs have previously been cured of TB. The Beijing strain, in particular, is highly infectious leading to development of MDR-TB among HHCs within few months of their exposure to the index case. All HHCs, including the previously TB treated HHCs of MDR-TB cases, should be actively investigated for multi-drug resistance TB as a public health priority under national programmes.

EP-145-05 HCW screening

L Anande,¹ R Nanavare,¹ V Chavan¹ ¹Group of TB Hospitals, Mumbai, India. e-mail: drlalanande@gmail.com

Background and challenges to implementation: Tuberculosis is an infectious disease caused by bacteria called *Mycobacterium tuberculosis*. Today tuberculosis has been recognized as an important international concern due to increase in incidence of acutely rapidly progressing forms, late detection of disease and wide spread of strains resistant and multiresistant to the treatment. In view of HCW, the challenge lies in combating the increase in number of multidrug resistant tuberculosis, prevent progression of latent infection to active tuberculosis, provision of insurance schemes and TB leave for individuals under treatment, active participation of NGOs, media, web domains for training modules, inclusion of treatment for extra pulmonary tuberculosis in government run programs and unstinted support from government to develop thoracic surgery departments in hospitals are vital.

Intervention or response: Health care workers are exposed to TB bacilli most often. Group of TB hospitals in Mumbai, India has initiated Infection control trainings conducted by in-house Infection control committee of the hospital. The committee is inclusive of internal and external speakers providing training to health care workers and patients to educate respiratory hygiene and coughing etiquettes. These include wearing N95 mask for HCW, other masks for patients and visitors, provision of high protein diet and regular health checkup with records maintained in diaries are implemented in hospital. The screenings of HCW was initiated in 2011 and since then have continued the trend quarterly. HCW is inclusive of ward attendants, sweepers, barber, time keeper, gardener, radiographer, doctor, nurse, clerk, peon, operation theatre assistants, contract basis labor and pharmacists to name a few. Until March 2015, total number of HCW acquired TB infection are 63. Further, the total number of HCW acquired MDR-TB is 36 where as Non-MDR are 27. Total number of HCW cured of infection is 20 and death due to infection is 11.

Results and lessons learnt: Consequently, the death rate of TB cases has decreased and cure rate has increased in

hospital. HCWs are expected to abide respiratory hygiene, update knowledge with education programs and participate in maximum numbers for screening activities to maintain their good health record.

Conclusions and key recommendations: It is vital to recognise good health of HCWs imparting knowledge, keep the trend of health checkup & maintain records thus make India TB Free.

EP-146-05 Tuberculosis outbreak among health care workers and trainees in a tertiary care hospital in Pune, India

A Basavaraj,¹ D Kadam,¹ A Patil,¹ A Chandanwale,¹ V Mave,^{2,3} D Jain,² A Deluca,⁴ R Bollinger³ ¹Byramjee Jeejeebhoy Government Medical College, Pune, ²Byramjee Jeejeebhoy Government Medical College Clinical Trials Unit, Pune, India; ³Johns Hopkins University School of Medicine, Baltimore, MD, ⁴Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: anita.basavaraj@rediffmail.com

Background: India has the world's largest burden of tuberculosis (TB) with an estimated 26% of the global burden of TB and 2 million new cases every year. TB risk among health care workers (HCWs) is known to be high, and documenting the risk for HCWs in India may drive improvements in TB guideline implementation. We therefore set out to investigate the disease prevalence in a group of at-risk HCWs. We also aimed to determine the frequency of treatment failure, mortality, and drug-resistance among HCWs at Sassoon General Hospital.

Design/Methods: A retrospective study of HCWs was conducted between June 2011 and December 2013 in a public teaching hospital. The primary outcome-TB prevalence and the incidence estimate- were measured by those self-reporting TB. Study assessments included HCW interviews and clinical exams, as well as medical record data abstraction. The primary outcome was to find TB prevalence estimate, calculated as the number of TB cases divided by estimated total HCWs. Descriptive statistics were used to measure secondary outcomes for frequency of treatment failure, adverse drug reactions, mortality and drug-resistance.

Results: Of 1886 HCWs evaluable, 47 cases of TB were identified. Fifteen (32%) were residents, 12 (26%) were interns, 13% were nursing students and the rest were staff nurses, medical students and other faculty. The estimated incidence of TB was 1611 per 100 000 HCW-years for all HCWs and 2719 per 100 000 HCW-years for medical trainees. The majority of TB occurred among general medical residents (15 [32%]) and in general medicine wards (23[49%]); 20 (43%) had pulmonary TB, 4 (11%) had mono- resistance to isoniazid and 3 (6%) had multi drug resistant (MDR)-TB. Two HCWs died from co-morbid conditions of cirrhosis of liver and ascites in alcoholic liver disease, 3 HCWs had persistent positive cultures, and 31 (66%) developed adverse drug reactions. One HCW developed severe hepatotoxicity in the form of acute fulminant hepatic failure and underwent hepatic transplant.

Conclusion: We found a 7-fold higher risk of TB among HCWs compared to the community risk and identified a ~2-fold higher risk of TB among medical trainees compared to the general HCW group. Our study is the first to report several INH-resistant TB and MDR-TB cases among HCWs in India and highlights the immediate need to implement appropriate administrative, personal and environmental infection control measures.

EP-147-05 Tuberculosis and latent tuberculous infection among health care workers in Kisumu, Kenya

J Agaya,¹ C Nnadi,² C Obonyo,¹ V Obiero,¹ V Lipke,² E O Okeyo,¹ K Cain,³ J Oeltmann² ¹Kenya Medical Research Institute, Kisumu, Kenya; ²US Centers for Disease Control and Prevention, Atlanta, GA, USA; ³U.S. Centers for Disease Control and Prevention, Kisumu, Kenya. e-mail: kcain@cdc.gov

Background: Health care workers (HCWs) in settings with high tuberculosis (TB) prevalence are at an elevated risk for TB compared to the general population. Data on baseline community-acquired TB infection in some of these settings, and on health facility types that may confer the greatest nosocomial risk for TB, are limited.

Methods: We conducted a cross-sectional survey among HCWs in Western Kenya during 2013. HCWs were recruited from dispensaries, health centers, and hospitals that offer both TB and HIV services. School workers (SWs) from the health facilities' catchment communities were randomly selected to serve as the community comparison group. Latent TB infection (LTBI) was diagnosed by tuberculin skin testing (TST) and subsequent examinations to exclude TB disease. Human immunodeficiency virus (HIV) status of participants was assessed. Using an adjusted logistic regression model, we determined the adjusted odds of LTBI among HCWs compared to SWs; and among HCWs only, we assessed work-related risk factors for LTBI.

Results: We enrolled 1005 HCWs and 411 SWs. Approximately 60% of both groups were female. A total of 211 of 958 HCW (22%) and 48 of 392 SW (12%) were positive on HIV evaluation. Prevalence of LTBI was 60% among HCWs and 48% among SWs. Adjusted odds of LTBI was 1.5 times higher among HCWs than SWs (95% confidence interval 1.2–2.0). HCWs at all three facility types had similar prevalence of LTBI ($P=0.72$), but increasing years of employment was associated with increased odds of LTBI ($P<0.01$).

Conclusion: HCWs at health care facilities in Western Kenya which offer TB and HIV services are at increased risk of LTBI, and the risk is similar across facility types. The World Health Organization-recommended TB infection control measures are urgently needed in health facilities to protect HCWs.

EP-148-05 Occupational TB as measure of impact of TB infection control program

G Volchenkov,¹ P Jensen² ¹Vladimir TB Control Center, Vladimir, Russian Federation; ²US Centers for Disease Control, Atlanta, GA, USA. Fax: (+7) 492 232 3265. e-mail: vlchnkv@yahoo.com

Background and challenges to implementation: Tuberculosis (TB) infection transmission in health care settings plays significant role in ongoing drug resistant TB epidemic of high burden countries. Health care workers may be one of the occupational groups most affected by high TB transmission risk. A combination of TB infection prevention and control (TB IPC) interventions are recommended to reduce or eliminate TB transmission in various settings.

Intervention or response: Intensive and complex TB IPC program supported by US CDC and WHO was implemented in the Regional TB Dispensary and other TB facilities of Vladimir region, Russia in 2003–2014. The program included FAST interventions and other administrative controls, selected environmental controls in high TB transmission risk areas and personal respiratory protection for high risk staff and surgical masks for contagious patients. We performed retrospective analysis of active TB notification data among health care workers of Vladimir region in 1994–2014 to assess the impact of these interventions on occupational TB rate as a measure of nosocomial TB transmission level.

Results and lessons learnt: Implementation of TB IPC program in TB facilities of the region resulted in sharp reduction of active TB disease notification among health care workers of both Regional TB Dispensary and all other TB facilities of the region. Average TB notification rate for Regional TB Dispensary staff in 1994–2003 was 1080 per 100K, and after TB IPC program implementation zero TB cases has been registered in 2008–2014 in this facility. No TB cases have been registered among health care workers of other TB facilities of the region since 2009. At the same time average annual relative risk of TB for physicians and nurses of the emergency hospital, where no airborne precautions has been used, was over 6,5 comparing to residence population of Vladimir city.

Conclusions and key recommendations: Occupational TB notification rate can be used as sensitive indicator of both TB transmission risk in the facility, unit or profession and as measure of effectiveness of TB IPC interventions. A comprehensive and effective TB IPC program may reduce nosocomial TB transmission risk in few years.

EP-149-05 Strengthening and accelerating the implementation of an integrated HIV-TB workplace response for health sector workers

D Elray,¹ F Fayers,¹ M T Mbatha,² S Mabhele³ ¹Hospersa, Pretoria, ²Urc, Pretoria, ³Ilo, Pretoria, South Africa. e-mail: hsc@hospersa.co.za

Background and challenges to implementation: South Africa currently ranks third in the world, in terms of the

tuberculosis (TB) burden. It is estimated that 80% of its 52 million people are infected with the TB bacillus. Furthermore 10% of these infected with the TB bacillus (latent TB) will develop TB in their lifetime. This percentage increases dramatically if the person is human immunodeficiency virus (HIV) positive. Health Care workers (HCWs) in South Africa are at a risk of up to 4 times higher than that of the broader public to contracting TB. It therefore becomes imperative that we ensure that HCW remain occupationally TB-HIV free. The incidence of Occupational TB in South Africa is increasing but remains grossly underreported. This underreporting is due to a range of contributing factors; fear of stigma, lack of knowledge on TB-HIV risk, lack of knowledge on occupational hazards and a lack of routine medical surveillance for HCW.

Intervention or response: Scaling up the engagement of health sector workers in fighting TB in both public and private sector health facilities

Methods: There were 18 workplace wellness events hosted by HOSPERSA, ILO and the USAID TB CARE II Project, and these targeted both public and private health facilities throughout the country, particularly aiming for increased uptake for TB & HIV Screening and testing amongst health sector workers. Training was held to empower 270 Nurses from various clinics/hospitals throughout the country on the clinical management of TB-HIV, MDR-TB and improved infection control measures. Three focus groups were held with young health care workers to understand their perceptions of TB-HIV risk at work. A baseline survey by way of a self-administered questionnaire was conducted and 250 HCW responded, the survey aimed to find out about structures in place to curb Occupational TB-HIV exposure in public health facilities.

Results and lessons learnt: Health care workers are still practicing inadequate implementation of infection control measures in healthcare facilities, which poses a risk for contracting TB. Routine reporting of occupational TB-HIV cases, to increase in the health facilities that this project reached.

Conclusions and key recommendations: The need for a national policy that promotes the protection of HCWs in terms of occupational exposure to TB and HIV is evident. Routine TB testing of HCWs does not exist. HCWs know that they are at Risk of Contracting TB-HIV but are not equipped to take preventative steps.

EP-150-05 Systematic review of the epidemiology and programmatic response to TB in South African health care workers

L Nicol,¹ S Mehtar,¹ K Dheda,² S Adams,² M Van Der Walt,³ M Osman⁴ ¹Stellenbosch University, Cape Town, ²University of Cape Town, Cape Town, ³South African Medical Research Council, Pretoria, ⁴City Health Directorate, Cape Town, South Africa. e-mail: liesl.nicol@gmail.com

Background: Tuberculosis in health care workers is the third most commonly reported occupational disease in SA. Transmission of TB in health care facilities to both

patients and health care workers has been reported from every country of the world, regardless of local TB incidence. The risk for transmission of TB in health care facilities varies by setting, occupational group, local prevalence of TB, patient population and effectiveness of TB infection control measures. With the aim of contributing to evidence-informed TB policy development in South Africa this systematic review collated all relevant research on the epidemiology of and programmatic response to TB in healthcare workers in South Africa.

Design/Methods: A comprehensive search for both published and unpublished research was conducted in April 2015. Based on specific inclusion criteria, research investigating TB incidence, prevalence, risk factors, prevention, treatment and care in health care workers in South Africa and research reporting on TB-specific infection prevention and control issues in South African health care facilities were systematically reviewed.

Results: Twenty-eight studies were included in the systematic review. Table 1 outlines the number of studies addressing each of the topics, the study dates (range) and setting. Most of the studies conducted in KwaZulu-Natal showed a higher incidence of TB disease in health care workers compared to the local population. A national survey of 133 primary health care facilities, conducted between 2006 and 2008, reported a 2–3 times higher incidence rate of TB disease in health care workers compared to the general population. Studies investigating TB infection, prevention and control (IPC) in South African healthcare facilities are relatively dated, with the most recent study conducted in 2011.

Conclusion: The optimal approach for TB screening in South African health care workers, the use of isoniazid preventative therapy (IPT) in South African health care workers and the implications of providing IPT to health care workers require investigating. More effective ways of promoting, teaching and implementing TB IPC processes in South African healthcare facilities need to be investigated.

Incidence of TB disease	8 studies	1986–2011	Public health facilities KZN, WC, MP, SA
Prevalence of TB disease and infection	4 studies	2008–2011	Public health facilities WC, Gauteng
Burden of TB disease (number of TB cases)	3 studies	2007–2011	Public health facilities SA, WC, Limpopo
Risk factors for TB	9 studies	1986–2011	Public health facilities KZN, WC, Limpopo, Gauteng
TB IPC in health care facilities	8 studies	2007–2011	Public health facilities KZN, WC, SA
Health care worker TB IPC knowledge, attitude and practice	7 studies	2007–2010	Public health facilities KZN, WC, SA
Improving TB IPC in health care facilities	3 studies	2007–2010	Public health facilities WC, MP, KZN
TB related occupational health services	1 study	2011	Public health facilities KZN
TB screening in health care workers	5 studies	2007–2012	Public health facilities Limpopo, KZN, SA
Acceptability of isoniazid preventative therapy in health care workers	1 study	2007/2008	Public health facilities SA
Treatment for TB in health care workers	5 studies	1990–2010	Public health facilities SA, KZN
TB related stigma among health care workers	2 studies	2007–2013	Public health facilities; SA, KZN

EP-151-05 Tuberculosis infection control: knowledge and attitudes among health workers in Uganda

E Buregyeya,¹ E Mitchell² ¹Makerere University School of Public Health, Kampala, Uganda; ²KNCV Tuberculosis Foundation, The Hague, Netherlands. Fax: (+256) 414 53 1807. e-mail: eburegyeya@musph.ac.ug

Background: The WHO recommends TB infection controls (TBIC) in health care facilities and these include; managerial, administrative, environmental and personal protective. In 2008, the Ministry of Health Uganda (MOH) and the Tuberculosis Assistance Programme initiated efforts to implement TBIC by training of HCWs. Good knowledge of a health problem, accompanied with the right attitude, can result in desired practices. Research among HCWs has found them to often lack knowledge about TB and infection control, which contributes the risk of TB transmission. This study was carried out to assess HCWs knowledge and attitudes towards TBIC.

Design/Methods: We conducted a cross-sectional study among HCWs in health facilities in the districts of Mukono and Wakiso in Uganda, from October 2010 to February 2011. We assessed HCWs' knowledge in basic TB (standards of TB diagnosis and treatment) and TB infection control (knowledge about TBIC measures such as use of masks/respirators, triaging and ventilation) and attitudes towards TBIC (perceptions about TBIC measures).

Results: Twenty four percent of the participants answered correctly all the questions about basic TB knowledge. Overall, 62% of the HCWs were judged to have adequate basic TB knowledge. At multivariable analysis, non-clinical cadres, were more likely to have poor basic TB knowledge [adjusted OR=0.43(95% CI=0.27–0.68)]. Only 7% of the respondents answered all the questions on TBIC correctly. Almost all the respondents knew that TB was transmitted through droplet nuclei, while only a third (34%; 174/532) knew that masks do not protect the wearer from getting TB. Overall, 69% (355/512) of the HCWs were judged to have adequate TBIC knowledge. At multivariable analysis, non-clinical cadres were more likely to have poor TBIC knowledge [adjusted OR=0.57(95% CI=0.36–0.91)]. Twenty-one percent (112/537) of the HCWs mentioned that their risk of contracting TB was the same whether the consultation window was open or closed. Just over half of the respondents (264/513) were rated as having positive attitudes towards TBIC. At multivariable analysis, non-clinical cadre AOR=0.48(95% CI=0.30–0.77) was more likely to have poor attitudes towards TBIC.

Conclusion: Our study findings highlight the inadequacy of HCWs knowledge in TBIC and poor attitudes towards TBIC. Poor knowledge about TB and TBIC, and poor attitudes towards TBIC were associated with being non-clinical. MoH should emphasis TBIC training among non-clinical staff.

EP-152-05 Transmission of tuberculosis in households in England

M Lalor,¹ L Anderson,¹ E Hamblion,¹ A Burkitt,² J Davidson,¹ I Abubakar,^{1,3} L Thomas¹ ¹Public Health England, London, ²Public Health England, Newcastle-upon-Tyne, ³University College London, London, UK. e-mail: maeve.lalor@phe.gov.uk

Background: A reliable estimate of the proportion of tuberculosis (TB) cases from recent transmission in England would inform public health measures to control TB. Estimates of transmission using strain typing data alone have several limitations. The aim of this analysis was to estimate the proportion of TB due to household transmission, by combining strain typing data with epidemiological data on links between cases.

Design/Methods: Household linked TB cases between 2010 and 2012 were identified from addresses reported at notification or during cluster investigation. Household linked TB cases were classified by 24 MIRU-VNTR strain typing data into four transmission categories; confirmed, probable, unknown and refuted.

Results: 7.7% (1849/24 051) of cases notified between 2010 and 2012 lived in a household with at least one other TB case. For 67% of these cases, strain typing data was unavailable for one or both cases; therefore transmission could not be confirmed or refuted. For those with strain typing data; 64% had confirmed, 11% probable, and 25% refuted transmission. 718 households where transmission was not refuted were identified, 20% contained more than two cases. The median time from symptom onset to treatment start was 65 days for the first case in households, decreasing with subsequent cases. The proportion of TB cases that were in a household varied by country of birth; Bangladesh (2.7%), Pakistan (5.0%), India (5.4%), Nepal (8.7%) Somalia (10.7%), UK (11.1%).

Conclusion: It is widely accepted that the majority of TB in England occurs due to reactivation of latent TB acquired abroad. Given that almost 8% of notified TB in England occurs in cases with household links, and that the majority of those with strain typing were confirmed to be due to transmission, demonstrates the important contribution of household transmission to TB in England. The recently launched Tuberculosis Strategy for England (2015–2020) outlines the need to improve TB control in England to prevent transmission including enhanced contact tracing and interventions to reduce diagnostic delay.

07. The rainbow session: treatment vaccination, surveillance or tuberculosis and everything in between

EP-153-05 Clinical profile and outcome of extra-pulmonary tuberculosis: a 3-year study from south Kerala

J Cherian,¹ J Subramoniyapillai,² K Periasamy,¹ P Dhayakar,¹ P Sadasivanpillai³ ¹Government Medical College Thiruvananthapuram, Trivandrum, ²State Tuberculosis Cell, Trivandrum, ³T.D. Government Medical College, Alappuzha, India. e-mail: dr.jjcherian@gmail.com

Background: Although the overall tuberculosis (TB) notification has decreased recently, extrapulmonary tuberculosis (EPTB) is on the rise. Various factors influencing the site of involvement and treatment outcome are age, sex, HIV status and geographical location. The objective of this study was to analyse the treatment outcome of various sites of EPTB and the factors influencing it. **Methodology** The study included patients diagnosed with EPTB from the southern seven districts of Kerala, between January 2010 and December 2012. Patients who registered for treatment under Revised National Tuberculosis Control Programme (RNTCP) and administered Directly Observed Treatment Short course (DOTS) were chosen. Data regarding their demographic profile, type of patient, Category of treatment, HIV status, site of involvement and treatment outcome was collected from the treatment registers. The variables unavailable in the registers were recorded as 'data unavailable'.

Results: Of the 39 267 patients registered for treatment for TB, EPTB constituted 8610 (22%) cases. 53.1% were males. 51.6% of the cases belonged to the age group 30–60 years. 90.7% of cases were newly detected and most of the cases (84.9%) received Category 1 regimen. Only 53.6% of the 8610 cases had their HIV status tested and among them 5.9% ($n = 271$) were positive. The most common site of involvement was lymph node (31.5%), followed by pleural effusion (18.6%), bone & joint (8.7%), intestine (5.1%), central nervous system (CNS) (4%) and genitourinary (GU) (1.8%). Other less common sites constituted 5.8%. Data regarding site was unavailable for 24.5% cases. 87.4% completed treatment, 4.3% defaulted, 3.7% died and 2.3% transferred out. Eleven patients failed treatment, three patients were shifted to MDR TB regimen and 190 patients did not have their outcome available. Factors that were associated with poor treatment completion rates included male gender ($P < 0.001$), age over 60 years ($P < 0.001$) and a positive HIV status ($P < 0.001$). The best treatment completion rates were seen in GU TB (92.3%) followed by lymph node TB (90.4%). CNS TB had the highest mortality (14.5%) and default (5.5%) rates.

Conclusion: The treatment completion rates among EPTB patients in this study were remarkable (87.4%). However, the partial incompleteness of data was a disadvantage while drawing conclusions on different

sites of involvement. The rising proportion of EPTB demands special guidelines from RNTCP to cater to this growing subset.

Table Treatment outcomes of various sites of EPTB

Site	Treatment Completed				Total N
	Yes		No		
	N	%	N	%	
Lymph node	2450	90.4	260	9.6	2710
Pleural Effusion	1379	86.2	220	13.8	1599
Bone and Joint	640	85.1	112	14.9	752
Genitourinary	143	92.3	12	7.7	155
CNS	251	73.0	93	27.0	344
Intestine	372	84.9	66	15.1	438
Others	428	85.6	72	14.4	500
Data unavailable	1847	87.5	265	12.5	2112
Total	7510	87.2	1100	12.8	8610

EP-154-05 Risk factors of loss-to-follow-up and death among tuberculosis patients receiving treatment in a resource-limited setting

I Alobu,¹ S Oshi,² D Oshi,² K Ukwaja³ ¹National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, ²Centre for Development and Reproductive Health, Enugu, ³Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, Nigeria. e-mail: ukwajakingsley@yahoo.co.uk

Background: Treatment interruptions and death during care are major challenges facing tuberculosis control. The aim of this study was to describe the epidemiological characteristics, timing and determinants of being lost-to-follow-up or death among adult tuberculosis patients in Nigeria.

Design/Methods: Using routine surveillance data, we conducted a retrospective cohort study of adult tuberculosis patients treated during 2011 and 2012 in two large health facilities in Ebonyi State, Nigeria. Multivariable logistic regression analyses were used to identify independent predictors for loss-to-follow-up and death during treatment.

Results: Of 1668 treated patients, the rate of loss-to-follow-up was 157 (9.4%), whilst 165 (9.9%) died. Also, 35.7% (56) of the patients with loss-to-follow-up and 151 (91.5%) of deaths occurred during the intensive phase of treatment. Risk of loss-to-follow-up increased with increasing age (adjusted odds ratio (aOR) 1.2; 95% confidence interval (CI) 1.1–1.9), smear-negative TB case (aOR 2.3; CI 1.5–3.6), extrapulmonary TB case (aOR 2.7; CI 1.3–5.2), and patients who received the longer treatment regimen (aOR 1.6; 1.1–2.2). Risk of death was highest in extrapulmonary TB (aOR 3.0; CI 1.4–6.1) and smear-negative TB cases (aOR 2.4; CI 1.7–3.5), rural residents (aOR 1.7; CI 1.2–2.6), HIV co-infected (aOR 2.5; CI 1.7–3.6), not receiving antiretroviral therapy (aOR 1.6; CI 1.1–2.9), and not receiving cotrimoxazole prophylaxis (aOR 1.7; CI 1.2–2.6).

Conclusion: Targeted interventions to improve treatment adherence for patients with the highest risk of loss-to-follow-up or death are urgently needed. This needs to be

urgently addressed by the National Tuberculosis Programme.

EP-155-05 Predictors of mortality and immediate causes of death in hospitalised TB patients undergoing an intensive phase of treatment in Kigali University Teaching Hospital

O Manzi,¹ L Bitunguhari,¹ J Clerinx² ¹University of Rwanda, Kigali, Rwanda; ²Institute of Tropical Medicine, Antwerp, Belgium. e-mail: oliviermanzi@yahoo.fr

Background: Tuberculosis (TB) and HIV coinfection are major causes of mortality in Africa, and inter-related. Predictors of mortality are not well characterised, especially during early inpatient treatment. We aimed to examine predictors of mortality in these patients in Rwanda.

Design/Methods: We conducted a prospective observational cohort study for consenting adult hospitalised TB patients diagnosed from January 2013 to December 2013; we assessed predictors of mortality among demographic, clinical, laboratory and medical imaging data. Immediate causes of death were constructed from analysis of cardinal symptoms in the week prior to death. **Results:** A total of 152 hospitalized TB patients (of 208 recruited) had full data available for analysis. HIV coinfection was present in 95 (62%), and 49 died during followup (overall mortality rate 32%). Pure pulmonary TB affected 31 (20%) patients, whereas extrapulmonary TB was seen in 84 (55%) and mixed TB in 54 (36%). Auramine stains were positive in 47/108 (44%) patients. In univariable analysis, dyspnea, abdominal tenderness, low platelet count, low oxygen saturation, TB pericarditis, disseminated TB and miliary TB were associated with death. In a multivariable analysis, only thrombocytopenia < 150000/ μ L (HR=4.08, $P < 0.001$; 95%CI 1.82–7.31) and dyspnea (HR = 3.65, $P = 0.009$; 95%CI 1.31–9.24) were independent predictors of mortality. HIV status, low CD4 count and high abdominal ultrasound lesion score were not associated with excess mortality. Septic shock was observed in 61% of patients who died. Half of TB associated mortality occurred within 15 days from TB diagnosis.

Conclusion: In hospitalised TB patients in Rwanda, extrapulmonary TB is the main clinical presentation, disseminated TB disease is frequent. Mortality is high, occurs early after diagnosis, and is not associated with HIV status or a low CD4 count. Thrombocytopenia and dyspnoea are independent predictors of mortality. Septic shock is the main clinical event preceding death.

EP-156-05 Prevalence of non-tuberculosis mycobacteria in patients with suspicion of tuberculosis in a high tuberculosis burden country: a prospective cohort study

M Bonnet,^{1,2} Y Pho,¹ J-P Dousset,³ S Heng,⁴ S Godreuil,⁵ WW Yew,⁶ S Kim Chamroeun,³ C Hewison⁷ ¹Epicentre, Paris, ²Institut de Recherche pour le Développement, Montpellier, France; ³Médecins Sans Frontières (MSF), Phnom Penh, ⁴Institut Pasteur Cambodge, Phnom Penh, Cambodia; ⁵INSERM U1058, Montpellier, France; ⁶Hong Kong Tuberculosis, Chest and Heart Diseases Association, Hong Kong, China; MSF, Paris, France. e-mail: maryline.bonnet@geneva.msf.org

Background: Prevalence and case management of non-tuberculosis mycobacteria (NTM) are poorly documented in high tuberculosis (TB) burden countries. We present the prevalence, risk factors and clinical implications of NTM in the district of Kampong-Cham, Cambodia.

Methods: Consecutive adult patients with clinical suspicion of TB were enrolled in a prospective cohort with baseline epidemiological, clinical, radiological and sputum mycobacterial investigations, and 12 months follow-up of patients with NTM isolates. Culture used Löwenstein-Jensen and MGIT and identification used the GenoType® Mycobacterium CM/AS assay. An advisory committee classified patients as NTM lung disease or colonisation using the 2007 American Thoracic Society guidelines and advised on NTM treatment.

Results: Of 1188 patients (51.4% female, 54 years median age), 218 (18.3%) were diagnosed with *Mycobacterium tuberculosis* and 124 had NTM isolates (10.4%). Among them, 11 were classified as NTM lung disease (8.6%) and 113 as colonisation (87.8%). Amongst smear positive patients, 10/196 (5.1%) grew only NTM. Most common NTM were *M. fortuitum* (23.4%), *M. intracellulare* (16.1%), *M. abscessus* (11.3%), *M. scrofulaceum* (10.5%) and *M. goodii* (10.5%). HIV-infection (aOR 3.4, 95%CI [1.2–9.8]) and past TB history (aOR 1.6, 95%CI [1.1–2.7]) were associated with isolation of NTM. Patients with NTM lung disease were more likely to have past TB history (63.4% vs. 6.0%), history of hospitalisation for respiratory disease (54.5% vs. 6.4%), HIV infection (27.3% vs. 1.1%), low body mass index (median 14.8 vs. 18.1 Kg/m²) and bronchiectasis (60.0% vs. 13.4%) or pleuropulmonary sequelae (60.0% vs. 31.9%) on chest X-ray compared to TB patients. Eight patients were started on NTM treatment (5 cured, 1 death and 2 still on treatment) and 8/116 (6.9%) non-treated patients died during follow-up.

Conclusion NTM represent more than 1/3 of sputum mycobacterial growth from TB suspects. The 5% of smear-positive patients due to NTM are at risk of being over treated for TB. Post tuberculosis lung sequelae and HIV infection are important NTM predisposing factors. Decision to start NTM treatment should be rapid and systematic in advanced HIV-infected patients. However in HIV-negative patients, the decision for starting treatment also depends on the NTM species and host co-morbidity, especially bronchiectasis. Addressing ben-

efit versus risk of therapy, notably with age consideration and medication tolerability is warranted.

EP-157-05 Abrupt decline in tuberculosis among foreign-born persons in the United States

B Baker,¹ C Winston,¹ Y Liu,² A France,¹ K Cain¹ ¹U.S. Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination, Atlanta, GA, ²CDC, Division of Global Migration and Quarantine, Atlanta, GA, USA. e-mail: izj4@cdc.gov

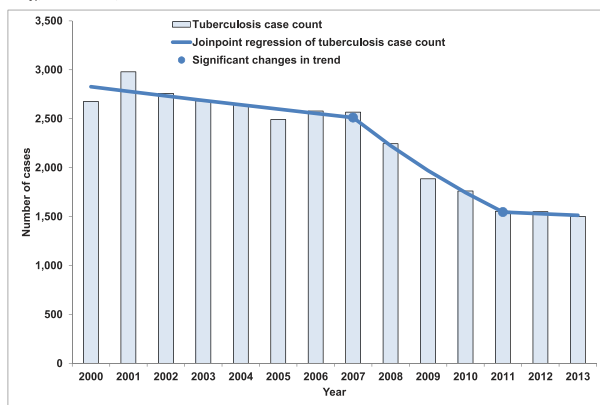
Background: While tuberculosis (TB) cases in the USA have declined over the past two decades, TB morbidity among the foreign-born has remained persistently elevated. A recent abrupt decline in TB cases among foreign-born persons provided an opportunity to examine contributing factors and inform future TB control strategies. We investigated the relative influence of four factors upon the decline: 1) changes in the foreign-born population through immigration and emigration, 2) changes in distribution of country of origin among the foreign-born population, 3) changes in the TB case rate among foreign-born subgroups, and 4) changes in the extent of TB transmission.

Design/Methods: Using data from the U.S. National Tuberculosis Surveillance System and the American Community Survey during 2000 to 2013, we examined TB case counts, TB case rates, and population estimates, stratified by years since U.S. entry and country of origin. Joinpoint regression modeling was used to assess significant changes in trend. We estimated the proportion of the case count decrease due to changes in TB case rate versus population shifts. We estimated the number of cases due to recent transmission in the United States using TB genotyping data.

Results: A 39.5% decrease in cases among recent entrants (<3 years since U.S. entry), beginning in 2007 and ending in 2011 ($P < 0.05$), accounted for 69.6% of the overall decline (Figure). Most (80.7%) of the decline among recent entrants from Mexico was due to a decrease in population, but the decline in cases among recent entrants from the other top five countries of origin was almost exclusively (95.5–100%) due to decreases in TB case rate. Among recent entrants, 6.3% of cases were likely due to recent transmission. Among non-recent entrants, an 8.9% decrease in cases was entirely (100%) due to a decrease in TB case rate and accounted for 30.4% of the overall decline.

Conclusion: Both recent and non-recent entrants contributed to the decrease in TB cases. The factors contributing to the decline among recent entrants varied by country of origin, but the decline among non-recent entrants was entirely due to a decrease in TB case rate. Strategies that address recent and non-recent entrants (e.g., investment in overseas TB control, testing and treatment of latent TB infection for high-risk subgroups among non-recent entrants) will be necessary to accelerate the decline in TB among foreign-born persons in the United States.

Figure. Tuberculosis case counts with Joinpoint regression model among recent entrants (<3 years since U.S. entry), United States, 2000–2013



EP-158-05 Trends of tuberculosis treatment outcome following community involvement in an under-resourced setting: the case of Bauleni compound, Lusaka, Zambia

V Mfungwe,¹ M Ota,¹ Y Onoe,¹ G Samungole,^{2,3} M Masaninga² ¹Research Institute for Tuberculosis (RIT)/Japan Anti Tuberculosis Association (JATA) Zambia, Lusaka, ²Ministry of Community Development, Mother and Child Health, Lusaka, ³Ministry of Community Development, Mother and Child Health, Lusaka, Zambia. e-mail: mfungwev@gmail.com

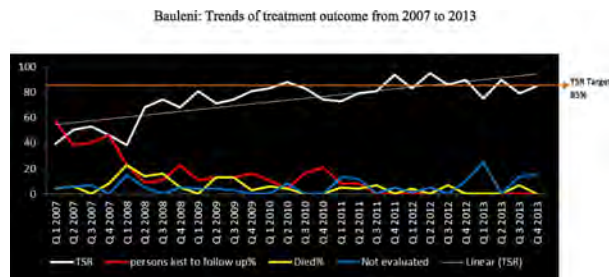
Background and challenges to implementation: Supervised tuberculosis (TB) treatment, which may have to include direct observation of therapy (DOT), helps patients take their drugs regularly and complete treatment, thus achieving cure and preventing the development of drug resistance TB. Supervision may be undertaken at a health facility, in the workplace, in the community. It should be provided by a treatment partner or supporter who is acceptable to the patient and is trained and supervised by health services. In Zambia, standardised tuberculosis prevention and control programme, incorporating Directly Observed Treatment, Short Course (DOTS) started in 1993. In 2006 and 2007, the treatment success rate of TB patients was unsatisfactorily low (47.0%) in Bauleni, one of the urban slums located in Lusaka urban district. A high proportion of this was persons lost to follow up (45.3%), which is a serious public health concern that needs to be addressed urgently.

Intervention or response: We embarked on a 6-year project to improve access of the community members to TB and TB-HIV co-infection case finding and patient care and support in Bauleni by training health workers and involving the community through the training of TB-HIV treatment supporters (TS) in community sensitization, case finding, patient care and support. This study investigated the outcomes of TB treatment in Bauleni to measure the impact of the implementation of the project. We analyzed the records of all new smear-positive TB patients registered in Bauleni from January 2007 to December 2013 based on the health centre TB register.

Treatment outcomes were categorised according to the national TB control program (NTP) guidelines. Microsoft Excel software was used to manage the data

Results: The annual average treatment success rate increased from 47.0% in 2007 to 82.3% in 2013, whilst the rate of persons lost to follow up declined from 45.3% in 2007 to 0% in 2013. The death rate reduced too from 4.5% in 2007 to 1.8% in 2013. Compared to the values of the preceding years, treatment success showed a consistent upward trend from 2007 (47.0%) to 2013 (82.25%)

Conclusions and key recommendations: After the implementation of the project, the treatment success rate of new smear-positive TB patients improved significantly. Monitoring, supervision and home visits and community education by TS may have contributed towards the achievement of 85% treatment success target and declining default and death rates.



EP-160-05 The duration of protection of infant BCG vaccination in England

P Mangtani,¹ R Keogh,¹ P Nguipod-Djomo,¹ L Trinder,¹ L Rodrigues¹ ¹London School of Hygiene & Tropical Medicine, London, UK. e-mail: punam.mangtani@lshtm.ac.uk

Background: Studies in Brazil and American Indian populations in the USA suggest duration of protection from BCG lasts several decades but evidence is scarce and relevance to other settings uncertain. In the UK, the BCG vaccine was given to school children, with selected vaccination to high-risk, usually ethnic minority, infants since the 1980s, covering half the health districts by 1992. School vaccination was replaced in 2005 by a national programme of BCG vaccination in infancy for high-risk populations.

Design/Methods: We carried out an observational study in England of cases of tuberculosis and frequency matched population based controls in minority ethnic groups aged 0–19 years. Trained interviewers conducted face to face interviews and requested permission to examine upper arms for a BCG scar. Records of past BCG vaccination are known to be incomplete and BCG scar is a traditional way to establish past BCG vaccination with high validity as an indicator of BCG vaccination in many populations. Information on potential confounders was collected including demographic and social variables. A complete case analysis is currently being carried out before multiple imputation for missing

scar information. Results of vaccine effectiveness by small periods of time since vaccination will be examined and presented, starting with the first 5 years and compared with the well established protective effect in the literature to assess robustness of the study.

Results: From 2012 to 2014 we recruited over 720 cases and 720 controls both with a response rate of over 60%. Interviewers noted a scar in 56% of cases and 65% of controls but with missing information in 16% and 10% respectively. Patterns of missingness indicated teens and young adults females of Bangladeshi and Pakistani women were less willing than other groups to be examined for a BCG scar. Initial complete case analyses suggested a protective effect in the first 5 years since vaccination.

Conclusion: We will present new evidence on how long BCG protects against disease which is important to reduce uncertainty. It will support appropriate decisions on any modification of future TB vaccine programmes eg universal infant BCG vaccination may be more economic than assumed. New improved vaccines may also need to show they offer protection against pulmonary disease greater than that offered by BCG alone.

08. High-definition insights into drug resistant tuberculosis

EP-161-05 Specific *gyrA* gene mutations predict poor treatment outcome in drug-resistant tuberculosis

L Rigouts,^{1,2} N Coeck,^{1,2} G Gumusboga,¹ A Maug,³ MA Hossen,³ H L Rieder,⁴ B De Jong,^{1,5,6} A Van Deun^{1,7}

¹Institute of Tropical Medicine, Antwerp, ²Biomedical Sciences, Antwerp University, Antwerp, Belgium; ³Damien Foundation, Dhaka, Bangladesh; ⁴University of Zurich, Zurich, Switzerland; ⁵Medical Research Council, Banjul, Gambia; ⁶New York University, New York, NY, USA; ⁷International Union Against Tuberculosis and Lung Disease, Paris, France. Fax: (+32) 476 333. e-mail: lrigouts@itg.be

Background: Increasing evidence points to the role of specific mutations in the gyrase genes of *M. tuberculosis* in phenotypic resistance to fluoroquinolones. However, the predictive value of these markers for clinical outcomes in multi-drug resistant patients is to date unknown. In this study, we aimed at determining molecular markers and breakpoints predicting second-line treatment outcomes in *M. tuberculosis* patients treated with fluoroquinolones.

Design/Methods: We analyzed treatment outcome data in relation to the *gyrA* and *gyrB* sequences, and minimal inhibitory concentrations for ofloxacin, gatifloxacin and moxifloxacin in pre-treatment *Mycobacterium tuberculosis* isolates from 181 multi-drug resistant tuberculosis patients in Bangladesh whose isolates were sensitive to injectable drugs.

Results: Resistance levels for ofloxacin were systematically higher relative to moxifloxacin and gatifloxacin. The *gyrA* 90Val, 94Gly and 94Ala mutations were most

frequent, with the highest resistance levels for 94Gly mutants. Increased pre-treatment resistance levels correlated with specific mutants, were associated with lower cumulative cure percentages, with no more cure among cases found resistant at 4 µg/ml. Any *gyrA* 94 mutation, except 94Ala, showed a significantly lower proportion of cure compared to all other *gyrA* mutations taken together (all non-94 mutants + 94Ala) (OR 4.2).

Conclusion: Our study suggests a breakpoint of 2 µg/ml on Löwenstein-Jensen and mutations at position 94 other than Ala to indicate high level resistance to gatifloxacin or moxifloxacin, predictive of poor treatment outcome in multi-drug resistant tuberculosis patients in whom the injectable agent is still effective.

EP-162-05 Contribution of efflux pumps to rifampicin resistance in clinical isolates of *M. tuberculosis*

A Narang,¹ S Porwal,¹ K Garima,¹ A Bhandekar,¹ K Shrivastava,¹ R Prasad,¹ M Bose,¹ M Varma Basil¹

¹Vallabhbhai Patel Chest Institute, Delhi, India. Fax: (+911) 2766 7420. e-mail: mandirav@rediffmail.com

Background: Mutations in a specific 81-base pair region of the *rpoB* gene, the Rifampicin (RIF) resistance determining region (RRDR), are responsible for 95% of rifampicin-resistant strains. Approximately 5% of clinical RIF-resistant *M. tuberculosis* isolates do not harbor mutations in the RRDR region, suggesting the existence of other mechanisms that may play a role in development of drug resistance. The role of efflux pumps in facilitating the emergence of resistance is now being recognised as a cause of drug resistance in *M. tuberculosis*. The present study investigated the expression of putative efflux related genes under RIF stress to investigate their role in resistance to RIF in *M. tuberculosis* isolates obtained from patients of pulmonary tuberculosis.

Design/Methods: We investigated the role of four putative efflux pump genes Rv0676, Rv0507, Rv1250 and Rv0194 in conferring RIF resistance to clinical isolates of *M. tuberculosis*. The study included 10 RIF susceptible and 19 RIF resistant isolates. The RRDR of the isolates was sequenced. The RIF resistant isolates included seven isolates with no mutations in the RRDR. The Minimum Inhibitory Concentration (MIC) of the isolates was analysed by Microplate Alamar Blue Assay and the isolates were exposed to subinhibitory concentrations of RIF for 24 hours. The expression of efflux genes was studied by Real Time Analysis using sigA as a normalizer and the results correlated.

Results: Amongst the 19 RIF resistant isolates, Rv0676c, Rv0507, Rv1250 and Rv0194 were upregulated in 10, 5, 7 and 10 isolates respectively. Five of the seven RIF resistant isolates, selected due to their wild type sequence, overexpressed one or more efflux pump genes. The MICs of all these five isolates were >1µg/µl. The efflux gene RV0194 was overexpressed in all these five wild type RIF resistant strains. Of the eleven RIF resistant *M. tuberculosis* isolates with mutations at the

531 codon, 7 overexpressed Rv0676c and four of these had high level resistance (MIC > 64 µg/µl). Rv0194 was upregulated in 4 isolates with 531 mutations. An isolate with mutation at 511 codon overexpressed Rv0676c, Rv1250 and Rv0194. The efflux genes were upregulated in only one of the RIF susceptible isolates, though the difference between the resistant and susceptible isolates was not statistically significant.

Conclusion: Efflux pumps may be upregulated as an initial response to drug stress in an individual and may thus play a role in RIF resistance.

EP-163-05 Use of whole genome sequencing to identify mutations related to phenotypic resistance to delamanid and bedaquiline in *M. tuberculosis*

A Cabibbe,¹ S Battaglia,¹ E Schena,¹ E Borroni,¹ P Miotto,¹ D M Cirillo¹ ¹San Raffaele Scientific Institute, Milan, Italy. e-mail: battaglia.simone@hsr.it

The rise of multi- and extensively- drug resistant tuberculosis (M/XDR-TB) is reducing the spectrum of available drugs for treatment, thus highlighting the need of new effective compounds. Among new anti TB drugs, delamanid (DLM) and bedaquiline (BDQ) are conditionally approved. Mutations responsible for BDQ-R are found in *atpE* gene. However, other spontaneous BDQ-R mutants harbour mutations in the non-target Rv0678 gene, a negative regulator of the MmpS5-MmpL5 efflux pump. These mutations may be linked to clofazimine resistance. DLM is a pro-drug requiring intracellular activation by Rv3547 protein. Mutations in Rv3547 gene or in *fbiA*, *fbiB*, *fbiC* and *fgd1* genes (F420 biochemical pathway) are involved in DLM-R phenotype. Taking advantage of Whole Genome Sequencing (WGS) approach, we analysed 9 genes putatively involved in BDQ-R and DLM-R on 236 *M. tuberculosis* isolates (96 susceptible to rifampicin (RIF) and isoniazid (INH), 11 RIF-R/INH-S, 96 MDR, 11 MDR+AG-R, 12 MDR+FQ-R and 10 XDR) representing 14 different lineages. We focused on *atpE*, Rv0678, *mmpL5*, *mmpS5* genes for BDQ-R; *ddn*, *fgd1*, *fbiA*, *fbiB* and *fbiC* genes for DLM-R. We identified several new non-synonymous mutations in genes putatively involved in BDQ-R. In particular, although no mutations were observed in *atpE*, the other analysed genes carried substitutions: 7 strains have mutations in Rv0678 gene [V3I, N4T (2), M17V, L32S, G87R, R134G]; 18 in *mmpL5* [P70L, D128N (3), S325G, A349T, E552G, L634Q, F696L (8), Q702K, Q707K]; 2 in *mmpS5* (G109S). We observed mutations possibly involved in DLM-R in: Rv3547 (3 isolates: R72W, E83D, W88STOP); *fgd1* (1: G314E); *fbiA* [8: Q120R (4), T302M (4)]; *fbiB* [64: F220L (56), D315A, L447R, K448R (6)]; *fbiC* [6: V41M, T273A (4), I693V]. From this data subset, we didn't observe any correlation among mutations in candidate genes for BDQ-R or DLM-R and the resistance pattern or genotype of strains included in the study. Previously reported lineage-specific substitution in *fgd1* (K270M: Haarlem; K296E: West Africanum 2) and *mmpL5* (D767N: Beijing) were also

detected. In addition to the phenotypic testing performed on a subset of 17 strains for DLM, drug susceptibility testing is under investigation on the other strains to better understand the role of these mutations in the emergence of BDQ-R and DLM-R. The WGS approach showed its usefulness in pre-treatment simultaneously analysing of a wide range of DR-related genes, reducing time for analysis of mutations linked to TB drug-resistance.

EP-164-05 Characterisation of resistance to rifampicin and isoniazid among Beijing *Mycobacterium tuberculosis* isolates in Kazakhstan

U Kozhamkulov,¹ A Akhmetova,¹ V Bismilda,² L Chingisova,² A Akilzhanova¹ ¹Center for Life Sciences, Nazarbayev University, Astana, ²National Center for Tuberculosis Problems, Almaty, Kazakhstan. e-mail: kzulan@mail.ru

Background: The incidence of tuberculosis in 2013 was 73.4 cases per 100 000 people, and the mortality rate was 5.6 per 100 000 people in Kazakhstan. Beijing/W family strains of *Mycobacterium tuberculosis* associated with a high risk of drug resistance are widely distributed in many parts of the world, including areas where it was not found previously. The aim of this study is characterization drug resistance to the rifampicin and isoniazid among Beijing/W family *M. tuberculosis* clinical isolates collected in Kazakhstan.

Design/Methods: The *M. tuberculosis* strains collected for this study were isolated from new TB cases patients in different regions of Kazakhstan. Spoligotyping was performed on DNA by using the standard method (Kamerbeek et al., 1997) using a reverse dot-blot spoligotyping commercially available kit (Ocimum Biosolutions Inc) with positive controls (*M. tuberculosis* strain H37Ra and *M. bovis* BCG) and negative control without DNA. Drug susceptibility of *M. tuberculosis* to isoniazid and rifampicin was determined using the absolute concentration method according to WHO recommendation. Genetic determination of *M. tuberculosis* drug resistance was identified through amplification and sequencing of the *rpoB* and *katG* gene regions and promoter regions of *mabA* (*fabG*)-*inhA*, *oxyR*-*ahpC* operons by automated ABI 3730 (Applied Biosystems) Genetic Analyzer, according to the manufacturer's instructions.

Results: The structure of the DR-region was determined by spoligotyping and identified 117 W-Beijing *M. tuberculosis* isolates including 68 (58.12%) MDR isolates, 30 (25.64%) susceptible isolates and 19 (16.24%) resistant other than MDR isolates. 69 *M. tuberculosis* clinical isolates were investigated to DNA sequencing analysis of the hypervariable (hot-spot) *rpoB* region and mutations in 4 codons were identified. Most of them were nucleotide substitutions in 531 codon (95.65%), especially Ser531Leu mutation (92.7%). Mutation in *katG* associated with a resistance to isoniazid among 78 isoniazid-resistance strains showed prevalence mutation in 315 codon (Ser315Thr substitution).

tion). This type of mutation noted in 98.71% cases. In one case detected mutation in -8 (T-C) position of promoter region *mabA* (*fabG*)-*inhA*.

Conclusion: Prevalence of MDR and other drug resistant clinical isolates (58.12% and 16.24%) among Beijing family strains of *M. tuberculosis* from different regions of Kazakhstan was shown.

EP-165-05 Sequencing-based detection of *rpoB* gene mutations in *Mycobacterium tuberculosis* strains from Malawi

T Chikaonda,^{1,2} I Kets,² N Nguluwe,¹ I Thengolose,¹ F Nyakwawa,³ W Stevens,² L Scott,² M Hosseinipour¹
¹UNC Project, Lilongwe, Malawi; ²University of the Witwatersrand, Johannesburg, South Africa; ³National Tuberculosis Control Programme, Lilongwe, Malawi. Fax: (+265)1755954. e-mail: tarchikaonda@gmail.com

Background: Detection of resistance to anti-tuberculosis drugs remains a significant challenge in Malawi due to limited diagnostics. New diagnostics, like the Xpert can both detect *Mycobacterium tuberculosis* and rifampin (RIF) resistance in a single, rapid assay. RIF resistant TB (RR-TB) has not been well studied in Malawi. In order to understand mechanisms of RIF resistance, we characterized 43 isolates from adult patients (≥ 18 years) for mutations in the 81bp region (codons 507 – 533) of the *rpoB* gene by DNA sequencing.

Methods: Sputum pellets were randomly selected from specimens sent for Drug Susceptibility Testing (DST) at National TB Reference Laboratory (NTRL) for processing at UNC Project laboratory. Pellets were re-suspended in 1.5ml phosphate buffer and an aliquot of 0.5ml was processed on Xpert. Another 0.5ml was cultured on MGIT 460 system. DNA was extracted from corresponding positive cultures of TB samples identified as RIF resistant by Xpert for sequencing in an automated DNA sequencer ABI Prism 3700 using BigDye terminator kit V3.1

Results: Mycobacterial strains ($n=43$) defined as RR-TB by Xpert were eligible for sequencing. To confirm RIF resistance, a 450bp fragment covering the core region of the *rpoB* gene was sequenced and yielded seven different mutations in 37/43 (86%) in codons 511, 512, 513, 516, 522, 526 and 531. The most common mutations were in codons 526 (38%), 531 (29.7%) and 516 (16.2%). No insertion, deletion or double mutations were observed. However, mutations were not found in 6/43 (14%) of the isolates, but were detected by Xpert probe B (4/6) and by probe E (2/6). Complete drop out of probe B and E was observed in one sample on either probe (1/4 and 1/2 respectively). Cycle threshold (Ct) values between 17.0 and 32.7 were observed in the remaining samples (4/6).

Conclusions: This is the first comprehensive molecular analysis of *rpoB* gene in RR-TB isolates from patients known to be at increased risk of drug resistance in Malawi. All isolates had one of the previously described *rpoB* mutations, containing nucleotide changes. No new mutations were identified in the current study. Interestingly, mutations were not detected in six strains despite being RIF resistant on Xpert. Resistance mechanism

remains unknown in isolates lacking *rpoB* gene mutations observed in this study. Further molecular cluster analysis such as spoligotyping and DNA finger printing is required to determine transmission dynamics of the mutated strain.

EP-166-05 Genetic markers of drug resistance and their association with clinical outcomes in patients with MDR-TB or XDR-TB

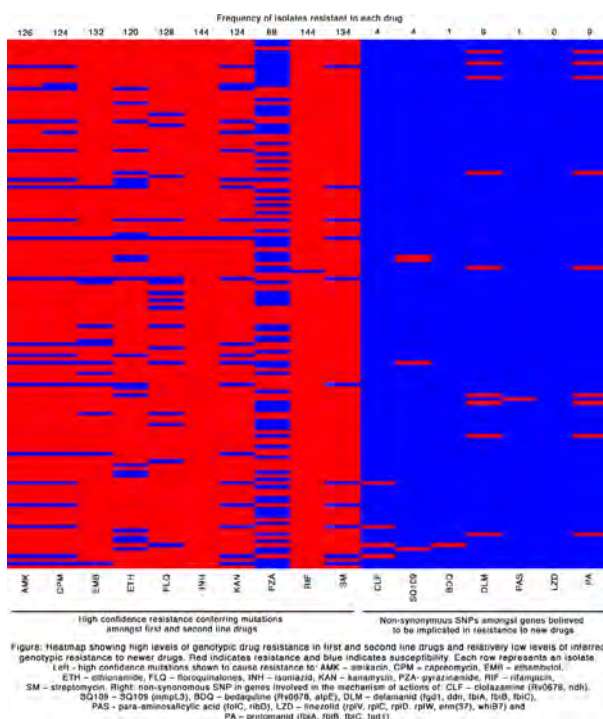
J Limberis,^{1,2,3} E Pietersen,^{1,2} J Jayakumar,^{1,2,3} G Theron,^{1,2,3} K Dheda,^{1,2,3} L Smith,^{1,2,3,4} R M Warren,⁴ T Clark⁵
¹University of Cape Town, Cape Town, ²University of Cape Town, Cape Town, ³University of Cape Town, Cape Town, ⁴University of Stellenbosch, Cape Town, South Africa. ⁵London School of Hygiene & Tropical Medicine, London, UK. e-mail: Imbjas002@myuct.ac.za

Background: Mycobacterial genetic associates of resistance to second line drugs and poor clinical outcomes [$\sim 75\%$ of extensively drug resistant (XDR-) TB patients die within 5 years] are poorly understood.

Methods: We conducted a 5-year prospective study on the outcome of XDR-TB patients in the Western Cape, South Africa. Diagnostic culture isolates underwent phenotypic susceptibility testing (DST), IS6110-RFLP strain typing, and Illumina whole genome sequencing (WGS). A bioinformatics pipeline was constructed and the presence of high confidence resistance conferring SNPs (listed in TBdream) described. Treatment outcomes were classified as favorable or unfavorable.

Results: Of the 145 isolates with WGS data, 112, 28, 3, and 2 isolates had XDR-TB, pre-XDR-TB, MDR-TB and mixed second line resistance, respectively. Compared to phenotypic DST, sequencing for resistance had a sensitivity of 99%, and 94% for resistance to the first line drugs and the second line drugs, respectively. Missense mutations were rarely identified in genes related to new or repurposed drugs (9 for both delamanid and pretomanid [none were in the high confidence delamanid resistance gene, *ddn*], 4 for SQ109, 1 for both bedaquiline and clofazamine, and none for linezolid; Figure). 49 isolates had a *ponA1* fitness mutation and none had *rpoB* compensatory mutations. 51/128 strains with a fluoroquinolone resistance-conferring mutation in *gyrA* had an *rpoB* mutation known to lower in vitro fitness cost. Inter-isolate comparison showed 1% of isolates with identical IS6110-RFLP patterns to have a different SNP barcode, while 26% of isolates with identical SNP barcodes had different IS6110-RFLPs. 22/129 patients had a favorable outcome. 93 SNPs were more frequent ($P \leq 0.05$) in patients with a favorable outcome, 20 of which were in virulence-associated genes. **Conclusion:** There was excellent concordance between genotypic DST and phenotypic DST suggesting that sequencing is likely to be useful clinically. Moreover, SNP-based strain typing had high agreement with a traditional fingerprinting method, thereby enabling tracking of strains. The absence of mutations in genes previously described to be associated with resistance to newly developed drugs holds promise for the treatment of drug-resistant TB. Known compensatory mutations

associated with drug resistance were rare. We also identified a preliminary SNP signature encoding genes involved in fundamental cellular functions associated with favorable outcome.



EP-167-05 Whole genome sequencing reveals accumulation of single nucleotide polymorphisms (SNPs) associated with treatment failure

L Malinga,¹ J Brand,¹ T Abeel,² A Earl,² M Van Der Walt¹
¹Medical Research Council, Pretoria, South Africa; ²Broad
Institute, Cambridge, MA, USA. Fax: (+27) 12 324 7922.
e-mail: lesibana.malinga@mrc.ac.za

Background: Multidrug drug resistant tuberculosis (MDR-TB) is a serious challenge, especially in high burden countries such as South Africa. Diagnosis and treatment is often delayed and this can lead to poor treatment outcomes. Due to ineffective treatment, *Mycobacterium tuberculosis* genome mutates and leads to bacterial fitness under antibiotic stress. Accumulation of short nucleotide polymorphisms (SNPs) could be responsible for treatment failure. We used whole genome sequencing (WGS) to analyse accumulation of drug target and compensatory SNPs between serial isolates of longitudinal cohorts failing treatment.

Design/Methods: MDR-TB strains were collected from 46 patients on second-line drug treatment in KwaZulu-Natal (KZN) and Eastern Cape (EC) between 2005 and 2009. All patients had phenotypically determined MDR-TB at baseline and had treatment outcomes documented. Each strain had baseline and at least one strain collected on follow up. From each strain, *M. tuberculosis* DNA was extracted from colonies grown on Löwenstein Jensen slants, and fragment and jumping paired-end

Illumina DNA libraries were constructed and sequenced on the Illumina HiSeq 2000 (Broad Institute in Cambridge, MA). Sequences were aligned to H37Rv genome and Pilon was run to generate a list of SNPs. Digital spoligotyping was performed to a database 43 unique spacer sequences.

Results: 92 sequences from 46 serial isolates of MDR-TB patients from KZN (29) and EC (17) were analysed. Among 46 patients, 11 (28%) had treatment success (i.e. cured or completed), 29 (63%) failures (i.e., died or defaulted) and four (13%) were lost to follow-up. Phylogenetic reconstruction revealed that primary genotype differed by province. The Beijing genotype was predominant in EC while EuroAmerican lineage (S, T, LAM, X) found in KZN. There was no difference in treatment outcomes between Beijing and EuroAmerican strains (55.2% vs. 44.8%, $P = 0.3$). 76% of cases failing treatment already had ≥ 5 SNPs at baseline. Among treatment failure cases, 42% patients accumulated 1-2 SNPs on follow-up isolates. We further identified positive epistasis between drug target and compensatory regions.

Conclusion: Continued evolution through SNPs accumulation and transmission of strains contributes to the MDR-TB genetic population fitness in these regions. The clinical significance of WGS for early detection of SNPs predictive of treatment failure needs further investigation.

EP-168-05 Use of DNA from AFB smears to perform high-throughput sequencing based surveillance for drug-resistant *Mycobacterium tuberculosis* in Afghanistan

J Mancuso,¹ M Rowneki,² N Hamraz,³ P Du,² G Davis,⁴
R Blakemore,⁵ D Alland,² N Aronson¹ ¹Uniformed Services
University, Bethesda, MD, ²Rutgers New Jersey Medical
School, Newark, NJ, USA; ³National Military Hospital, Kabul,
⁴Combined Security Transition Command-Afghanistan,
Kabul, Afghanistan; ⁵Sackler School of Graduate Biomedical
Sciences, Tufts University, Boston, MA, USA. e-mail:
james.mancuso@usuhs.edu

Background: Although Afghanistan is one of the 22 countries with the highest burden of tuberculosis (TB), little is known about the prevalence of the drug-resistant forms of TB. Since understanding the prevalence of resistance to drugs such as pyrazinamide and the fluoroquinolones is critical to devising new treatment regimens, surveillance of resistance trends must expand to cover more drugs. The objective of this study was to evaluate the prevalence of drug-resistant tuberculosis in Afghanistan using molecular techniques that can be adopted to detect resistance to a wider range of drugs.

Design/Methods: We obtained slides identified as positive for acid-fast bacilli during routine clinical practice from two provinces in Afghanistan. Slides were re-scored by study personnel according to the WHO/IUATLD standard semi-quantitative grading system. We extracted DNA from all slides graded 1+ or higher. Sample DNA was amplified and uniquely barcoded via multiplex PCR. Barcoded samples were pooled and high-throughput targeted re-sequencing of 16 drug-resistance associated

loci was performed on the Illumina MiSeq platform. Identified mutations were compared with a library of known drug-resistance associated mutations.

Results: We collected and examined 200 slides, of which 160 (80%) were 1+ or above. Sequence depth and quality varied between loci and samples. We obtained interpretable sequence data for between 5% and 75% of our samples, depending on the loci. One of 73 samples (1.4%) with interpretable sequence data had a mutation to *rpoB*, 1 of 8 samples (12.5%) had a mutation to *gyrA*, and 4 of 51 samples (7.8%) had a mutation in *pncA*. These mutations are associated with resistance to rifampicin, fluoroquinolones, and pyrazinamide respectively. We did not observe any mutations associated with resistance to isoniazid, ethambutol, aminoglycosides, or other TB drugs.

Conclusion: Few mutations associated with drug resistance to TB were seen in samples from these provinces of Afghanistan, but technical challenges in extracting and amplifying DNA from sputum microscopy slides remain. Changes to the PCR amplification strategy currently being tested should further improve sequencing coverage. Our estimates of drug resistance were lower than previous estimates reported by WHO in 2013, which were based on only 45 samples. High-throughput sequencing has the potential to provide information that can be used to guide both clinical management and public health policy.

EP-169-05 Association between specific mutations conferring resistance to rifampicin and isoniazid and baseline resistance to other anti-tuberculosis drugs

E Click,¹ E Kurbatova,¹ H Alexander,¹ T Dalton,¹ J Ershova,¹ P Cegielski,¹ J Posey¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. Fax: (+1) 404 639 1566. e-mail: eoc9@cdc.gov

Background: The Hain GenoType M. *tuberculosis* DRplus assay (Hain test) uses line probe based technology to detect the specific mutations in the *Mycobacterium tuberculosis* *rpoB* gene that confer resistance to rifampin, and in the *katG* and *inhA* genes that confer resistance to isoniazid. The Hain test not only provides important diagnostic information but may potentially aid in understanding the functional and clinical significance of specific mutations conferring resistance at the molecular genetic level. We investigated the association between specific genetic mutations in *rpoB*, *katG*, and *inhA* and baseline characteristics of cases of multidrug-resistant (MDR) tuberculosis (TB).

Design/Methods: In a prospective cohort study in 7 countries, patients with MDR-TB diagnosed using phenotypic methods and with concordant results for isoniazid and rifampin drug resistance detected by the Hain test, where available, ($n=447$) were included in the study. We used bivariate analysis to estimate associations.

Results: Participants were predominately HIV negative (58%, 260/477); 71% (317/447) had previously received

first line anti-tuberculosis drugs and 13% (60/447) had previously received second-line drugs. Relative to the most common *rpoB* mutation, S531L (observed in 369/447 83%), *rpoB* D516V was associated with baseline resistance to three injectable drugs kanamycin, amikacin and capreomycin (RR 15.6, 95%CI 7.26-33.4) and to ethambutol (RR 1.4, 95%CI 1.2-1.6) and was protective for resistance to rifabutin at a concentration of 2.0 µg/ml (RR 0.36, 95%CI 0.26-0.49). Relative to cases with isolates that have both *inhA* and *katG* mutations ($n=86/447$, 27%), cases with isolates that only have *inhA* mutations only were more likely to have resistance to ethionamide at baseline (RR 1.79, 95%CI 1.2-2.67).

Conclusion: Specific mutations conferring resistance to rifampin and isoniazid may be differentially associated with baseline drug resistance patterns in MDR TB patients and merit further investigation into the biological basis of these associations.

09. Behind bars: TB in correctional settings - II

EP-171-05 Alarming rates of tuberculosis transmission in Brazilian prisons

D Paião,¹ E Lemos,¹ M Pompilio,¹ S Simionatto,¹ A Motta-Castro,^{1,2} J Andrews,³ A Ko,⁴ J Croda^{1,2} ¹Federal University of Grande Dourados, Dourados, Mato Grosso do Sul, ²Oswaldo Cruz Foundation, Campo Grande, Mato Grosso do Sul, Brazil, ³Stanford University School of Medicine, Stanford, CA, ⁴Yale School of Public Health, New Haven, CT, USA. e-mail: juliocroda@gmail.com

Background: In Brazil, the incidence of active TB among prisoners is >1000 cases per 100 000 population, which is more than 25 times higher than in the general population. Although prisoners represent only 0.3% of the population, they accounted for 8% of notified cases of TB in Brazil in 2013. Despite the high burden of tuberculosis in prisons in Brazil and other countries, there have been few empirical data on infection rates within prisons, which are critical in evaluating the relative contribution of recent transmission versus reactivation in driving tuberculosis incidence.

Design/Methods: We performed a prospective cohort study of prisoners from 12 prisons in the 5 largest cities in the state of Mato Grosso do Sul, Brazil (Campo Grande, Corumbá, Dourados, Ponta Porã and Três Lagoas) in order to estimate the annual incidence of TST conversion and active TB and evaluate risk factors for these outcomes. A stratified proportional sample of 3380 subjects was selected from a population of 7221 inmates. We administered a baseline questionnaire and tuberculin skin test, followed subjects for 1 year in cohort study, and performed a repeat TST. TST positivity was defined as ≥ 10 mm (≥ 5 mm for HIV-infected individuals). TST conversion was defined as ≥ 10 mm induration and at least 6 mm increase in size of induration in a subject during follow-up who had a baseline TST <10 mm. We

used multilevel, multivariable logistic regression to assess independent predictors of TST conversion and active TB. **Results:** Among the 3,380 participants recruited for this cohort, 1,666 were unavailable at one-year follow-up. The overall TST conversion rate was 26.0% (95%CI 23.2%-28.0), with higher rates in male prisons (28.7%) than in female prisons (9.7%) ($P < 0.001$). Mixed race (AOR 1.51; 95%CI 1.22-2.04) and black (AOR 1.94; 95%CI 1.16-2.97) were positively associated with TST conversion, while diabetes (AOR 0.29; 95%CI 0.09-0.96) was negatively associated. The incidence of active tuberculosis was 2.8 (95%CI 2.0%-3.8%) in the cohort and ranged from 1.5% to 5.9% among the 12 prisons ($P < 0.001$). Baseline TST positivity (AOR 1.72; 95%CI 1.07-2.75), less than 4 year of schooling (AOR 2.33; 95%CI 1.37-3.85), knowing someone with TB (AOR 3.07; 95%CI 1.74-5.44) and drug use over the last year (AOR 2.09; 95%CI 1.29-3.38) were associated with active TB in the multilevel multivariate analysis. Prisoners accounted for 8.2%-42.2% of tuberculosis cases in their respective cities.

Conclusion: Extremely high annual risk of infection and incident active tuberculosis were observed in this twelve-prison cohort. Recent transmission, rather than reactivation, is likely driving these alarming disease rates. Urgent measures focused at disrupting the chain of transmission are needed to address the crisis of tuberculosis in Brazilian prisons.

Variables	Male								Female			
Location	ERIC	PEI	EMER	PHAC	CVAL	IFCGL	SPCL	EPICL	EPICAN	EPFL	EPFIC	EPFICF
	Corumbá	Três Lagoas	Paraná	Dourados	Carapicuíba	Carapicuíba	Carapicuíba	Carapicuíba	Corumbá	Três Lagoas	Paraná	Carapicuíba
Prisoner population	304	430	299	1,820	144	308	1,068	1,987	113	82	99	375
Accusated subjects followed per 1 year	134	111	111	327	34	55	214	255	39	32	27	65
TST negative subjects	83	87	83	265	29	88	150	169	34	20	24	66
TST conversion rate*	19	19	12	72	11	6	42	72	3	2	1	10
TST conversion rate*	23 (14)	22 (13)	14 (7)	38 (12)	30 (19)	21 (6)	37 (18)	43 (13)	9 (18)	6 (18)	3 (11)	15 (7)
TB case notification	2	0	3	11	1	0	6	15	1	0	0	1
TB incidence %	1.49	0	2.35	3.92	2.94	0	2.80	3.56	2.54	0	0	1.18

* Percentage and 95% confidential interval

EP-172-05 Tuberculosis in prisons

C L P Oliveira,¹ J L Da Silva,¹ V Dos Santos,¹ E S De Oliveira,¹ R S De Jesus,¹ D Pelissari,² D Chaves Kühleis,² D Barreira² ¹Porto Alegre Health Secretary, Porto Alegre, Rio Grande do Sul, ²Ministry of Health, Brasília, Distrito Federal, Brazil. e-mail: danielchaves@saude.gov.br

Background and challenges to implementation: Tuberculosis (TB) is a serious public health issue in Brazil, especially in prisons. In 2013, the population of inmates in the country totaled 600 000 people, which represents 0.3% of the Brazilian population. Of the 70 000 new TB cases diagnosed per year nationwide, 7.6% comes from prisoners. Recognizing the high incidence of TB in this population and the difficulties to implement health actions within the prison system, the National Tuberculosis Programme submitted a project for TB Reach in 2013, a financial program connected to the Stop TB Partnership. The project aims to increase TB detection in prisons from districts of Rio de Janeiro, Porto Alegre and Charqueadas, by GeneXpert® implementation allied to

innovative strategies of Advocacy, Communication and Social Mobilization (ACSM). We estimate that in the end of the project, approximately 35 thousand inmates will be examined.

Intervention or response: Initially, the project was implemented in the Central Prison of Porto Alegre. From October to December 2014, the TB case detection was held in one of the nine galleries of the prison, by spontaneous demand, at the time the inmate enters the prison. All individuals did the X-ray exam and were questioned about the presence of cough. For those with radiological alteration, sputum sample was taken (when existent) for GeneXpert, culture and antimicrobial susceptibility testing. Samples without quality for the Xpert were referred for sputum smear microscopy (BK). **Results and lessons learnt:** 1849 people were examined with 15 from spontaneous demand, 190 that were already incarcerated and 1,644 at entry into the prison system. Of 1,849 prisoners, 272 (14.7%) had altered results in X-rays. 237 patient samples were collected for holding BK, culture and GeneXpert. Of these, 27 were positive for BK, culture or Xpert and 18 were positive only by Xpert, representing a total of 45 laboratory confirmed cases with 16.5% of positivity.

Conclusions and key recommendations: The results suggested high TB positivity in Central Prison of Porto Alegre. The screening for TB at the entry into the prison system, galleries and spontaneous demand, proved to be an important strategy for early TB detection and, in the long run, to stop the transmission chain of the disease. In addition, ACSM activities with inmates may have contributed to their collaboration in the screening of tuberculosis among the population already incarcerated.

EP-173-05 Tuberculosis screening in prisons in Rwanda: the potential impact of combining digital X-ray screening and Xpert® MTB/RIF in TB diagnosis

E Ruseesa,¹ G Mutembayire,¹ J Mugabekazi,² M Gasana¹ ¹Ministry of Health, Kigali, ²World Health Organization, Kigali, Rwanda. e-mail: ruseesa@yahoo.co.uk

Background and challenges to implementation: From 2005, the Rwanda National TB Programme (NTP) introduced the policy of tuberculosis (TB) screening using clinical signs for every new prisoner entering the prison. Since December 2013, we introduced X-ray screening for identified TB high risk groups.

Intervention or response: The implementation of X-ray TB screening started in prisons. The screening was done using digital X-ray technique where all inmates in all 14 prisons in Rwanda were targeted to be screened. All inmates with abnormal chest x-ray images gave sputum samples for both LED microscopy and Xpert® MTB/RIF examination.

Results and lessons learnt: From December 2013 to April 2015, the activity has been implemented in all 14 prisons in Rwanda. A total of 52 007 out of 54 560 (95%) prisoners were X-ray screened for TB. Among them, 6362 (12%) had an abnormal chest x-ray image

suggestive of TB disease, and were therefore classified as presumptive TB. 6181 (97%) and 6052 (95%) presumptive TB gave sputum sample for microscopy and GeneXpert examination respectively. A total of 336 new TB cases were diagnosed. 264 (79.5%) cases of them were diagnosed only by Xpert examination. 10 cases (3%) among the new TB cases were Rifampicin resistance positive. Compared to the routine TB detection program where an average of 120 new bacteriologically confirmed pulmonary TB cases were detected annually (2010-2012) in prisons, while in 2013-2014 we detected 240.

Conclusions and key recommendations: TB screening using digital X-ray technique may lead to detection of many TB cases not routinely detected by the clinical screening especially in TB high risk groups. The role of GeneXpert in TB diagnosis is highly significant.

EP-175-05 Contact investigations in congregate settings as a key strategy for TB case finding and control: experiences from Lira prisons in Uganda

E Kizito,¹ P Donggo,² M Kenneth,¹ S Stavia,³ M Ruhweza,¹ B Woldemariam,¹ P G Suarez¹ ¹Mangement sciences for Health, Kampala, ²Lira Regional Referral Hospital, Lira, ³Ministry of Health, Kampala, Uganda. e-mail: kizitoen@gmail.com

Background and challenges to implementation: One of the components of the WHO Stop TB strategy is to address the needs of TB contacts, and of poor and vulnerable populations. Inadequate ventilation, overcrowding and inadequate TB infection control practices in congregate settings increase the risk of transmission of all forms of Tuberculosis. During 2014, Lira regional referral hospital in Northern Uganda diagnosed 12 patients with drug sensitive TB and 2 patients with multi-drug resistant TB all of whom were serving jail sentences in nearby prisons. Over the years, such patients would be transferred to the hospital for treatment but there was no documented contact screening and investigation for all inmates.

Intervention or response: Lira Regional Referral Hospital with support from the USAID funded TRACK TB Project conducted education sessions about TB for the prisons authorities and inmates with a focus on TB transmission and infection control including the need to promptly identify and evaluate presumptive TB cases. Multi-disciplinary teams comprising of Nurses, clinicians and laboratory technologists visited each of the prisons to conduct the sensitization session and screening of all inmates using the Intensified case finding tool (ICF).-Sputum samples were collected from all inmates that were found to have TB symptoms (presumptive TB cases) and subjected to an MTB/RIF test.

Results and lessons learnt: A total of 300 inmates were screened for TB, all were males just like the index cases and their average age was 32 years. All these contacts were HIV negative. Fifty-three symptomatic contacts were identified and had samples subjected to the MTB/

RIF test; 3 contacts (1%) were diagnosed with were diagnosed with TB as shown in the cascade in Figure 1.

Conclusions and key recommendations: Contact investigation in Lira prison led to identification of inmates with undiagnosed TB which increased the risk of transmission within the congregate setting. We recommend TB contact screening for both household and close contacts of inmates diagnosed with TB in addition to the periodic and routine TB screening at entry into the prison setting.

EP-176-05 Bringing technology to prisons of low-income countries to end TB: the experience of Haiti

J May,¹ K Duverger,¹ M Bury,¹ W Morose² ¹Health through Walls, Miami, FL, USA; ²National TB Program, Port-au-Prince, Haiti. Fax: (+1) 305 893 5009. e-mail: drjpmay@aol.com

Background: With an annual incidence of 1675 cases of TB per 100 000 (2013), the National Penitentiary holds the highest burden among 17 detention sites in Haiti. The absence of intensive TB program and lack of funds allowing the use of sophisticated diagnostics have permitted to detect TB only among very ill and symptomatic patients, although many cases were not detected, especially negative cases. The introduction of new technology from the National TB Program (PNLT), and USAID-funded NGO, Health through Walls, at the request of the Haitian Prison Authority, and use of new strategy such as screening at entry, contact tracing have increased detection of TB and improved outcomes. The introduction of new technology in the largest penitentiary of Haiti has had a significant impact on the health and living conditions in the prison of Port-au-Prince.

Results: 4718 prisoners entering in the penitentiary system were screened in 2013 and 5703 in 2014. Of the 10 421 prisoners screened, 141 of them have been diagnosed with TB in 2013 and 318 in 2014. The tool used in 2013 was symptom screening and digital X-ray, followed by sputum smear and culture for positive screenings. In 2014, GeneXpert was introduced to help diagnose more TB cases and detect MDR-TB according to the algorithm of PNLT. We have noticed that the tool introduced in 2014 mixed to the aggressive follow-up of non symptomatic abnormal X-ray, the molecular test has permitted to increase the detection rate and double the number of cases. MDR-TB has been detected among two through GeneXpert. All have been put under treatment using DOTS. Mortality rate from TB has decreased by 38%.

Conclusion 141 TB cases have been diagnosed in 2013 and 318 in 2014, demonstrating an increase in TB detection at Haiti's National Penitentiary. While Haiti is classified as a low-income country, the application of new technology has been effectively implemented despite few resources. The lesson learned is that new technology and a good collaboration with the country's national TB program, NGOs and prison authority can help control TB in overcrowded, low-income prisons. The model will be expanded to others detention sites of the country.

EP-177-05 Prisons and tuberculosis: developing a prison-based tuberculosis support model in Zambian prisons

N Sanjobo,¹ O Simooya,¹ L Lochting² ¹IN BUT FREE Prisons Project, Kitwe, Zambia; ²LHL International, Oslo, Norway. e-mail: nsanjobo@cbu.ac.zm

Background and challenges to implementation: Prison communities constitute high risk populations for tuberculosis (TB). Most prisons in Zambia are overcrowded and coupled with poor ventilation and long hours of cell confinement, such conditions facilitate the spread of TB. Despite being exposed to such unpleasant living conditions, having prisoners in one place could be an ideal environment for TB control and an opportunity to facilitate effective TB control measures.

Intervention or response: Since 2012, IN BUT FREE Prisons Project with support from LHL International has been executing a TB programme in Zambia. The project covers over 5000 prisoners and 430 prison officers. The objective of the intervention is to build capacity of prisoners and officers in TB. The programme uses volunteer prisoners and officers trained as Peer Supporters. Each prison elects their executive committees comprising prisoners and officers. These committees are responsible for coordinating work at each prison and report to the project team monthly. Peer supporters meet weekly to review progress. Thursdays are dedicated as cell teaching days and all trained peers are afforded opportunity to lead discussions in their cells. Peer supporters are also accorded opportunities to share information on TB, HIV and AIDS with fellow prisoners and officers at parade square every week. Sensitization campaigns are carried out through one on one discussion, drama performances, cell teachings, edu-sport, poems, distribution of Information, Education and Communication materials. Peer supporters assist in identifying possible suspected TB patients and refer them for investigations and treatment. Peer supporters also monitor and support their colleagues while on treatment.

Results and lessons learnt: 430 Prisoners and 105 Officers have been trained as Peer Supporters. A computer has been procured for the largest prison. Posters on TB and HIV, Brochures and TB Booklets have been printed and distributed. A video on TB in prison has been produced. Mentoring and support visits are conducted quarterly. Drama Groups have been established. Health education and TB case detection is available to prisoners. Patient referral system has been developed and follow up is carried out.

Conclusions and key recommendations: The involvement of prisoners and prison officers is fundamental to achieving an effective response to TB control in prisons in the new agenda for lung health.

EP-178-05 A first insight into high prevalence of undiagnosed tuberculosis cases in Mbuji-Mayi Central Prison in DR Congo

M Kaswa Kayomo,¹ G Bakaswa,¹ D Muteteke,¹ M Boelaert,² B De Jong² ¹National Tuberculosis Programme, Kinshasa, Democratic Republic of the Congo; ²Institute of Tropical Medicine, Antwerp, Belgium. e-mail: meckkay2002@yahoo.fr

Background: In low income countries, such the DRC, due to the financial and logistical issues, the current Xpert ® MTB/RIF machines available are located in national or provincial reference laboratories and more dedicated to RMP detection among MDR suspects. Xpert MTB/RIF utilization in intensified case finding and its impact on TB burden in prisons in DRC where a generalized HIV epidemic does exist has not yet been examined.

Design/Methods: We report the outcomes of an active TB case finding performed in the Mbuji-Mayi Central Prison in the Kasai Oriental Province, DRC in 2015. In addition, because RMP is the pillar of first-line TB treatment and the potential risk of spread of drug-resistant *M. tuberculosis* within the prison and exportation to the general population exist, we also studied the drug susceptibility (RMP) patterns of *M. tuberculosis* isolated from inmates in this prison and the associated risk factors.

Results: Of the 918 inmates found out in the prison, we did collect 350 sputum specimens. Among the 336 specimens tested, we retrieved 147 TB cases and 14 TB rifampicin resistant (TB-RR) cases. All TB and TB-RR have been put in treatment. However, these numbers are expected to change on the rise.

Conclusion: With overcrowding conditions, poor ventilation, and malnutrition, the risk of ongoing spreading is still very high.

10. The neglected cousins: trends and treatment of non-tuberculous mycobacteria

EP-179-05 Identification and characterization of non-tuberculous mycobacterial infection among people living with HIV presenting with TB symptoms in Botswana

J Basotli,¹ T Agizew,¹ K Radisowa,² Z Rey,³ T Tamuhla,¹ H Alexander,³ A Auld,³ A Finlay^{1,3} ¹Centers for Disease Control and Prevention, Gaborone, ²National Tuberculosis Reference Laboratory, Gaborone, Botswana, ³U.S. Centres for Disease Control and Prevention, Atlanta, GA, USA. Fax: (+267) 390 2713. e-mail: jbasotli@cdc.gov

Background: Botswana has the second-highest HIV prevalence globally, with one in four adults HIV-infected, and tuberculosis (TB) a common cause of morbidity and mortality. Recently we reported a higher-than expected prevalence of non-tuberculous mycobacteria (NTM) isolation from symptomatic people living with HIV

(PLHIV) attending 22 HIV care and treatment centers. We characterized the NTM species in this population given NTM species differ in clinical relevance. Isolation of *Mycobacterium kansasii* and *M. malmoense* from pulmonary specimens often are associated with disease, whereas *M. gordonae* and *M. simiae* are typically contaminants. *M. avium* complex (*M. intracellulare* and *M. avium*), and *M. abscessus* form an intermediate category.

Methods: PLHIV attending 22 HIV care and treatment centers were systematically screened for TB symptoms and sputum collected for liquid culture and identification. Culture growth was identified as NTM using the SD-Bioline TB Ag MPT64 Kit and Ziehl-Neelsen microscopy. NTM isolates underwent species identification by the Hain GenoType CM and AS line probe assays (LPAs).

Results: From 08/2012 to 10/2014, 1960 PLHIV presented with TB symptoms submitted at least one sputum specimen for culture testing. Among these, 429 (21.9%) had ≥ 1 positive culture result, 247 (57.6%) of which were identified as NTM. NTM species were identified for 205/247 (83.0%) patients, including five mixed species. *M. intracellulare* was the most common species isolated, 107/205 (52.2%). Other NTMs commonly associated with pulmonary disease included *M. malmoense* 8 (3.9%), *M. avium* 4 (2.0%), *M. abscessus* 2 (1.0%), and *M. kansasii* 1 (0.5%) (Table). Typical contaminants *M. gordonae* and *M. simiae* were identified in 15 (7.3%) and 9 (4.4%) isolates, respectively. Also, 32 (15.6%) NTMs could not be identified by the LPAs. At least 135 (65.9%) of NTM isolates were not obvious contaminants and require clinical follow-up.

Conclusions: Our preliminary finding is the first report on isolation and identification of NTM among a cohort of HIV-infected persons with TB symptoms in Botswana. Out of 13 species identified, *M. intracellulare* was predominant as has been reported in similar settings. Environmental sampling is underway to look for potential sources of contaminants. The higher-than expected prevalence of possibly disease-causing NTM species warrants further investigation and consideration during preparation of national TB guidelines.

Table NTM isolated among PLHIV presenting with TB Symptoms in Botswana

NTM species	Number	Frequency
<i>M. intracellulare</i>	107	52.2%
<i>M. gordonae</i>	15	7.3%
<i>M. simiae</i>	9	4.4%
<i>M. malmoense</i>	8	3.9%
<i>M. scrofulaceum</i>	6	2.9%
<i>M. fortuitum</i>	6	2.9%
<i>M. asiaticum</i>	5	2.4%
<i>M. avium</i>	4	2.0%
<i>M. abscessus</i>	2	1.0%
<i>M. genavense</i>	2	1.0%
<i>M. lentiflavum</i>	2	1.0%
<i>M. kansasii</i>	1	0.5%
<i>M. phlei</i>	1	0.5%
Mixed NTM*	5	2.4%
Others†	32	15.6%
Total	205	100.0%

*Mixed species: more than one species identified per patient

†NTMs that require additional tests for species identification

EP-180-05 Profile of non-tuberculous mycobacteria patients in Brazil, 2012–2014

N Saita,¹ D Pelissari,¹ F Dockhorn,¹ D Gomes Dell'orti,¹ F M Reis,¹ R Ruy De Souza,¹ P Bartholomay Oliveira,¹ D Barreira¹ ¹National Tuberculosis Programme, Brasília, Distrito Federal, Brazil. e-mail: nanci.saita@saude.gov.br

Background: Information System of Special Treatments for Tuberculosis (SITE-TB) is an online system used by secondary and tertiary reference units in order to notify, monitor and evaluate the diagnosed cases requiring special treatment, including cases of nontuberculous mycobacteria (NTM). The NTM cases are included in SITE-TB to facilitate the logistics of drugs, since in Brazil the NTM is not a notifiable disease.

Objectives: To describe the profile of patients with NTM recorded in SITE-TB in the period 2012 to 2014, according to clinical and demographic information.

Design/Methods: This is a descriptive study of new NTM cases in Brazil, from 2012 to 2014. We used data from SITE-TB and the following variables were analyzed: gender, age, race, educational level, form of the disease, HIV status, type of NTM, comorbidities and outcomes.

Results: In the period from 2012 to 2014, 604 new NTM cases were recorded in SITE-TB. 52% were male; 21% had between 55 to 64 years; 50% were white; 24% studied 4 to 7 years. As the clinical form, 78% were pulmonary. The more common NTM species associated were: *Mycobacterium kansasii* (16%), *Mycobacterium avium* (12%) and *Mycobacterium abscessus* (10%). For the comorbidities: 15% were smokers; 7% had diabetes mellitus; 7% were alcoholics; and 19% had HIV positive. As to the outcomes, 48% are still in treatment and 29% cured.

Conclusion: The incidence of tuberculosis by *Mycobacterium tuberculosis* is admittedly more common in men, however, it was observed that the NTM affects similarly men and women. The distribution according to type of NTM in Brazil was similar to that reported in other countries. Of note is the high percentage of smokers and the TB-HIV co-infection. The National Tuberculosis Program in Brazil encourages the notification of NTM cases in SITE-TB, since 2013. Therefore, data reported are limited and do not represent the totality of national cases for the analyzed period.

EP-181-05 Rapid SPs identification of NTM by molecular genetic assay from culture

C Iravatham,¹ P Chelluri,² M Vijaykumar,³ D Mallikarjuna⁴ ¹Dr.Iravatham's Clinical Laboratory, Hyderabad, ²Shadan Medical college, Hyderabad, ³AP Chest Hospital, Hyderabad, ⁴Bhimavaram Hospital, Hyderabad, India. Fax: (+91) 40 6662 3533.

Background: Differential diagnosis between non tuberculous mycobacteria (NTM and *M. tuberculosis* complex has always been a catch-22 situation for

clinicians and microbiologists. Suspected NTM isolates had to be sent to referral lab for sps identification. either by HPLC or conventional biochemical method which are both time consuming and laborious. Advent of molecular diagnostic assays has contributed a great deal towards early diagnosis and initiating treatment. Design: To evaluate DNA strip technology for sps identification of NTM from culture slope

Methods: Patients not responding to Anti TB treatment were referred for further lab investigation ($n = 13$). Samples included pus from non healing sub cutaneous abscess (sequelae to post laparoscopic procedure) ($n = 9$), sputum ($n = 1$), BAL ($n = 1$), breast abscess ($n = 1$), lymph node tissue ($n = 1$). HIV was status negative in all patients. Male: female ratio was 5:8. Mean age male 48.5; female 38.7. Samples screened for AFB by ZN and Fluorescent stain, Line probe assay (Lipa) done directly on clinical samples to rule out *M. tuberculosis* complex and also check for HR resistance. AFB culture done by conventional LJ and MGIT system. Antibigram done by MIC method for ATT first line drugs (SHER), quinolones and aminoglycosides and by microdilution for Clarithromycin, Co-trimoxazole and Linezolid. sps identification from positive culture slope done by DNA strip assay using Genotype mycobacterium CM kit (Hain), simultaneously compared with conventional biochemical or HPLC method.

Results: All samples screened were positive for AFB. Culture positive within two weeks. Sps identified by DNA strip assay were: *M. fortuitum*/*M. mageritense* ($n = 9$) from post laparoscopic procedure, *M. abscessus*/*M. immunogenum* ($n = 2$) breast abscess and sputum; *M. chelonae*/*M. immunogenum* ($n = 1$) BAL; *M. scrofulaceum* ($n = 1$) from cx tissue. Turn around time for the assay < 8 hours. Conventional biochemical and HPLC tests confirmed the rapid growers and HPLC *M. scrofulaceum*. Antibigram profile: All isolates resistant to SHER. Sensitivity pattern varied for quinolones and aminoglycosides in rapid growers suggesting possibility of mutation.

Conclusion: Early diagnosis upto sps level and intervention will have positive impact on treatment outcome. Limitation Assay can be performed from culture slope and not from clinical sample.

EP-182-05 Characteristics and treatment outcomes of nontuberculous mycobacterial pulmonary disease in a mycobacterial disease reference clinic

S Zweijpfenning,¹ C Magis-Escurra,¹ J Van Ingen,¹ M Boeree,¹ W Hoefsloot¹ ¹Radboud University Medical Center, Nijmegen, Netherlands. e-mail: sannezweijpfenning@gmail.com

Background: The incidence of nontuberculous mycobacterial pulmonary disease (NTM-PD) is increasing in the last few years in the Netherlands. Evidence concerning treatment is poor. In this study we give an overview of clinical aspects, treatment and outcome of all patients with suspicion of clinical relevant NTM-PD referred to

the center of expertise for mycobacterial infections (University lung center Dekkerswald, Nijmegen, The Netherlands).

Methods: We conducted a retrospective study of all patients seen between 2008 and 2013 with at least one NTM isolate and diagnosed using the American Thoracic Society (ATS) diagnostic criteria. Patients with non classical radiographic features that were not described in the ATS-criteria were included as well.

Results: 334 patients were reviewed. Sixty-three patients with NTM-PD were included. Thirty-two of them were female and mean age was 60.8 ± 12.9 years. *M. avium* complex (MAC) was the predominant species ($n = 37$, 58.7%); *M. malmoense* and *M. kansasii* were seen in 7 and 6 patients. *M. abscessus* was seen in 4 patients, *M. chimaera* in 1 patient, *M. simiae* in 3 patients, *M. xenopi* in 2 patients and 3 patients had combined infections. The most predominant radiologic features were consolidations or infiltrates (61.9%) and nodules (60.3%). Most patients had underlying COPD (73.0%), bronchiectasis was present in 54.0%, 39.7% smoked at time of diagnoses and 34.9% had a history of smoking. 53.1% ($n = 17$) of patients treated for MAC-PD were given a rifamycin-ethambutol-macrolide regimen (REM). Five patients received REM in combination with clofazimine and 7 patients received REM in combination with amikacin and clofazimine. Five patients with MAC were not treated. All six patients with pulmonary *M. kansasii* disease were treated with rifampicin and ethambutol; four also received isoniazid. The overall cure rate was 74.1%; 71.9% for MAC, 83.3% for *M. kansasii* and 66.7% for *M. malmoense*. In our study population all-cause mortality was 25.9%; during treatment; 10 patients experienced treatment failure and 4 patients; 7.4% relapsed.

Conclusions: In our setting, MAC was the predominant NTM and treatment largely followed ATS guidelines. Treatment success rates are comparable with data from the literature. The poor outcomes and toxicity underline the need for clinical trials addressing NTM-PD treatment.

	MAC N=37 (58.7%)	<i>M. malmoense</i> N=7 (11.1%)	<i>M. kansasii</i> N=6 (9.5%)	Others species N=13 (20.6%)
Outcome				
Recurrence	3 (9.4)	0	0	1 (10.0)
Mortality	11 (34.4)	1 (16.7)	1 (16.7)	1 (10.0)
Therapy failure	7 (21.9)	2 (33.3)	0	1 (10.0)
Cure	23 (71.9)	4 (66.7)	5 (83.3)	8 (80.0)
Clinical cure	3 (9.4)	0	1 (16.7)	0
No cure	6 (18.8)	2 (33.3)	0	1
Chronic treatment	5 (15.6)	1 (16.7)	0	0
Treatment not finished, no negative cultures	0	0	0	1 (10.0)

EP-184-05 Non-tuberculous mycobacterial disease: the reality in Lisbon

F Teixeira Lopes,¹ S Alfarroba,¹ A Dinis,¹ N Ribeiro,¹ M Gomes,¹ A Tavares¹ ¹Centro Diagnóstico Pneumológico Dr. Ribeiro Sanches, Departamento de Saúde Pública da Administração Regional de Saúde de Lisboa e Vale do Tejo, Lisboa, Portugal. e-mail: franciscateixeiralopes@gmail.com

Background: The incidence of non-tuberculous mycobacteria disease (NTM), although not fully known, is

currently estimated as 1 to 1.8/100 000 inhabitants. As NTM are ubiquitous in the environment, their presence is not always synonymous of disease. There are clinical, imaging and microbiological criteria that determine the need for treatment and therapeutic regimens. The aim of this paper is to characterize the NTM disease reported in Lisbon in the last 3 years.

Methods: Retrospective study on NTM notified by the CDP Dr. Ribeiro Sanches (Lisbon) from 2012 to 2014 to characterize the population, clinical presentations, diagnostic criteria, treatment regimens and therapeutic results.

Results: In the last three years 37 cases of NTM were reported, corresponding to 0.7/100 000 cases/year. Most were female (62%) with mean age of 56.7 yrs. Risk factors were identified in 33 patients including bronchiectasis (17 patients), HIV infection (10), history of neoplasm (7) and COPD (5) among others. More frequent registered mycobacteria were *Mycobacterium avium* complex (17), *M. abscessus* (4) and *M. chelonae* (3). Isolation was obtained from sputum (16 cases), bronchial lavage (16), blood cultures (2 *M. avium*), pleural fluid (1 *M. gordonae*) and skin biopsy (1 *m. intracellulare*). Most cases were first infections (36). The vast majority (89%) had only pulmonary manifestations, with one case of pulmonary and cutaneous co-infection and another with disseminated disease. Most patients had radiological findings (34), the most common being bronchiectasis with inflammatory changes (7) and cavitating nodules (6). Therapy had a median duration of 9.1 months. There were four therapy withdrawals and two interruptions, one due to optic neuritis and another for gastrointestinal intolerance. All therapeutic schemes included a macrolide and the vast majority used ethambutol (33) and rifampin/rifabutin (28), according to published guidelines. Recurrence was identified in only 1 patient.

Conclusions: The diagnosis and treatment of NTM disease remains a clinical challenge. Epidemiological data are scarce and therapeutic standards require updates. We admit an underdiagnosis of NTM in Lisbon according to literature. In our center, most of the patients were treated according to the recommendations although the average length of treatment was shorter than recommended. One of the possible reasons is the difficulty to sensitize patients to therapeutic adherence after symptomatic improvement.

ORAL ABSTRACT SESSIONS

11. Improving TB treatment outcomes

OA-379-05 Effectiveness of a conditional cash transfer programme in tuberculosis cure rate: a retrospective cohort study in Brazil

A Torrens,¹ M Sanchez,² J Nery,³ D Barreira,¹ D Rasella⁴

¹Brazil Ministry of Health, Brasília, Distrito Federal, ²University of Brasília, Brasília, Distrito Federal, ³Federal University of Brasília, Brasília, Distrito Federal, ⁴Independent, Rio De Janeiro, Distrito Federal, Brazil. Fax: (+556)183007775. e-mail: ana.torrens@saude.gov.br

Background: Tuberculosis (TB) is a poverty related disease. The Bolsa Família Program (BFP) is currently the largest conditional cash transfer program in the world that targets low income families. By improving the material conditions and access to health services have the potential to improve access to quality TB care. This study aims to evaluate the effectiveness of the BFP in tuberculosis treatment success.

Design/Methods: This study aims to evaluate the effectiveness of the BFP in tuberculosis treatment success. It is a retrospective cohort study. The study population is newly diagnosed TB cases in Brazil in all months of 2010 exposed and not exposed to BFP income transfer during TB treatment. The association measures relative risk and confidence intervals between exposure to cash transfer and treatment successes (proven cure plus treatment complete) was estimated by Poisson regression with robust variance model.

Results: The cure rate among those exposed to BFP income transfer during TB treatment was 81.7%, 5.4% higher than among those not exposed during follow up which was 76.3%. Multivariate analysis estimated a relative risk of 1.07 (95%CI) of the income benefit of BFP in tuberculosis treatment successes when adjusted for the covariates age, race, TB type, diabetes mellitus, HIV status, directly observed treatment, illiteracy, zone of residence, number of rooms and floor material of household and family per capita income.

Conclusion: The results of the study show that conditional cash transfer programs may increase TB patients cure rate of. This study, conducted with all TB patients in Brazil eligible to PFB benefits, one of the largest cash conditional transfer programs for low income families in the world, is relevant because treatment success continues a great challenge for TB control in the country.

Table 3. Tuberculosis treatment outcome according to BFP benefits exposure, Brazil, 2010.

Variables	Treatment successes*	
	RR (IC 95%)	
	Rough	Adjusted
Bolsa Familia Program income transfer	1,07 (1,06-1,52)	1,07 (1,04-1,11)
<15years		1
15-50years		0,94 (0,90-0,97)
>50years		0,95 (0,91-0,99)
Black		0,95 (0,93-0,97)
Diabetes mellitus		0,99 (0,95-1,04)
HIV positive		0,78 (0,73-0,82)
HIV unknown status		0,92 (0,90-0,94)
Extra pulmonary		1,01 (0,97-1,04)
Self-administrated treatment		0,88 (0,86-0,90)
Rural area		0,98 (0,96-1,02)
Number of rooms<4		1,00 (0,98-1,02)
Inappropriate floor material**		0,96 (0,94-0,99)
Family per capita income<25 dollars		0,97 (0,95-1,00)
Illiteracy		0,98 (0,95-0,99)

*proven cure plus treatment completed

**dirt, seized wood and other non-specified material

Source: Sinan/MS, Cad.Úncio/ MDS, BFP monthly payroll/ Federal Bank

OA-380-05 Development and validation of a simplified prognostic score for tuberculosis under the tuberculosis programme in a sub-Saharan African setting

E W Pefura-Yone,^{1,2} A D Balkissou,^{1,2} V Poka,¹ H K Fatime Abaicho,³ P T Enono-Edende,³ C Kuaban,^{1,4} A P Kengne⁵ ¹Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, ²Yaounde Jamot Hospital, Yaounde, ³Institut Supérieur de Technologie Médicale, Yaounde, ⁴Faculty of Health Sciences, University of Bamenda, Bamenda, Cameroon; ⁵Medical Research Council, Cape Town, South Africa. e-mail: pefura2002@yahoo.fr

Background: Death during treatment is a major challenge for tuberculosis (TB) control programs in developing countries. Currently, there is no simple tool for use in routine TB programs in high TB burden countries to stratify patients for mortality risk. The objective of this study is to generate and validate a simple score for predicting the risk of death during TB treatment.

Design/Methods: This was a cohort study based on data from clinical charts of patients aged ≥ 15 years, who undertaken diagnosis and treatment for tuberculosis at the referral center of the Yaounde Jamot Hospital between January 2012 and December 2012 (derivation sample), and January 2013 to December 2013 (validation sample). Predictors of mortality during TB treatment were obtained from logistic regression models. Regression coefficients (β) were used to generate the simple prognostic score (SPS) for predicting death during TB treatment. The c-statistic was used to assess the discriminatory ability of the model.

Results: The characteristics of the 1544 (59.5% men) patients included in the derivation sample were similar to those of 1317 (60.1% men) patients included in the validation sample. There were 110 deaths (cumulative mortality rate: 7.1%) in derivation sample and 103 deaths (7.8%) in validation sample. The SPS was calculated as follows: age (years)-5 $\times$ adjusted body mass index (kg/m²) + (clinical form of TB: smear negative pulmonary TB, +30 points; extra-pulmonary TB, +15 points; smear positive pulmonary TB, 0 point) + (HIV infection: yes, +45 points; no, 0 point). The discrimination of this score was excellent in derivation sample (c-statistic [95%CI]: 0.803, 0.762-0.844, $P < 0.001$) and validation sample [c-statistic: 0.817 (0.777-0.856), $P < 0.001$]. Five mortality risk categories were identified: class I (low risk, SPS < -60), Class II (moderate risk, $-60 \leq$ SPS < -30), Class III (high risk, $-30 \leq$ SPS < 0), class IV (very high risk, $0 \leq$ SPS < 30) and class V (critical risk, SPS ≥ 30). The probability (standard error of estimate) of death during TB treatment was 1.3% (0.2), 5.7% (1.0), 15.9% (2.6), 24.2% (3.7) and 29.5% (4.5) respectively in the classes I, II, III, IV and V in the validation population.

Conclusion: We have developed and validated a simple prognostic score for TB using routinely data collected in the TB programs. This score can allow rapid risk stratification of TB patients for close monitoring and appropriate management of these patients.

OA-381-05 The impact of referring patients with tuberculosis from a mega-tuberculosis centre to a peripheral health care centre on loss to follow-up

E W Pefura-Yone,^{1,2} H K Fatime Abaicho,³ A D Balkissou,^{1,2} A P Kengne⁴ ¹Yaounde Jamot Hospital, Yaounde, ²Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, ³Institut Supérieur de Technologie Médicale, Yaounde, Cameroon; ⁴Medical Research Council, Cape Town, South Africa. e-mail: pefura2002@yahoo.fr

Background: Several historical tuberculosis (TB) treatment centers in developing countries are still diagnosing and treating a disproportionate number of patients with TB. The Yaounde Jamot Hospital (YJH) is a referral and historical hospital center for TB diagnosis and treatment (TDC) in Cameroon. Over the last 5 years, 1600 to 1800 patients with TB were detected each year at the YJH, with most of them subsequently receiving treatment in this institution. Since three years, a decentralization program has been initiated, aiming at referring patients from YJH to other TDC in Yaounde. The objective of this study was to assess the impact of referring patients with TB from the mega-TDC of the YJH to other TDC on the rate of lost to follow-up.

Methods: In this retrospective cohort study, the records of patients diagnosed with TB at YJH from January 2012 to December 2013 were reviewed. Patients were divided into two groups: those referred from HJY for another TDC (referred group) and those treated at YJH (YJH group). The Kaplan-Meier estimator and log-rank test

were used to compare the rate of lost to follow-up in both groups. The proportional Cox regression model was used to estimate the hazard ratio of lost-to follow-up in the referred group in comparison to the YJH group.

Results: Of the 3794 patients enrolled, 59.7% were male and their mean age standard deviation (SD) was 35.8 (12.9) years. During the study period, 553 (14.6%) patients were referred to another TDC and 3241 (85.4%) were treated in YJH. Patients in the referred group had a mean age (SD) of 34.2 (12.7) years and those in YJH group had a mean age of 36.1 (12.9) years ($P < 0.001$). The clinical forms of TB were distributed similarly in both groups with 70.9% smear positive pulmonary TB cases in the referred group and 67% in the YJH group. The rates of treatment success, death and lost to-follow-up were respectively 81.4%, 2.4% and 11.2% in the referred group. The equivalent figures for the YJH group were respectively 68%, 9.3% and 15% ($P < 0.001$). The Kaplan-Meier estimator showed that the probability of being lost to follow-up was lower in the referred group (log-rank test, $P = 0.007$). In univariable analysis, the hazard ratio (95%CI) for lost to follow-up in the referred group compared to YJH group was 0.70 (0.54 to 0.91), $P = 0.008$. In multivariable analysis including the baseline characteristics significantly associated with lost to follow-up in univariable analysis, patients reference from YJH to other TDC remained a protective factor of the lost to follow-up with adjusted hazard ratio (95%CI) of 0.55 (0.41 to 0.74), $P < 0.001$.

Conclusion: The reference of patients from the mega-TB center of YJH to other treatment centers significantly reduces the risk of being lost to follow-up. An effort should be made to ease the pressure on large TB treatment centers by referring well-characterized TB patients to small satellite centers for treatment and follow-up.

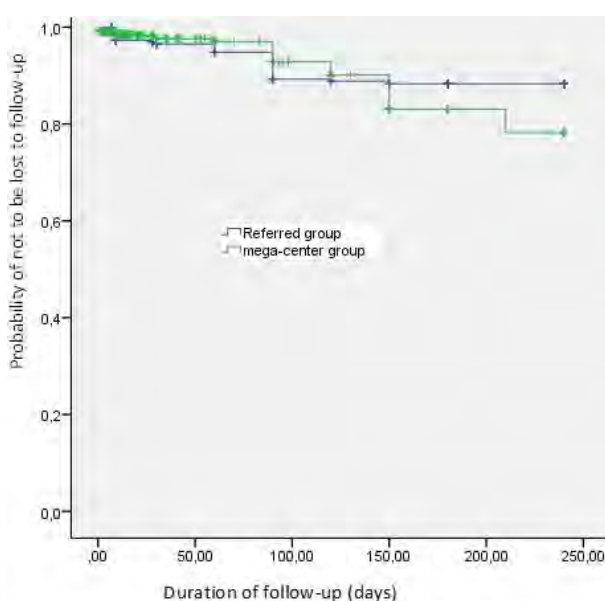


Figure 1: Kaplan-Meier curves depicting probability of non-discontinuation of treatment according to the duration of treatment

OA-382-05 High MDR-TB rates among successfully treated new smear-positive TB patients using the intermittent regimen under the DOTS strategy

D Garg,¹ N Garg² ¹Chest Center Jhandewalan, New Delhi, ²Health Center, Punjab Bhawan, New Delhi, India. e-mail: dkgarg56@gmail.com

Background: Under Revised National Tuberculosis Control Programme (RNTCP), India follows WHO recommended DOTS strategy using intermittent regimen to treat drug sensitive tuberculosis without any policy of long term follow up of patients. The emergence of resistance to drugs used to treat tuberculosis has become a significant public health problem and an obstacle to effective TB control. An MDR-TB case is defined as a presumed MDR-TB patient who is culture positive & has *M. Tuberculosis* resistant to isoniazid & rifampicin. Sputum sample from an MDR-suspect of any criteria A, B or C was tested by Culture & DST at an RNTCP accredited laboratory. Criteria B which includes all smear positive previously treated pulmonary TB cases at diagnosis is being followed since January 2012.

Design/Methods: This study included total 1458 MDR-TB suspects (including 322 retreatment relapse cases) during the period Jan. 1, 2012 to December 31, 2014 in Jhandewalan district, New Delhi, India covering a population of 5.5 lacs. Two sputum samples (one early morning & other supervised spot) were sent in falcon tubes to the IRL for diagnosis of MDR-TB by drug sensitivity test LPA (Line Probe Assay) or CBNAAT (Cartridge Based Nucleic Acid Amplification Test). The patients were interviewed to evaluate the past history of treatment and records were checked for data validation.

Results: Total 144 (9.9%) MDR-TB cases were diagnosed. Out of 322 retreatment relapse cases there were 47 (14.6 %) MDR-TB cases. 26 MDR cases (17 M, 9 F, all above 14 yrs of age) were from new smear-positive (NSP) cases successfully treated with Cat I. Thus MDR cases from NSP form 18% (26/144) of the total and 55% (26/47) of the MDR cases from retreatment relapse patients. Moreover 34.6 % (9/26) of these cases were cured less than 1 year back.

Conclusion: In view of the findings mentioned above, we conclude that there is high MDR-TB among successfully treated new smear-positive cases with intermittent regimen under RNTCP. The treatment completion declared based on sputum microscopy creates doubt. There may be reactivation & genetic mutation of the remaining bacilli. Recommendations: 1) the programme may reassess its treatment regimen of Cat I regarding the frequency of doses & duration of treatment, 2) treatment completion may be declared based on liquid culture technique, and 3) provision of timely follow up of successfully treated cases to find out the relapse at the earliest.

OA-383-05 Low rifampicin levels in patients treated with intermittent anti-tuberculosis regimens in India

G Ramachandran,¹ H K Agibothu Kupparam,¹ C Vedachalam,¹ J Lavanya,² S Swaminathan¹ ¹National Institute for Research in Tuberculosis, Chennai, ²Chennai Corporation, Chennai, India. e-mail: geetha202@rediffmail.com

Background: In the Revised National Tuberculosis (TB) Control Programme (RNTCP) in India, patients are treated for TB with thrice-weekly regimens. We determined plasma concentrations of rifampicin (RMP), isoniazid (INH) and pyrazinamide (PZA) and examined factors that influenced drug levels and treatment outcomes.

Design/Methods: Adult TB patients with pulmonary/extrapulmonary TB, receiving thrice-weekly anti-tuberculosis treatment (RMP 450mg/600mg for weight $\leq$ 60kg), INH 600 mg, PZA 1500mg) in the RNTCP in Chennai Corporation were studied. At steady state, two-hour post-dose concentrations of RMP, INH and PZA were determined by high performance liquid chromatography, after directly observed drug administration. Cured/treatment completed was considered a favourable outcome and death/failure an unfavourable outcome. Multivariate and logistic regression analyses by stepwise method respectively were used to determine factors that influenced drug levels and treatment outcomes.

Results: The study population consisted of 1266 patients (mean age 39.6 years; males 67%; mean body mass index (BMI) 19.4kg/m²). 86%, 11% and 19% of patients had sub-therapeutic RMP, INH and PZA concentrations (sub-therapeutic cut-off: RMP < 7µg/ml; INH < 2µg/ml; PZA < 20µg/ml). Females had higher drug levels than males ($P = 0.012$ and < 0.001 for RMP and PZA respectively), those with BMI > 18.5 kg/m² had lower drug levels ($P = 0.063$, < 0.001 , < 0.001 for RMP, INH and PZA respectively) and those with blood glucose > 200mg/dl had lower INH and PZA levels ($P < 0.001$ for INH and PZA). RMP levels were significantly influenced by sex and BMI, INH by age, BMI and blood glucose and PZA by sex, BMI, blood glucose, type of TB and smoking. Outcomes were available in 212 smear positive patients, of whom 17 had an unfavourable response. RMP concentrations were significantly lower in unfavourable than favourable responders (0.67 vs. 3.5 µg/ml; $P < 0.001$). Factors that influenced treatment outcome were low 2-hour RMP concentration ($P = 0.015$; 95%CI 1.1 – 1.8; AOR = 1.4) and low BMI ($P = 0.033$; 95%CI 1.1 – 23.7; AOR = 5.2).

Conclusion: The majority of patients on thrice-weekly anti-tuberculosis therapy had sub-therapeutic RMP. Low RMP levels and undernutrition were associated with unfavourable treatment outcomes. There is a need to consider increasing drug doses in those with higher BMI and diabetes. This study has important clinical implications as suboptimal blood levels could lead to failure and acquired drug resistance.

OA-384-05 Cost-effectiveness of different models of treatment for DR-TB patients in KwaZulu-Natal, South Africa

M Loveday,¹ K Wallengren,² J Brust,³ A Voce,⁴ N Padayatchi,⁵ J Ngozo,⁶ Z Radebe,⁶ E Daviaud¹ ¹South African Medical Research Council, Cape Town, ²ThinkSA, Durban, South Africa; ³Montefiore Medical Center & Albert Einstein College of Medicine, New York, NY, USA; ⁴University of KwaZulu-Natal, Durban, ⁵Caprisa, Durban, ⁶KwaZulu-Natal Department of Health, Pietermaritzburg, South Africa. Fax: (+27) 865 126 019. e-mail: marian.loveday@mrc.ac.za

Background: Given the size of the DR-TB burden in South Africa and the cost of treating each DR-TB patient, policy makers and TB programme managers need to know the cost of each model of care, and which model of care is most cost effective. In this study we report actual costs together with the cost-effectiveness of a spectrum of different models of care for DR-TB patients.

Methods: In our operational prospective cohort study DR-TB patients were treated with 4 different models of care. At the centralised hospital and decentralised sites (district hospitals) patients were initially hospitalised. In the two community-based models of care patients were not hospitalised and the daily injectable was administered at either a local clinic or a mobile injection team. Using a provider perspective, we collected costs to the health service only, excluding household costs. We performed a cost analysis to enable us to compare the cost of each model of care together with the cost-effectiveness. Cost-effectiveness was defined as the cost per MDR-TB patient successfully treated, that is, cured or completed treatment.

Results: Successful treatment rates varied across the different models of care, from a low of 54% at the centralised hospital to a high of 72% at Decentralised 1. For each treatment model the cost per patient treated varied considerably (Centralised \$30 067, Decentralised 1 \$24 516, Decentralised 2 \$33 554, Clinic \$9519, Mobile \$10 616) (Table). The cost per successful treatment was highest in models of care in which patients were hospitalised (Centralised \$55 680 and Decentralised 2 \$64 776), where it was more than 3 times higher than the community-based models of care (Clinic \$15 865 and Mobile \$18 495). Hospitalisation was the major cost driver accounting for 67-82% of the total costs in the 3 models of care in which patients were hospitalised. Length of hospitalisation and the subsequent costs varied (Table). In the community-based models drugs and tests were the major cost drive accounting for 40-52% of the treatment costs.

Conclusion: Community-based care for patients with MDR-TB is more cost-effective than either care in a decentralised or centralised setting as evidenced by the lower cost per patient successfully treated. This exploratory study suggests that community-based care is both effective and cost-effective. However, our study sample in the community-based sites was small and a larger study is needed to confirm these findings.

Table 1: Cost per treatment model and per MDR-TB patient cured (all costs in dollars)*

Cost per Patient Treated (USD\$14)	IPD (\$)	OPD (\$)	Clinic (\$)	Mobile (\$)	Laboratory tests/Audiology (\$)	Treatment (\$)	Total Cost (\$)	Treatment success (%)	Cost/ Treatment Success (\$)
Centralised hospital	24 108	1 356	824		1 652	2 327	30 067	54	55 680
Decentralised 1	16 547	2 169		786	1 780	2 785	24 516	72	34 050
Decentralised 2	27 537	1 306			2 132	2 579	31 554	52	64 776
Community-based: Clinic		2 419	2 086		3 025	2 990	9 519	60	15 865
Community-based: Mobile		2 426		3 928	1 730	2 532	10 616	57	18 495

* Exchange rate 15 = 10.44 (and) (UN (2015) Operational Rates of Exchange available: <http://treasury.un.org>. Accessed 3rd March 2015.

OA-385-05 Predictors of 2 month culture conversion in pulmonary tuberculosis

W Smythe,¹ J Pasipanodya,² P Denti,¹ C Merle,³ P Olliaro,⁴ T Gumbo,² H McIlleron¹ ¹University of Cape Town, Cape Town, South Africa; ²Baylor Research Institute, Dallas, TX, USA; ³London School of Hygiene & Tropical Medicine, London, UK; ⁴UNICEF/UNDP/World Bank/WHO Special Programme on Research & Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland. Fax: (+27) 214 481 989. e-mail: smywyn001@myuct.ac.za

Background: Between patient pharmacokinetic (PK) variability could lead to poor treatment outcomes. We identified predictors of 2 month culture (defined as 'outcome') in adults with newly diagnosed pulmonary tuberculosis (TB) in the OFLOTUB phase 3 randomized controlled trial at clinics in 3 African countries.

Design/Methods: Classification and regression tree (CART) analyses was used to identify factors predictive of outcome and their interactions. Potential predictors of outcome included peak concentration (C_{MAX}) and area under the steady state concentration-time curve (AUC) for rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB) & gatifloxacin (GFX), age, sex, body mass index, HIV status, baseline cavitation and number of lung zones affected, baseline sputum smear, and regimen 'standard' including RMP, INH, EMB & PZA vs. 'test' with GFX replacing EMB. Ten-fold cross validation, the receiver operating characteristics and parsimony were used in model selection.

Results: CART identified steady state RMP AUC >33.45 mg*h/L and age <30 years as best predictors of outcome in the standard and test arms, respectively. Patients in the test arm were 6.1 times more likely to have good outcome if they were under 30 years of age (95%CI: 1.9-19.4). The odds of a good outcome in the control regimen was 3.6 (95%CI: 1.6-8.2) when the steady state RMP AUC was above 33.45 mg*h/L which corresponds to a C_{MAX} of ≈7.8 mg/L. Notably, CART analysis demonstrated GFX exposure to have at best a relative variable importance of 30% compared to the 74% of RMP. Correspondingly, neither steady state GFX AUC nor C_{MAX} were associated with outcome. Antagonism between moxifloxacin and RMP demonstrated in hollow-fiber system model (HFS) experiments could explain failure of RMP exposure to predict outcome in the test regimen. Supporting this, the association between RMP exposure and outcome was significantly less in the test regimen, which included GFX. Patients with RMP steady state AUCs in the top quartile were 6 times (95%CI: 2-22) vs. 1.1 times (95%CI: 0.4-3.5) more likely to achieve

good outcome than patients with RMP AUCs in the lowest quartile in the control and test arms respectively. **Conclusion:** In TB patients on a standard regimen, measures of RMP exposure better predict culture conversion than non-PK factors including cavity and HIV status. The role of RMP AUC and C_{MAX} in bacterial kill is consistent with HFS experiments. Thus, for shortening therapy, the background regimen needs to be dose optimized.

OA-386-05 TB treatment outcomes among participants in the XTEND trial

K Fielding,¹ K McCarthy,^{2,3} S Ginindza,² V Chihota,^{2,3} S Charalambous,^{2,3} G Churchyard,^{1,2,3} A Grant^{1,3} ¹London School of Hygiene & Tropical Medicine, London, UK, ²The Aurum Institute, Johannesburg, ³University of the Witwatersrand, Johannesburg, South Africa. Fax: (+44) 20 7636 8739. e-mail: katherine.fielding@lshtm.ac.uk

Background: South Africa has replaced sputum microscopy with Xpert MTB/RIF as the first-line diagnostic test for TB. The XTEND study, a pragmatic cluster randomized trial, evaluated the effect of Xpert on patient outcomes in persons with suspected TB. We report on TB treatment outcomes of XTEND study participants.

Design/Methods: 20 laboratories in 4 provinces were randomized to intervention (immediate Xpert implementation) or control (microscopy, with Xpert implementation deferred) arms. At 2 primary health clinics served by each laboratory, a systematic sample of adults with suspected TB, identified by clinic staff, was invited to participate. Participants were followed up for 6 months. TB treatment initiations and outcomes were identified using paper and electronic TB registers and participant self-report, excluding those with drug-resistant TB. Poor treatment outcome was defined as death, lost to follow-up or failure (versus cure/completed treatment). The intervention effect was estimated using methods for cluster randomized trials, adjusting for baseline differences.

Results: Between June-November 2012, 4972 persons with suspected TB were screened for the study. 4656 persons enrolled and followed for 6 months over which time 522 (282 in microscopy and 240 in Xpert arm) had started on TB treatment (excluding 19 with drug-resistant TB). Of these, 43% were female, median age 36 yrs, 19% had body mass index (BMI) <18kg/m², 17% had previous TB and 69% were HIV-positive at enrolment, of whom 26% had ever taken antiretroviral therapy (ART). Among *n* = 522, there was some imbalance by arm for BMI, ART use and previous TB. Treatment outcomes were known for 89% (466/522) of participants; 87% (406) were cured/completed treatment (78%; / 522), 8% (37) had died, 4% (17) were lost to follow-up, 4 had transferred out and 2 had documented treatment failure. By arm, 12.5% (31/249) and 11.7% (25/213) had poor treatment outcome, in the microscopy and Xpert arms; adjusted risk ratio (Xpert vs. microscopy) was 1.05 (95%CI: 0.70-1.59, *P* = 0.8). Poor treatment outcome was more common among those HIV-positive, irrespective of ART status. Among those

HIV-positive 33/43 (77%) of poor outcomes were deaths.

Conclusion: Replacing smear microscopy with Xpert did not alter outcomes of drug-sensitive TB. Mortality was the leading cause of poor treatment outcomes; additional interventions are needed to address this, particularly among HIV-positive people.

12. MDR-TB: impacts of detection and early treatment

OA-387-05 The yield of household contact investigation of MDR-TB index cases in two regions of Ethiopia

N Demmelash,¹ D J Dare,¹ M R Nigussie,² I Jemal Abdulahi,³ T Kebede,^{1,8} M Aseresa Melese,¹ D Habte,⁸ Y Haile,^{4,5} P G Suarez¹ ¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, ²Amhara Regional Health Bureau, Bahir Dar, ³Oromia Regional Health Bureau, Addis Ababa, ⁴United States Agency for International Development, Addis Ababa, Ethiopia; ⁵Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: nhiruy@msh.org

Background and challenges to implementation: Systematic screening of high risk groups including contacts of MDR-TB patients is a key strategy to detect MDR-TB cases. However, there is limited experience with the routine implementation of household contact investigation for MDR-TB index cases in low-income settings. In this report, we present our experience in implementing contact screening for MDR-TB index cases from two regions of Ethiopia.

Intervention or response: Building on the experience of contact screening for drug sensitive TB in Amhara and Oromia regions of Ethiopia, the USAID funded MSH/HEAL TB project supported health facilities to conduct systematic TB contact screening for MDR TB patients using a standardized tool. HEAL TB supported with preparation, printing and distributing of standard operating procedures (SoPs), oriented health workers on their use, provided regular mentoring, and assisted with data collection and reporting. According to the SoP, treating clinicians requested all index cases to bring their household contacts for screening at health facilities where those with symptoms were further evaluated for presence of TB. The site staff recorded patient data on a logbook and did follow up screening on a quarterly basis.

Results and lessons learnt: During 2013-2014, we screened 414 contacts of 130 index MDR-TB patients, which gave an average of 3.2 contacts per index case. We identified 30 active TB cases, either wouldn't have been detected or detected late (23 MDR and 7 drug-sensitive). The overall yield was 7.25% (95% Confidence interval (CI); 5.12%-10.16%), with MDR-TB accounting for the 76% of the cases identified. The yield of MDR-TB was thus 5.56%; CI, 3.73%-8.19% (5,555 MDR-TB cases per 100 000 MDR-TB contact population) while that of

drug sensitive TB was 1.69% (CI, 0.82%-3.45%) which is equivalent to 1691 per 100 000 MDR-TB contact population. Of those diagnosed with MDR-TB, 4 (17%) were children below 15 years of age. In comparison, the yield of MDR-TB among non-contact presumptive MDR-TB cases identified through the routine referral system during the same time period was 2.94% (CI, 2.60%-3.34%).

Conclusions and key recommendations: The yield of MDR-TB contact investigation was about twice higher than the yield obtained from the screening among non-contact presumptive MDR-TB cases. We recommend that MDR-TB contact investigation be a routine practice of MDR-TB treating centers.

OA-388-05 Impact of a public-private mix intervention on MDR-TB detection in Karachi, Pakistan: experiences from the TB Xpert® Initiative

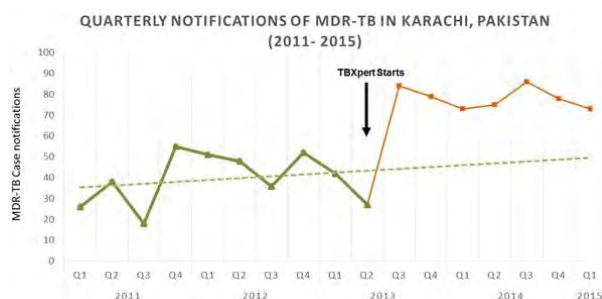
W M Awan,¹ A Zaidi,¹ A Malik,^{1,2} S Khowaja,¹ U Khan,¹ J Creswell,³ H Hussain,^{1,2} A Khan¹ ¹Interactive Research & Development, Karachi, ²The Indus Hospital, Karachi, Pakistan; ³Stop TB Partnership, Geneva, Switzerland. e-mail: wardah.awan@irdresearch.org

Background: Pakistan has the fourth highest multi-drug resistant TB (MDR-TB) burden in the world. Case-detection for MDR-TB is low & treatment facilities remain under-utilized due to operational limitations in case-finding, MDR-TB suspect referrals and restrictive diagnostic algorithms for Xpert South Africa, MTB/RIF. **Design/Methods:** An active-case finding intervention was carried out from July 2013 to March 2015 in Karachi. Verbal screening for TB was carried out through community screeners at a network of private providers in low-income towns of Karachi. TB suspects were referred to private diagnostic centers for X-ray and Xpert® MTB/RIF testing. GeneXpert machines and technicians were also provided to six public sector tertiary care hospitals, one private laboratory and one PMDT site. Screening for TB was carried out at various locations in the hospitals and linkages were developed with neighboring public and private hospitals, laboratories and pharmacies for referrals of TB suspects. All TB suspects were tested through GeneXpert irrespective of previous history of TB treatment. Field staff supported sputum expectoration, treatment initiation and case-registration activities. Cases with rifampicin resistance were referred to one of three PMDT sites in the city for further evaluation. MDR-TB surveillance data was obtained from the NTP to obtain case notifications from Karachi. A trend line was fitted to historical case-notifications prior to the Q3 2013, and used to forecast notifications during the intervention period to determine additionality of MDR-TB cases.

Results: A total of 41 104 TB suspects were tested using Xpert MTB/RIF assay of which 7260 were bacteriologically positive. Rifampicin resistance was found in 481 cases of which 425 were initiated on second-line drugs. A total of 322 cases were confirmed for MDR-TB on drug-

susceptibility testing. Overall, 548 MDR-TB cases were reported from the Karachi district during the intervention period, resulting in an trend adjusted additionality of 216 cases, an increase of 67% over the baseline. Amongst all MDR-TB patients detected, 68 cases (12.4%) were primary MDR-TB.

Conclusion: A multi-faceted PPM intervention consisting of private-sector engagement, screening at public sector sites and testing through Xpert MTB/RIF significantly increased MDR-TB case detection Karachi. Baseline GeneXpert testing on treatment-naïve cases yielded a significant number of MDR-TB cases and should be considered in high-MDR burden settings.



OA-389-05 Universalisation of rapid MDR-TB testing is associated with more rapid initiation of optimal patient therapy

M Tovar,^{1,2} E Ramos,¹ T Valencia,¹ A Valencia,³ Y Cortez,³ J Sandoval,³ J Agreda,³ C Evans⁴ ¹Innovation for Health and Development, Lima, ²Innovacion Por la Salud Y el Desarrollo, Asociación Benéfica Prisma, Lima, ³DIRESA, Regional National Tuberculosis Program, Callao, Peru; ⁴Infectious Diseases & Immunity, Imperial College London, and Wellcome Trust Imperial College Centre for Global Health Research, London, UK. e-mail: marco.tovar@upch.pe

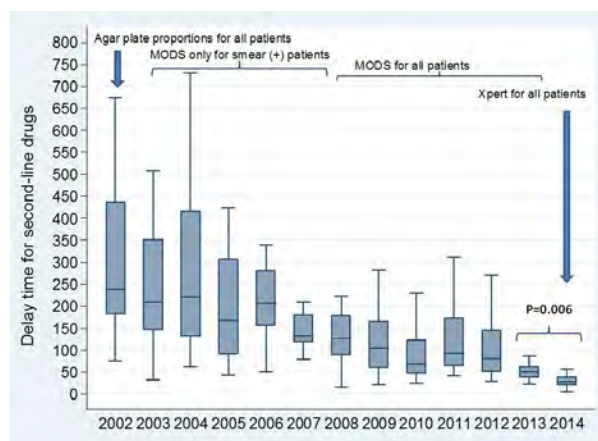
Background: Rapid multidrug resistant tuberculosis (MDR-TB) testing, same-day molecular testing and universalisation of MDR-TB testing are recommended but are expensive and have uncertain effects on patient care under operational conditions. In Peru, patients usually commence empiric first-line therapy as soon as TB is diagnosed, whilst MDR-TB testing is performed. This first-line therapy is unlikely to cure MDR-TB so if MDR-TB is diagnosed then the first-line therapy is changed to specific second-line therapy for MDR-TB, which is more likely to be curative if it commences earlier in the patient's illness. Objective: To study whether universalization of MDR-TB and same-day MDR-TB testing were associated with earlier initiation of appropriate second-line drug therapy for MDR-TB.

Design/Methods: From 2002-2014, all patients commencing TB therapy at 16 health post in shantytowns in north Lima, Peru, were invited to give informed written consent to participate in this study. We recorded the date of starting empiric first-line therapy and the date of starting second-line MDR-TB drugs, if they were administered. According to NTP guidelines, in 2002

only TB patients with known MDR-TB risk factors had MDR-TB testing and this was done in the Peruvian National Institute of Health (NIH) with the indirect agar plate proportions assay that sometimes took months to complete. From 2003-2008, a research project in the Research and Development Laboratory of Universidad Peruana Cayetano Heredia (LID) additionally offered all patients with smear-positive TB Microscopic-Observation Drug-Susceptibility (MODS) testing, that takes 7-21 days. From 2008 to now, according to NTP guidelines, all patients had MODS tests in the NIH laboratory. Since early 2014, a research project in the LID additionally offered all patients Xpert® MTB/RIF, which provides same-day rifampicin-susceptibility testing, a surrogate for MDR-TB testing.

Results: We recruited 5251 pulmonary TB patients and 368 of them initially received empiric first-line therapy that was subsequently changed to second-line therapy for MDR-TB. For these 368 patients, the delay from initiation of inappropriate empiric first-line therapy for initially unrecognised MDR-TB until change to appropriate second-line drugs decreased 4-fold from median 239 days in 2002 to 50 days in 2013 ($P < 0.0001$). The introduction of Xpert same-day MDR-TB testing was associated with a further halving of the delay until appropriate second-line therapy for MDR-TB after median 25 days in 2014 ($P = 0.006$, Figure).

Conclusion: Both the universalisation of rapid MDR-TB testing and the implementation of same-day molecular rifampicin susceptibility testing, in association with strengthening of the Peruvian National TB program, were associated with statistically significant improvements in time to appropriate patient therapy.



OA-390-05 The drug-resistant TB treatment gap and treatment initiation delays in South Africa: impact of Xpert® implementation

H Cox,¹ L Dickson-Hall,¹ N Ndjeka,² A Grant,³ A Van't Hoog,^{4,5} W Stevens,^{6,7} J Workman,¹ M Nicol^{1,8} ¹University of Cape Town, Cape Town, ²National Department of Health, Pretoria, South Africa, ³London School of Hygiene & Tropical Medicine, London, UK; ⁴Amsterdam University, Amsterdam, ⁵Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; ⁶University of the Witwatersrand, Johannesburg, ⁷National Health Laboratory Services, Johannesburg, ⁸National Health Laboratory Services, Cape Town, South Africa. e-mail: lindydickson4@gmail.com

Background: Globally, the majority of drug-resistant (DR) TB cases remain undiagnosed, and among those that are, access to appropriate second-line treatment is limited. South Africa has improved rifampicin-resistant (RR) TB case detection from 7386 in 2010 to 26 023 cases in 2013 through universal access to RR-TB diagnosis with the Xpert® MTB/RIF test, but only 41% were reported to access second-line treatment by the National Department of Health in 2013.

Methods: To assess the extent of the gap between diagnosis and treatment initiation and the time to receiving the first dose of a standardised second line regimen for RR-TB, we retrospectively identified two nationally representative cohorts of newly diagnosed RR-TB cases in 2011 (pre-Xpert) and 2013 (post-Xpert) from laboratory records. Cases were followed through registers, health facility records and interviews to determine treatment initiation, timing and pre-treatment loss to follow-up (including death).

Results: Among 2698 cases in 2011 and 2696 cases in 2013, 575 and 1154 initiated treatment within 28 days respectively, following specimen registration at the laboratory. This time to treatment is considered to be a reasonably desirable period in developing countries. By 6 months 1,653 (61%) in 2011 and 1,863 (69%) ($P < 0.001$) in 2013 had initiated an MDR treatment regimen, although this proportion varied significantly across the 9 South African provinces (range 52-82%), and was highest among provinces with greater access to decentralized treatment. In the 2013 cohort, 53% of cases who initiated treatment were recorded on the national DR-TB treatment register. The median time to treatment initiation was 59 days in 2011 and 26 days in 2013 ($P < 0.001$). Time to treatment in 2013 also varied significantly across provinces (range of medians by province was 19-51 days in 2013). Among the 1631 (60%) cases in 2013 in whom RR was diagnosed by Xpert, the median time to treatment was 20 days, compared to 43 days for those diagnosed with other methods.

Conclusion While the treatment gap is lower than routine reporting suggests, the proportion of diagnosed cases not starting treatment remains high. However, given the dramatic increase in case detection with Xpert implementation, many more patients are receiving treatment overall, and delay in treatment initiation has been substantially reduced. The full benefit of Xpert

implementation on RR TB will only be realised if care linkage and scale up is improved.

OA-391-05 Emergence of additional resistance during standardised MDR-TB treatment

M Mphahlele,¹ R M Warren,² E Streicher,² M Van Der Walt,³ P Van Helden,² K Jacobson⁴ ¹Jhpiego South Africa, Pretoria, ²University of Stellenbosch, Cape Town, ³South African Medical Research Council, Pretoria, South Africa; ⁴Boston University School of Medicine, Boston, MA, USA. e-mail: mphahlelematsie@gmail.com

Background: To address the increasing incidence of MDR-TB, the South African National TB Program implemented a standardised treatment regimen in 2000 consisting of a 4-month intensive phase with the 5 drugs, pyrazinamide, ethambutol, ethionamide, ofloxacin, and either amikacin (AMK) or kanamycin (KAN), followed by a 12- to 18-month continuation phase removing AMK/KAN. This policy also advocated for MDR-TB treatment to occur in hospitals until culture conversion. The objective of the study was to assess the individual patient impact of implementing a standardized MDR-TB treatment regimen in two South African provinces, the Eastern Cape (EC) and North West (NW), by retrospectively quantifying the acquisition of drug resistance to second-line drugs in serial cultures.

Design/Methods: We enrolled 556 MDR-TB patients from the Eastern Cape and North West Provinces. We investigated whether baseline DST pattern, HIV status, and treatment outcomes were associated with the acquisition of drug resistance. To differentiate reinfection from persistence, spoligotyping was performed on the MDR-TB isolates obtained at the time of treatment initiation and compared with last available isolate.

Results: Sixty-four percent ($n = 356$) of patients had poor treatment outcomes (died, defaulted, failed treatment). Of 556 MDR-TB patients, 106 (64 females and 42 males) had DST and spoligotyping results. Of these, 48 had an initial and last available isolate. In 12 (25%) patients the spoligotype patterns changed suggesting reinfection. In 9 (18%) of these patients the reinfecting strain had a resistance profile that showed additional resistance relative to the initial isolate. Of the remaining 36 patients, 13 (27%) acquired additional resistance while on treatment as their isolates remained identical during the course of disease.

Conclusion: Resistance amplification was observed in 46% of MDR-TB patients with available isolates. Implementation of standardised MDR-TB treatment in the absence of knowledge of baseline resistance in circulating MDR-TB strains appears to increase the risk of resistance amplification during treatment. Furthermore, hospitalisation of MDR-TB patients for treatment appears to increase the risk of nosocomial reinfection with strains that are more resistant than the initial infecting strains. This work is supported by the South African Medical Research Council.

OA-392-05 An assessment of site readiness of hospitals in South Africa to decentralize MDR-TB services

M Mphahlele,¹ A Peters,¹ J Pienaar,¹ N Ndjeka,² J Farley³

¹Jhpiego South Africa, Pretoria, ²Department of Health, Pretoria, South Africa; ³Johns Hopkins University, Baltimore, MD, USA. e-mail: jacqueline.pienaar@jhpigo.co.za

Background and challenges to implementation: Prior to 2011, national policy in South Africa (SA) mandated hospitalization of all drug-resistant TB (DR-TB) patients. This resulted in long delays, inadequate bed capacity and infection control and patients' inconvenience. To address these challenges the DR-TB programme plans to decentralize DR-TB management to the community.

Intervention or response: The purpose of this descriptive study was to evaluate clinical sites for DR-TB readiness to ensure quality services prior to decentralization. Fifty-two facilities (8 Community Health-Care centers, 3 Primary Health-Care clinics, 9 MDR-TB hospitals plus 33 district-based hospitals) were evaluated from July 2014 to March 2015. Facilities were prioritized based on: 1) MDR-TB burden 2) MDR-TB quality care for sites providing care and 3) absence of any decentralized unit in the district. Nineteen of 53 (36%) facilities were providing DR-TB services. A standardized decentralization tool was used to collect information on health services and infrastructure status. Key informants were interviewed and healthcare worker practices were observed. Following the initial assessments, quality improvement plans for each facility were developed.

Results and lessons learnt: Facility readiness to decentralize DR-TB services varied between the 52 facilities. Overall, 83% had access to laboratory services for diagnosis of DR-TB. Most sites had access to X-ray services (79%) but very few (25%) had audio equipment to assess ototoxicity. Thirty (58%) had DR paper-based data reporting tools, of which five facilities (17%) had a laptop for electronic data capturing, however none of these sites were reporting data electronically. A limited number of facilities had dedicated doctors (52%) and nurse trained in initiating (10%) DR-TB. There was a slow roll out of decentralization at PHCs level, among the three primary health-care clinics only one had a roving doctor who initiated treatment once a week.

Conclusions and key recommendations: Limitations remain that may slow decentralization of DR-TB to the community. While the majority of facilities meet minimum staff and infrastructure requirements, training on DR-TB was inadequate and should be fast-tracked. Equipment for monitoring ototoxicity should be prioritized for implementation. Task-sharing with more nurse involvement will be key to success, but is slow to occur. Quality monitoring including electronic drug-resistant registers should be implemented.

OA-393-05 Variations in and risk factors for drug-resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis

G Yiga¹ ¹Save a Life Foundation, Kalangala, Uganda. e-mail: igerfrey@yahoo.com

Background: Prevalence of multidrug resistant tuberculosis (MDR-TB), defined as in vitro resistance to both rifampicin and isoniazid with or without resistance to other TB drugs, in sub-Saharan Africa (SSA) is reportedly low compared to other regions. These estimates are based on data reported to the World Health Organization (WHO) on drug resistance surveys, which may suffer from a reporting bias. We set out to evaluate the variation in prevalence of drug resistant tuberculosis (DR-TB) and its determinants across SSA countries among new and previously treated TB patients.

Design/Methods: The aim was to perform a systematic review and meta-analysis of DR-TB prevalence and associated risk factors in SSA. PubMed, EMBASE, Cochrane and bibliographies of DR-TB studies were searched. Surveys at national or sub-national level, with reported DR-TB prevalence (or sufficient data to calculate a prevalence) to isoniazid (INH), rifampicin (RMP), ethambutol (EMB), and streptomycin (SM) conducted in SSA excluding the Republic of South Africa, published between 2003 and 2013 with no language restriction were considered. Two authors searched and reviewed the studies for eligibility and extracted the data in pre-defined forms. Forest plots of all prevalence estimates by resistance outcome were performed. Summary estimates were calculated using random effects models, when appropriate. Associations between any DR-TB and MDR-TB with potential risk factors were examined through subgroup analyses stratified by new and previously treated patients.

Results: A total of 726 studies were identified, of which 27 articles fulfilled the inclusion criteria. Studies reported drug susceptibility testing (DST) results for a total of 13 465 new and 1776 previously treated TB patients. Pooled estimate of any DR-TB prevalence among the new cases was 12.6% (95%CI 10.6-15.0) while for MDR-TB this was 1.5% (95%CI 1.0-2.3). Among previously treated patients, these were 27.2% (95%CI 21.4-33.8) and 10.3% (95%CI 5.8-17.4%), respectively. DR-TB (any and MDR-TB) did not vary significantly with respect to study characteristics. Variations between any DR-TB and MDR-TB with potential risk factors were examined through subgroup analyses stratified by new and previously treated patients.

Conclusion: The reported prevalence of DR-TB in SSA is low compared to WHO estimates. MDR-TB in this region does not seem to be driven by the high HIV prevalence rates.

OA-394-05 A rifampicin-resistant diagnosis on Xpert® MTB/RIF frequently leads to initiation of a weakened standardized MDR-TB regimen

K Jacobson,^{1,2} M Barnard,¹ M Buckley,² E Streicher,¹ T Dolby,³ L Scott,⁴ A Van Rie,^{5,6,7} R M Warren¹

¹Stellenbosch University, Tygerberg, South Africa; ²Boston University School of Medicine / Boston Medical Center, Boston, MA, USA; ³National Health Laboratory Service, Cape Town; ⁴National Health Laboratory Service, Johannesburg, South Africa; ⁵University of Antwerp, Antwerp, Belgium; ⁶Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA. e-mail: marywb@bu.edu

Background: Xpert MTB/RIF detects *Mycobacterium tuberculosis* complex (*M. tuberculosis* c) and rifampicin (RIF) resistance, enabling physicians to rapidly initiate multidrug resistant tuberculosis (MDR-TB) treatment. South African guidelines instruct that RIF-resistant (RR) patients start standardized MDR-TB therapy with pyrazinamide (PZA), ethionamide (ETH), kanamycin (KAN), moxifloxacin and terizidone before knowledge of resistance to these drugs. We aimed to quantify the time delay to reporting of second-line (SL) drug susceptibility test (DST) results and the proportion of patients placed on suboptimal therapy.

Methods: We retrospectively identified all patients diagnosed with RR TB by Xpert at the National Health Laboratory Service, Cape Town, South Africa, between November 2011 and June 2013. We also prospectively collected a sample of RR TB patients diagnosed in Eastern Cape, Free State, and Gauteng Provinces. We calculated the time from specimen collection to reporting of SL DSTs and susceptibility patterns. We performed targeted DNA sequencing when phenotypic susceptibility patterns were not available.

Results: During this time period, 904 samples were RR by Xpert in the Western Cape (WC), of which 466 (55.8%) had SL DST results. For the 496 RR samples collected in the other 3 provinces, SL DST results were available for 141 (28.4%) patients. Median time from sputum taken to second-line DST results was 54 days (IQR 27-259) in the WC and 60 days (IQR 42-77) in other provinces. Time to DST results was shorter for smear positive samples ($P < 0.0001$). Of the 171 WC patients with DST results for PZA, ETH, KAN and ofloxacin, 47% would be considered to have started an ineffective regimen (< 4 effective drugs) with only 1 likely effective drug in 8%, 2 in 9%, and 3 in 30%. In the other 3 provinces, 26% of 66 patients would be considered to have started an ineffective regimen with only 1 effective drug in 6%, 2 in 6% and 3 in 9%. This difference is driven by rates of ETH resistance (6.6% vs. 60.5%).

Conclusion: Under current programmatic conditions, many patients diagnosed with RR TB by Xpert are started on a weakened 5-drug MDR regimen, with the information to adjust therapy only available after 8 weeks or never at all. SL DSTs were less frequently available in the 3 provinces where only 1 specimen is requested at diagnosis rather than 2. Such time delays

and lack of SL results risk worsened outcomes and may fuel resistance amplification in the population.

13. LTBI in high- and low-burden settings

OA-395-05 Early biomarkers associated with progression of latent tuberculosis infection to clinically active disease: a longitudinal cohort study

N Rakotosamimanana,¹ V Richard,^{1,2} V Raharimanga,¹ T M Doherty,³ B Gicquel,⁴ A Zumla,⁵

V Rasolofo Razanamparany¹ ¹Pasteur Institute of Madagascar, Antananarivo, Madagascar; ²Pasteur Institute of Dakar, Dakar, Senegal; ³GSK, Copenhagen, Denmark; ⁴Pasteur Institute, Paris, France; ⁵University College London, London, UK. e-mail: niaina@pasteur.mg

Background: An estimated one third of the world's population is latently infected with *Mycobacterium tuberculosis*, of whom 10% will likely progress to active tuberculosis (TB) disease at some time in their lives. We performed a longitudinal cohort study on blood and infection markers to address the need of sensitive and clinically practical prognostic markers of at-risk individuals.

Design/Methods: A cohort of household contacts of newly diagnosed pulmonary TB patients were recruited, blood analyzed and investigated for TB symptoms at different periods for up to two years in Antananarivo, Madagascar. Controls were matched healthy individuals from the same community. Immune status was assessed by TST, and full blood counts (FBC) were determined.

Results: 595 HIV-negative individuals: 104 newly diagnosed pulmonary TB patients, 305 household contacts and 186 controls were enrolled. Age negatively correlated with risk of progression to active disease (OR=3.98, 95CI 1.05-14.99; $P < 0.05$, for < 16 years). Age paired analysis showed that in contacts, an elevated monocyte count in peripheral blood was associated with risk of developing active TB ($P < 0.001$). Further, of the 12 contacts that later developed TB, 10 (83%) had a TST induration > 14 mm at the entry of the study (OR=6.1, 95CI 1.31-28.32; $P = 0.02$). A monocyte percentage $> 7.4\%$ together with a TST > 14 mm was associated with a greatly elevated risk of progression to TB disease (OR=14.13 [3.58-55.75], $P < 0.001$).

Conclusion: The routinely-used clinical tests, TST and FBC may have potential as simple biomarkers for risk of developing active TB in recently-exposed individuals. Further evaluations of these biomarkers for identification and treatment of these individuals are required.

OA-396-05 Understandings of tuberculous infection, TB disease and isoniazid preventive therapy in KwaZulu-Natal, South Africa

J Boffa,^{1,2} M Mayan,³ S Ndlovu,⁴ R Cowie,^{1,3} R Sauve,¹ D Wilson,⁵ D Fisher^{1,3} ¹University of Calgary, Calgary, AB, Canada; ²University of KwaZulu-Natal, Durban, South Africa; ³University of Alberta, Edmonton, AB, Canada; ⁴Izimbali Zesizwe, Pietermaritzburg, ⁵Edendale Hospital, Pietermaritzburg, South Africa. e-mail: jody.boffa@ucalgary.ca

Background: In 2011 the South African Department of Health implemented 6-month isoniazid preventive therapy (INH) to prevent tuberculosis (TB). All people living with HIV (PLWH) were eligible if active TB symptoms were absent. Prior to this, there was no local language equivalent for latent TB infection, as pulmonary TB was only recognised once it had become infectious. We aimed to describe community understandings of TB infection and disease in light of preventive strategies and determine perceptions of INH following implementation.

Methods: Guided by community-based research principles and the ethnographic method, we worked with three communities of the Edendale Hospital catchment area, where predominantly underemployed black South Africans reside in poor housing; HIV prevalence is 15% and TB incidence is 1%, with 7% multi-drug resistance. We conducted eight focus group discussions (FGDs) (57 participants total) with three population pools: PLWH to learn about potential users' perspectives, people without HIV to glean peer perceptions, and taxi drivers to capture male working class perspectives of TB and INH. FGDs took place in isiZulu and were later translated into English for qualitative content analysis in Nvivo 10. Community Advisory Teams were consulted to assist with and validate the interpretation of themes.

Results: Health was generally considered a lack of disease or pain. Communities were thought to be healthier in the past, when HIV, TB, and diabetes were uncommon. Dirty environments or particular lifestyle behaviours were thought to contribute to illness. Participants recognised cough and weight-loss as TB symptoms and knew the link and distinction between HIV and TB. Only participants in the PLWH group had heard of INH and grasped that some kind of pre-disease TB state must exist, though none knew of the terms latent TB infection or 'TB elele' (sleeping TB). A minority of PLWH had been offered or initiated on INH, although members of all three populations inquired about eligibility for enrolment. Barriers to clinic service included wait times, poor communication with clients, and feelings of inferiority preventing questions or clarification.

Conclusion: Overall, common TB symptoms and the link to HIV were well recognized. Some PLWH were aware of INH, but knowledge of latent TB infection was uncommon. A focus on patient-centred care and more opportunities to access information about TB prevention may improve uptake of future TB prevention regimens.

OA-397-05 Optimal testing choices for latent tuberculosis infection in high-risk populations in a low incidence country: a latent class analysis strategy

S Ghosh,¹ M Johnson,² D Katz,¹ G Fanning-Dowdell,³ R Punnoose,³ C Ho,¹ J Stout² ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, ²Duke University Medical Center, Durham, NC, ³Northrup Grumman, Atlanta, GA, USA. e-mail: smita.ghosh@cdc.hhs.gov

Background: The absence of a gold standard to diagnose latent tuberculosis infection (LTBI) complicates efforts to estimate sensitivity and specificity of commercially available tests. Understanding the tests' performance characteristics is especially important in low incidence countries where targeted testing and treatment of high-risk populations are key for tuberculosis control and elimination. Researchers from the TB Epidemiologic Studies Consortium (TBESC) conducted a head-to-head performance comparison of the three widely available tests among high-risk populations in the United States.

Design/Methods: Persons at high risk for LTBI (e.g., foreign-born, close contacts) or for progression to active TB disease (e.g., HIV-infected) were enrolled from July 2012–September 2014 at 14 urban sites and tested with all 3 tests: the tuberculin skin test (TST) and two interferon-gamma release assays (Quantiferon®) TB Gold In-Tube (QFT) using >0.35 IU/ml as positive, and T-SPOT.TB (TSPOT) using >8 spots as positive). Latent class analysis (LCA), a statistical technique suitable for estimating group membership in the absence of a gold standard (e.g., presence/absence of true LTBI), was used to 1) identify subgroups where test performance varied substantially and 2) compare LTBI prevalence estimates, sensitivities, and specificities for U.S.-born and foreign-born, HIV-infected and HIV-uninfected and two age categories (<5 years and ≥5 years old).

Results: The 11 386 participants included 9057 (80%) foreign-born >5 years old, 514 (4.5%) foreign-born <5 years old, 1461 (13%) HIV-infected, and 354 (2.5%) members of other high-risk groups. Test characteristics differed significantly ($P < 0.001$ for all comparisons) among key sub-groups (Table). QFT was consistently most sensitive in all sub-groups and TSPOT most specific, but TSPOT had low sensitivity in children <5 years old and in HIV-infected persons. When classifying borderline TSPOT results (5–7 spots) as positive, overall results remained the same. TST was sensitive in all groups except HIV-infected and U.S.-born persons, but had low specificity in foreign-born persons.

Conclusions: Based on LCA, QFT and TSPOT performed comparably in most high-risk groups and had greater specificity than TST in foreign-born persons, particularly among young children. However, TSPOT was considerably less sensitive in children <5 years old and in HIV-infected persons. QFT may be a better choice for testing these vulnerable sub-groups.

Table. Test performance of three commercially available tests for latent tuberculosis infection (LTBI) in high-risk populations based on latent class analysis

High-risk groups	Persons with LTBI in study sample No. (%)	Prevalence estimates of LTBI using LCA (%)	QFT		TSPOT		TST	
			sens. (%)	spec. (%)	sens. (%)	spec. (%)	sens. (%)	spec. (%)
HIV-negative								
Foreign-born, age <5 years	483 (4.4)	3.1	94.5	99.5	54.5	100.0	95.8	75.0
U.S.-born, age ≥5 years	947 (8.4)	16.1	93.2	96.2	89.3	99.3	88.1	91.9
Foreign-born, age ≥5 years	8,285 (73.5)	26.9	93.1	96.1	88.1	98.7	91.8	68.6
HIV-positive								
U.S.-born, age ≥5 years	1,311 (11.6)	3.1	97.2	95.5	69.6	99.7	61.0	96.4
Foreign-born, age ≥5 years	148 (1.3)	18.7	98.0	92.5	66.2	99.9	97.8	90.9

Abbreviations: latent tuberculosis infection (LTBI); United States (U.S.); latent class analyses (LCA); QuantiFERON Gold in-tube test (QGIT); T-SPOT.TB test (TSPOT); tuberculin skin test (TST); sensitivity (sens.); specificity (spec.)

OA-398-05 High completion rate for 12 weekly doses of isoniazid and rifapentine as treatment for latent tuberculosis infection in the Bureau of Prisons, USA

M Lobato,¹ S Lang,² L Sosa,² S Wheeler,³ S Bur,³ N Kendig³ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, ²Connecticut Department of Public Health, Hartford, CT, ³Bureau of Prisons, Washington, DC, USA. Fax: (+1)860 509 7743. e-mail: mark.lobato@ct.gov

Background: About 4% of tuberculosis (TB) cases reported in the United States occur among persons incarcerated at the time of diagnosis. The Federal Bureau of Prisons (BOP), which houses over 200 000 inmates, is in a unique position to provide latent TB infection (LTBI) treatment to prevent development of TB disease. Past efforts to treat LTBI with isoniazid (INH) monotherapy have been hampered by poor treatment completion rates. Recent studies have shown that 12 once-weekly doses of INH and rifapentine (RPT) given by directly observed therapy (DOT) is not inferior to 9-months of INH in preventing development of TB disease.

Methods: Seven BOP facilities participated in the pilot implementation of INH-RPT for LTBI treatment. Treatment monitoring data were entered in the BOP Electronic Medical Record. DOT visits, weekly symptom screens, and demographic, behavioral, and medical risk factors were collected for inmates treated during July 2012–February 2015.

Results: A total of 463 inmates started treatment using INH-RPT. The median age was 36 years (range: 20–71 years); 70% were male. The population was 76% Hispanic, 12% non-Hispanic white, 8% black, 2% Asian, and 1.5% American Indian. Two thirds of inmates treated were foreign born and 20% were contacts to a known TB case. Of 463 total inmates treated, 424 (91.6%) successfully completed treatment. Among the 39 (8%) inmates who stopped treatment, 17 discontinued due to an adverse event, 9 were transferred to another facility or were released from BOP custody before completion, 8 refused further treatment, and 5 did not complete due to provider error. Signs or symptoms associated with treatment discontinuation included nausea/ vomiting, headache, abdominal pain, elevated serum liver transaminases, and fever. Five patients who stopped treatment due to symptoms successfully completed using either INH or rifampin. Inmates with no symptom complaints were more likely to complete treatment than those who experienced at least one

symptom during the course of treatment, 94.6% vs. 88.8%, $P = 0.02$.

Conclusions: INH-RPT is a viable alternative to INH monotherapy for treating LTBI in the BOP with significant practical advantages (reducing DOT doses from 76 to 12). The treatment completion rate was high with low rates of adverse reactions. The shorter treatment duration might facilitate treatment of short stay inmates. Based on the pilot evaluation, INH-RPT is now the standard recommended regimen for LTBI treatment in the BOP.

OA-399-05 Implementation of QuantiFERON®–TB Gold In-Tube test for diagnosing latent tuberculosis among newly diagnosed HIV-infected patients in South Africa

J Golub,¹ L Lebina,² C Qomfu,² S Chon,¹ S Cohn,¹ K Masonoke,² E Variava,^{2,3,4} N Martinson^{1,2} ¹Johns Hopkins University, Baltimore, MD, USA; ²Perinatal HIV Research Unit, Johannesburg, ³Klerksdorp-Tshepong Hospital Complex, Klerksdorp, ⁴North West Department of Health, Klerksdorp, South Africa. Fax: (+1) 443 287 7955. e-mail: jgolub@jhmi.edu

Background: Tuberculosis (TB) remains the leading killer among people living with HIV (PLWH) in South Africa. Recent guidelines state that all newly diagnosed HIV-infected patients in South Africa should, following screening for active TB disease, receive a tuberculin skin test (TST), and a determination of the duration of recommended isoniazid preventive therapy (IPT) is dependent upon the TST result and current antiretroviral (ART) status. Evidence strongly suggests that implementation of TST in HIV clinics is suboptimal throughout the country.

Methods: We are conducting a cluster-randomized trial to compare the impact on IPT uptake of a strategy to collect blood for QuantiFERON®–TB Gold In-Tube (QGIT) at time of CD4 blood draw for newly diagnosed HIV-infected patients, with the current standard of care - provision of TST. Fourteen public HIV clinics in the North West Province were randomized to either QGIT or TST only. Consenting patients were interviewed immediately following HIV diagnosis and baseline medical record abstractions were conducted within 3 weeks of diagnosis. Here we present characteristics of the first 443 enrolled in the study, and 213 QGIT results.

Results: Enrollment at the first TST clinic began in November 2014 and the first QGIT clinic in January 2015. Through March 31 2015, 411 patients eligible for QGIT or TST were enrolled; 225 in QGIT clinics and 186 in TST clinics. Median age was 33 (IQR 26–41), 64% were female and median CD4 count was 303 cells/mm³ (IQR 161–476). Among females, 33% were pregnant at time of HIV diagnosis. Among 225 QGIT eligible, 12 (5%) did not provide blood for testing. Among 213 with QGIT results, 89 (42%) were positive, 90 (42%) were negative and 34 (16%) were indeterminate. Excluding indeterminate results, 50% were positive and 50% were negative. Indeterminate rate ranged from 7% to 21% across clinics. Patients with positive and negative QGIT

results did not differ by age, sex or smoking or alcohol use. Median CD4 counts for QGIT positive, negative and indeterminates were 318, 259 and 160, respectively.

Conclusion: Approximately half of all newly diagnosed HIV-infected patients with a QGIT result were positive, though 15% had an indeterminate result. Though operational comparisons to TST cannot yet be made in this cluster randomized trial, our preliminary results suggest that implementation of QGIT into public HIV clinics in South Africa may be feasible, but indeterminates are a potential limitation.

OA-400-05 Expected outcomes of serial testing with interferon-gamma release assays in North American health care workers: a Markov model

A Zwerling,¹ M Moses,¹ A Cattamanchi,² C Denkinger,³ N Banaei,⁴ S Kik,⁵ D Dowdy,¹ M Pai⁶ ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²University of California San Francisco, San Francisco, CA, USA; ³IND, Geneva, Switzerland; ⁴Stanford University, Stanford, CA, USA; ⁵KNCV, The Hague, Netherlands; ⁶McGill University, Montreal, QC, Canada. e-mail: alice.zwerling@mail.mcgill.ca

Background: Interferon-gamma release assays (IGRAs) have been adopted as an alternative to the tuberculin skin test (TST) for serial testing in healthcare workers (HCWs) in low-incidence settings. IGRAs are known to have multiple sources of variation, and show high rates of conversions and reversions. The net effect of such variability on serial testing remains unknown.

Design/Methods: We used a micro-simulation Markov model to project diagnostic outcomes in a simulated HCW cohort under different serial screening strategies after accounting for the major sources of variability in serial QuantiFERON®-TB Gold In-Tube (QFT) results. An initial QFT value was assigned using cross-sectional data; at each subsequent year (in a 10 year cycle) a new QFT value was calculated based on 1) random intra-individual variation, 2) TST-induced boosting, 3) variation in blood volume and 4) pre-analytical delay. Distributions of each source of variability were derived through a systematic review and from best available evidence. We then projected ten-year outcomes and required test volumes under different cutoffs for defining a positive test and under different assumptions about whether initial positive results required confirmation with another positive QFT result before initiating preventive therapy.

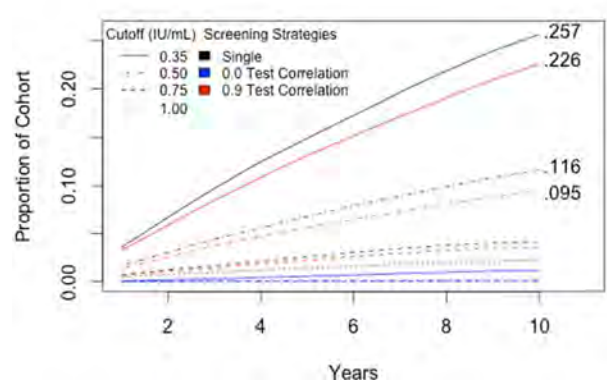
Results: In a high-risk setting (1.0% annual risk of TB infection), a strategy in which a negative to positive change with threshold QFT value of ≥ 0.35 IU/ml would lead to 34.1% of the population testing positive by the end of 10 years, of whom only 8.4% were truly infected at the time of their positive test. Increasing the cutoff for a positive repeat test to 1.0 IU/ml reduced the proportion of the population testing false-positive in ten years from 25.7% to 2.3% (Figure), but at the expense of reducing the proportion of true TB infections diagnosed from 72% to 60%. The value of a confirmatory test depended strongly on the correlation between initial and confir-

matory test results. If the correlation between initial and confirmatory test was high, outcomes were very similar. If uncorrelated, confirmatory testing even at a threshold of 0.35 IU/ml reduced the ten-year false positive percentage to 1.2% (Figure).

Conclusion: Using QFT for annual serial testing among HCWs in a low-incidence setting may lead to tremendous over-diagnosis of conversions. Using a higher cutoff for a QFT conversion or confirming positive results with a second test may reduce the false positive rate.

Figure 1. Expected Proportion of Individuals Testing False-Positive Over Ten Years of Serial Testing with QuantiFERON-TB in a Low-Incidence Setting

Solid lines show the cumulative proportion of healthcare workers expected to test positive for latent tuberculosis infection (LTBI) if tested serially with QuantiFERON-TB on an annual basis, using different cutoffs for a positive test (solid versus dashed lines) and different testing strategies (with black denoting a single test, blue a confirmatory test for all initial positives assuming no correlation to the initial test, and red a confirmatory test assuming a Pearson correlation of 0.9 between the initial and confirmatory tests).



OA-401-05 National roll-out of LTBI screening in England

M Loutet,¹ D Zenner¹ ¹Public Health England, London, UK. e-mail: miranda.loutet@phe.gov.uk

Background and challenges to implementation: Latent TB infection (LTBI) screening and treatment is an essential tool to support the WHO Post-2015 Global TB Strategy. The Collaborative TB Strategy for England 2015-2020 between Public Health England (PHE) and the English National Health Service (NHS) aims to make significant advances in TB control in England. National systematic implementation of new entrant LTBI screening is a fundamental component in order to achieve the strategy ambitions. The aim of this paper is to describe initial outcomes of this programme.

Intervention or response: All migrants, aged 16-35 years who have entered the UK from a high incidence country ($\geq 150/100\ 000$ and sub-Saharan Africa) within the last 5 years and had been previously living in that high incidence country for ≥ 6 months are eligible for screening. Individuals are identified for screening at GP registration, screened in primary care and treated in primary or secondary care. PHE collects data on LTBI screening, including the social and disease risk factors for TB, and the screening and treatment process in order to allow for monitoring and evaluation of the programme.

Results and lessons learnt: Initial results are available from the London borough of Newham (TB rate of 113.7/100 000) which has been screening for LTBI since July 2014 in line with the national strategy guidelines. 61 General Practices in Newham have identified 5683 eligible individuals, of which 3272 (57.6%) had IGRA (Quantiferon) tests. 866 of 3272 (26.5%) have had a positive result. Additionally, this programme has the potential to identify active TB cases early. In Newham, 8 active TB cases were detected and referred to chest clinic.

Conclusions and key recommendations: Newham illustrates the feasibility of LTBI screening among areas of high TB incidence, where General Practitioners are engaged to screen all those eligible. However, it is difficult to know how treatment uptake will vary across England. This programme has the potential to have an enormous impact on TB rates in the UK. The data will ultimately be linked to notified active TB cases to provide evidence of the effectiveness of LTBI screening to reduce the number of active TB cases in a non-study setting.

OA-402-05 A population-based cohort study of trends in BCG effectiveness against tuberculosis with time since vaccination in Norway

P Nguipod-Djomo,^{1,2,3} E Haldal,¹ K Rønning,¹ I Cappelen,¹ L Rodrigues,² I Abubakar,³ P Mangtani^{2,3}
¹Norwegian Institute of Public Health, Oslo, Norway; ²London School of Hygiene & Tropical Medicine, London; ³Public Health England, London, UK. e-mail: patrick.nguipod-djomo@ishtm.ac.uk

Background: Little is known on how BCG vaccine protection against tuberculosis (TB) changes with time after vaccination, particularly beyond 10 years.

Design/Methods: To assess long-term BCG effectiveness (VE) against tuberculosis, we obtained historical Tuberculin Skin Test (TST) and BCG information from participants of the last round 1962-1975 of a Norway mandatory mass TB screening and BCG vaccination programme, and linked it to National TB register, the National Population and Housing Censuses (1960/1970) for socio-economic position (SEP) and the Population Register for emigrations and deaths. Norwegian-born TST negative subjects (eligible for BCG vaccination) were followed-up from the last screening to their first episode of TB or censoring. Using Cox regressions, we estimated VE for up to 40 years since BCG, adjusted for age as a time-varying effect, calendar time, county-level TB rates and demographic and SEP indicators.

Results: Follow-up was on average over 40 years, for 83 421 unvaccinated and 297 905 BCG vaccinated subjects, with 260 first TB episodes. Tuberculosis rates were 3.3 per 100 000 person-years in unvaccinated and 1.3 per 100 000 person-years in vaccinated subjects. Adjusted average VE over the 40+ years follow-up was 49% (95%CI: 26% to 65%). After controlling for confounding and excluding TB in the first- two years after screening, VE was estimated for the following periods after vaccination: up to 9 years, 61%(95%CI: 24% to 80%), 10-19 years, 58%(27% to 76%), 20-29,

38%(-32%to71%), and 30 to 40+, 42% (-24to73%). Specific estimates against pulmonary TB for the same time intervals were respectively 67% (27% to 85%), 63% (32% to 80%), 50% (-19% to 79%) and 40% (-46% to 76%).

Conclusion: Our findings are consistent with a longer-lasting BCG protection with average VE of 50% over 40 years, with waning in time and estimated protection of 40% 30 to 40 years after vaccination. BCG may be more cost-effective than previously estimated, with fewer people needed to vaccinate per case prevented. Consideration should be given to the interaction of BCG with new TB vaccine candidate.

14. From specimens to outcome: new information for molecular diagnosis

OA-403-05 Diagnostic accuracy of the Xpert® MTB/RIF cycle threshold level to predict smear positivity in respiratory samples: a systematic review and meta-analysis

B Lange,^{1,2} M E Balcells,³ R Blakemore,^{4,5} N Lemaitre,⁶ J J Palacios,⁷ J Teo,⁸ G Theron,⁹ K Kranzer¹⁰ ¹Centre for Infectious Diseases/Centre of Chronic Immunodeficiency, Freiburg; ²University Hospital Freiburg, Freiburg, Germany; ³Pontificia Universidad Catolica de Chile, Santiago De Chile, Chile; ⁴Division of Infectious Diseases, Newark, NJ, ⁵New Jersey Medical School, Newark, NJ, USA; ⁶Université de Lille-Nord de France, Lille, France; ⁷Hospital Universitario Central de Asturias, Oviedo, Spain; ⁸National University Hospital, Singapore, Singapore; ⁹University of Cape Town, Cape Town, South Africa; ¹⁰London School of Hygiene & Tropical Medicine, London, UK. Fax: (+49) 761 2701 8190. e-mail: Berit.Lange@uniklinik-freiburg.de

Background: Following its global scale-up, Xpert® MTB/RIF is now the most widely used molecular assay for the rapid diagnosis of tuberculosis (TB). The number of PCR cycles after which detectable product is generated (cycle threshold value (CT)) has been shown to correlate with mycobacillary burden as measured by time to culture positivity using liquid culture systems and smear microscopy. The aim of this study is to investigate the association between Xpert MTB/RIF CT values and smear status through a systematic review of the available literature, and meta-analysis to establish a receiver-operating-characteristic (ROC) curve between CT values and bacillary load.

Methods: Medline, Embase, Global Health, Current Controlled Trials and the Cochrane database of systematic reviews was searched using a compound search strategy. Studies including pulmonary samples and Xpert MTB/RIF, smear microscopy and culture results were potentially eligible. Studies on the association between CT values and smear status or days to culture positivity were included in the descriptive review. Authors of potentially eligible studies were asked to provide individual level data for meta-analysis. Mean CT value difference between smear positive and negative samples

was calculated as well as ROC curves adjusting for clustering by study and by patient.

Results: From 498 identified citations 74 were deemed potentially relevant, 10 studies were included in the descriptive review. Eight studies provided individual level data including 4437 respiratory samples from 2631 patients. A total of 968 patients had positive Xpert MTB/RIF results for at least one respiratory sample, 630 patients had positive results from two samples and 2 patients had positive results from 3 samples. The mean CT value difference between smear positive and smear negative samples was 7.6 (95%CI 6.9-8.2). ROC analysis revealed an AUC of 0.85 (95%CI 0.82-0.87). A CT value cut-off of 27.7 results in a sensitivity of 85% (CI95 83-87) and specificity of 67% (95%CI 66-77) and a CT value cut-off of 32 results in a sensitivity of 95% (95%CI94-96) and a specificity of 35% (CI95% 30-41) for smear-positive samples. Stratification by HIV led to a slightly decreased sensitivity for HIV-positive patients (see the Table).

Conclusion: This review confirms the strong association between Xpert MTB/RIF CT values and smear status. Thus CT value result may be a good replacement for smear status of respiratory samples in certain contexts.

Table Area under the curve (AUC), sensitivity and specificity with 95% confidence intervals (95%CI) for smear positivity with different C_T value cut-offs in the meta-analysis on individual level data derived from 8 different studies

	AUC*	Cut off (C _T value)	Sensitivity	CI95% †	Specificity	CI95% †
HIV positive (216 samples of 151 patients)	0.85 (0.77-0.92)	25.3 27.7 32	67 79 93	58-75 70-85 88-96	88 79 49	74-95 65-88 36-63
HIV negative (611 samples of 423 patients)	0.84 (0.78-0.89)	25.3 27.7 32	73 83 94	69-77 79-86 92-97	81 62 33	71-88 51-71 24-43
All ‡§ (1574 samples of 968 patients)	0.85 (0.82-0.87)	25.3 27.7 32	75 85 95	73- 78 83 - 87 94-96	83 67 35	76-87 66 -77 30-41

* Accounting for clustering by patient and by study.

† Calculated with robust standard errors to account for clustering by patient.

‡ A sensitivity analysis disregarding the two biggest studies with 208 samples yielded an AUC of 0.84 (CI95 0.78-0.9)

§ Only 827 samples had information on HIV available, AUC in those with HIV status available was 0.84 (CI95 0.80-0.88). 720 samples had no information on HIV available, AUC for those was 0.87 (CI95% 0.84-0.90)

OA-404-05 Implementation of Xpert® MTB/RIF under India's National TB Control Programme

S Dhawan,¹ S Mannan,² A Sangwan,³ S Chadha,¹ A Sreenivas,² C N Paramasivan,⁴ K S Sachdeva,⁵ N Kulshreshtha⁵ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²World Health Organization, New Delhi, ³Clinton Health Access Initiative, New Delhi, ⁴Foundation for Innovative New Diagnostics, New Delhi, ⁵Central TB Division, Ministry of Health and Family Welfare, New Delhi, India. e-mail: shikha.dhawan@gmail.com

Background: As feasibility of deployment of Xpert® MTB/RIF was successful, India's National TB Control Programme scaled up implementation of Xpert. In 2014, the NTP had 89 Xpert sites across India. The programme has the policy to use Xpert for diagnosis of presumptive drug resistance cases and has prioritized its use in people living with HIV/AIDS and paediatrics. We assessed the implementation of Xpert MTB/RIF under programmatic conditions.

Design/Methods: Data on Xpert tests was collected in 2014 from 76 functional Xpert sites across 27 provinces on monthly basis using a standard tool consisting of information on laboratory performance.

Results: Of the 112 273 tests done across 76 Xpert sites, there were 1413 (1.3%) referrals from private sector, 10 952 (9.8%) PLHIV and 11 240 (10%) paediatric. 105 243 (93.7%) valid tests were obtained on first test. These included bacteriologically confirmed tuberculosis in 63 624 samples (positivity 56.7%, 6.6% HIV co-infected, 2% pediatric), Rif resistance was detected in 11 709 (18.4%) samples (3.3% HIV co-infected, 1.9 % pediatric). *M. tuberculosis* was not detected in 41 619 (37.1%) samples. Of the initial 8370 (7.4%) test failures, repeat testing was done on 6156 (73.8%) by retesting same or second available sample in which additional 3196 (2.8%) TB cases were obtained including 552 (0.5%) Rif resistance. Out of all those who underwent tests, 35 889 (69.1%) TB and 5429 (46.4%) Rif resistant TB patients were started on treatment as reported by sites.

Conclusion: Information on treatment initiation on diagnosed TB patients was not uniform and consistent at some sites. This highlights the need to ensure better coordination between the diagnostic laboratories and TB program managers at sub-district level for strengthening overall tuberculosis care cascade. Although utilization of Xpert is poor for testing PLHIV and paediatric in 2014, NTP's ongoing Xpert projects for paediatric and ART Centres will show improvement in the coming years. 13 sites were non-functional in 2014 due to supply chain management issues of cartridges, module failures and lack of trained manpower. Overcoming programmatic and operational challenges in implementing and maintaining the Xpert machines is essential for optimal utilization of these near point of care molecular diagnostic. For early diagnosis by Xpert and early treatment initiation, NTP needs to innovate in public private partnerships and involve different stakeholders.

OA-405-05 Triplicate versus single sputum samples improves sensitivity for efficacy determination in studies of anti-tuberculosis regimens

A Diacon,¹ E Van Brakel,¹ N Lounis,² P Meyvisch,² B Van Baelen,² T De Marez,³ E Jenkins,⁴ B Dannemann³
¹Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; ²Janssen Research and Development, Beerse, Belgium; ³Janssen-R&D, LLC, Titusville, NJ, USA; ⁴Janssen UK, High Wycombe, UK. e-mail: ahd@sun.ac.za

Background: Sputum culture conversion from positive to negative remains the standard endpoint in studies of anti-TB regimens. Most protocols require a single sputum to be collected for culture at fixed time points. In study TMC207-C208 the treatment efficacy for multi-drug resistant TB was assessed with triplicate sputum at each visit over a 120-week study period. We investigated whether the aggregate result from triplicate sputum differed from the result of the first sputum collected at each visit. **Method** This analysis included 160 participants who collected at least one triplicate (≥ 30 minutes between sputum). Each sputum was submitted separately for liquid culture in the Bactec™ MGIT960™ system. Visits were performed pre-treatment and thereafter at weekly, 2-, 4- and 12-weekly intervals up to 8, 24, 36 and 120 weeks, respectively. Single sputum were scored as positive, negative or contaminated. Triplicates were scored as positive if ≥ 1 sputum of the triplicate was positive, as negative if ≥ 1 sputum was negative and none was positive, and as contaminated if none were valid (positive or negative).

Results First, second and third sputum in 3467 triplicates had comparable rates of positive, negative and contaminated scores (averages of 34.6%, 55.1% and 10.3%, respectively). Rates of positive, negative and contaminated scores for first and triplicate sputum were 34.3% and 42.3%, 54.3% and 55.1%, and 11.3% and 2.6%, respectively. The changes were mainly due to invalid first sputum becoming negative triplicates and negative first sputum becoming positive triplicates. The first and the first and second sputum combined were positive in 81.4% and 94.0% of 1467 positive triplicates, and negative in 90.4% and 98.2% of 1911 negative triplicates.

Conclusions The collection of triplicate instead of single sputum increased the proportion of visits with positive sputum culture results by 8%, and reduced the rate of visits with invalid results from 11.3% to 2.6%. A greater proportion of valid sputum results means fewer unscheduled visits for repeat sputum collection and/or fewer data points unavailable for efficacy analysis. In comparative studies, a lower rate of undetected positive visits is likely to improve a study's power to detect a difference between regimens. This can reduce the required number of study participants and might offset the extra cost of triplicate sputum culture.

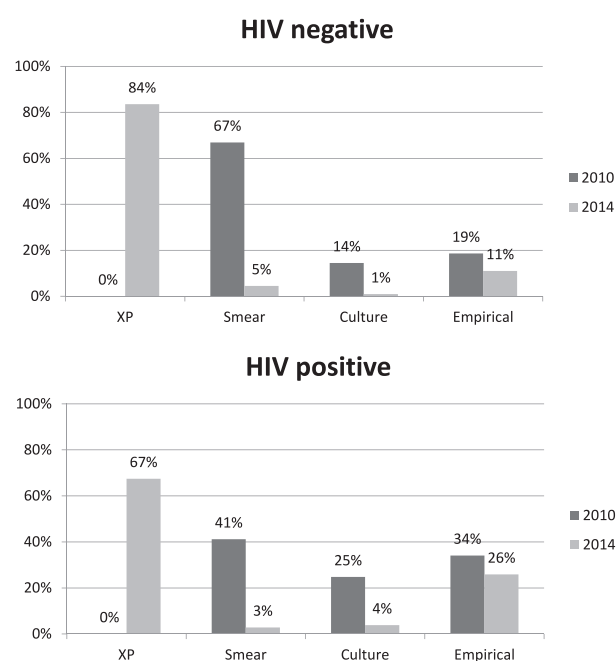
OA-406-05 The impact of routine Xpert® MTB/RIF on empirical TB treatment in Cape Town, South Africa

S Hermans,^{1,2} J Caldwell,³ R Kaplan,² R Wood²

¹Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, ²Desmond Tutu HIV Centre, University of Cape Town, Cape Town, ³City of Cape Town, Cape Town, South Africa. e-mail: sabine.hermans@hiv-research.org.za

Background: Xpert® MTB/RIF (XP) has been projected to increase tuberculosis (TB) case detection by 30%. However four large randomised trials on the use of XP in sub-Saharan Africa did not show an impact on the number of cases diagnosed, which has been attributed to a replacement of empirical treatment by microbiologically confirmed diagnosis. The impact of XP on treatment decisions in a routine care setting is not known. Cape Town started roll-out of XP in August 2011 which was completed in June 2013. We aimed to investigate the impact of XP in a routine care setting on empirical TB treatment stratified by HIV status.

Design/Methods: In a historical cohort study we compared all adult pulmonary TB (PTB) cases in a 1 year period before (2010) and after (2014) roll-out of Xpert MTB/RIF in Cape Town. We utilised data from the City of Cape Town electronic TB register to calculate the proportion of microbiologically confirmed TB cases (either XP, smear or culture). Patients with more than one positive test result were presumed to be diagnosed on the basis of either XP, smear or culture, in this order. All results were stratified by HIV status. We used multivariable logistic regression analysis to determine risk factors of empirical treatment in HIV-positive PTB cases.



Results: In 2010, 21 562 PTB cases were diagnosed versus 19 260 in 2014. An XP result was recorded in 88% of PTB cases in 2014. Overall, the proportion of

microbiologically confirmed PTB increased from 74% to 82% ($P < 0.001$). This increased from 81% to 90% in HIV-negative PTB and from 66% to 74% in HIV-positive PTB (both $P < 0.001$). Treatment decisions moved from being mainly smear-based to mainly XP-based irrespective of HIV status (see Figure). In HIV-positive cases, reliance on TB culture reduced substantially but empirical TB treatment still remained high at 26%. Empirical treatment in HIV-positives was associated with older age (per 10 year increase, adjusted OR [aOR] 1.15 [95%CI 1.09-1.21], $P < 0.001$) and lower CD4 count (per 50 cells decrease, aOR 0.98 [95%CI 0.97-0.99], $P = 0.002$).

Conclusion: Routine use of XP in a setting with a high burden of TB and HIV did not lead to increased numbers of pulmonary TB diagnoses, but increased microbiological confirmation by 8%. More than a quarter of HIV-associated pulmonary TB cases were still treated empirically, highlighting the remaining difficulties in diagnosing TB in the HIV-infected population.

OA-407-05 Preservation of sputum samples with cetylpyridinium chloride for tuberculosis cultures and Xpert® MTB/RIF in low-income countries

H Hiza,¹ B Doulla,² M Sasamalo,¹ F Mhimbira,¹ J Hella,¹ L Jugheli,³ L Fenner^{1,3} ¹Ifakara Health Institute, Bagamoyo, ²Ministry of Health, Dar Es Salaam, Tanzania; ³Swiss Tropical and Public Health Institute, Basel, Switzerland. e-mail: hhiza@ihi.or.tz

Background: Preservation of sputum samples during transport and culture contamination with environmental bacteria is a major challenge in tuberculosis (TB) laboratories in hot and humid climate zones. Cetylpyridinium chloride (CPC) is known to reduce the commensal flora in sputum samples. However, there is only limited information from evaluation studies in sub-Saharan Africa.

Objectives: We aimed 1) to study the effect of CPC preservation on culture results depending on the duration of decontamination; and 2) to investigate the performance of Xpert® MTB/RIF in CPC pretreated samples.

Methods: Consecutive sputum samples (at least 4ml) from smear-positive TB patients were collected at a TB Clinic in Tanzania, and transported in cooled boxes to a BSL2+ TB Laboratory. Samples were equally split in two aliquots, one sample was treated with CPC (1:1 ratio of sputum and CPC), and stored at ambient temperature (25°C) for seven days until processed. Samples were decontaminated using 1% NaOH decontamination for 20, 15 or 10 min. The second aliquot was immediately processed using the routine 1.5% NaLC-NAOH decontamination for 20 min. All decontaminated samples were subsequently cultured on Löwenstein-Jensen solid media at 37°C for 8 weeks. Cultures were read using the WHO grading system and confirmed by Ziehl-Neelsen staining. In addition, 50 CPC treated samples were tested by Xpert MTB/RIF.

Results: We analyzed 146 sputum samples treated either with or without CPC. CPC pretreated samples showed a higher culture yield compared to non-treated sputum samples across all decontamination times: 90% versus 50% with a decontamination time of 20 min ($P < 0.0001$, Fisher's exact test), 94% versus 68% with 15 min ($P < 0.0001$), and 94% versus 73% with 10 min ($P = 0.012$). The quantitative culture grading was consistently higher in CPC pretreated compared to non-treated samples (Table). The proportion of contaminated cultures was less frequent in CPC pretreated samples across all decontamination times (range 2-6%), compared to non-treated samples (range 15-16%). Of 50 CPC pretreated samples with a positive culture, all samples were also Xpert MTB/RIF positive (50/50).

Conclusion: Preservation of sputum samples with CPC with subsequent decontamination for 15 min is a simple and inexpensive method for TB laboratories in low-income countries to facilitate the transport logistics. It increases culture yield while decreasing contamination rate, and importantly pretreated samples can also be used for Xpert MTB/RIF.

Table. Culture results of 146 sputum samples split in two equal aliquots and treated either with or without Cetylpyridinium Chloride (CPC) before processing, with varying times of decontamination.

Culture grading (WHO)	20 min decontamination		15 min decontamination		10 min decontamination	
	Non-CPC	CPC	Non-CPC	CPC	Non-CPC	CPC
Contaminated	7 (15%)	1 (2%)	8 (16%)	1 (2%)	7 (15%)	0 (0%)
Negative	17 (35%)	4 (8%)	8 (16%)	2 (4%)	6 (13%)	3 (6%)
<20 colonies	2 (4%)	3 (6%)	2 (4%)	2 (4%)	0 (0%)	0 (0%)
1+	5 (10%)	7 (15%)	11 (22%)	9 (18%)	2 (4%)	7 (15%)
2+	8 (17%)	16 (33%)	11 (22%)	18 (36%)	12 (25%)	13 (27%)
3+	9 (19%)	17 (35%)	10 (20%)	18 (36%)	21 (43%)	25 (52%)
Total	48 (100%)	48 (100%)	50 (100%)	50 (100%)	48 (100%)	48 (100%)

OA-408-05 Development of a multiplex real-time PCR assay for detection of *Mycobacterium tuberculosis* from sputum collected in PrimeStore MTM®

L Daum,¹ S A Worthy,¹ J D Rodriguez,¹ R Peters,² B Fourie,² G Fischer¹ ¹Longhorn Vaccines & Diagnostics, San Antonio, TX, USA; ²University of Pretoria, Pretoria, South Africa. e-mail: longhorn-vandd@sbcglobal.net

Background: We recently reported a sensitive and timely *Mycobacterium tuberculosis* (*M. tuberculosis*) real-time PrimeMix PCR detection assay targeting the multi-copy IS6110 genomic element (Daum et al., IJTLD, May, 2015). However, some *M. tuberculosis* strains are known to be IS6110 deficient and therefore undetected by assays that exploit this target. Up to 56% of *M. tuberculosis* strains collected from India were shown to contain 5 or less copies of the IS6110 element. In one report from Mexico 20.8% of *M. tuberculosis* isolates lacked IS6110 (Lopez-Alvarez et al., BMC Microbiology, 2010). Accurate and timely *M. tuberculosis* detection is the first and most critical step for effective *M. tuberculosis* therapeutic measures. Aim: A multiplex real-time PCR assay for the detection of IS6110 and IS1081 multi copy *M. tuberculosis* segments was developed into a single step PrimeMix® PCR blend. The limit of detection using quantified *M. tuberculosis* was determined and multiplex

results were compared to a real-time PCR uniplex assay. In addition, this multiplex PCR assay was evaluated on a panel of specimens collected in South Africa.

Methods: A real-time multiplex assay targeting the *M. tuberculosis* IS6110 and 1081 multi copy targets was developed from conserved regions obtained from multiple sequence alignments of *M. tuberculosis* strains in GenBank. For limit of detection, a quantified stock culture of H37Rv (106 CFU/ml) was serially diluted and placed into PrimeStore® for real-time PCR detection. Additionally, an IPC assay targeting a non-specific DNA fragment present in a clinical collection medium (PrimeStore®) was utilized for monitoring specimen integrity from collection to detection. A random sample of positive and negative clinical specimens was utilized consisting of sputum collected and shipped at ambient temperature in PrimeStore MTM® from rural sites in Africa.

Results: The multiplex *M. tuberculosis* assay was sensitive across five 10-fold serial dilutions of quantified *M. tuberculosis* genomic DNA and exhibited no cross reactivity to a reference panel of non- *M. tuberculosis* complex organisms. The multiplex *M. tuberculosis* assay correctly identified 30/30 specimens and was comparable to a real-time *M. tuberculosis* uniplex equivalent. Additionally, IPC present in PrimeStore® was detected in all specimens.

Conclusions: The multiplex *M. tuberculosis* assay targeting both IS6110 and IS1081 is sensitive and specific; exhibiting equivalent results compared to a single PCR target. This assay is a sensitive dual target method for *M. tuberculosis* detection, particularly in specimens from geographical areas where *M. tuberculosis* may lack the IS6110 target.

OA-409-05 The effect of automated nucleic acid amplification assays on mortality in routine care settings: meta-analysis of individual participant data

A Khaki,¹ G Di Tanna,² K Fielding,² G Theron,³ M Nicol,³ K Dheda,³ G Churchyard,⁴ J Metcalfe¹ ¹University of California San Francisco, San Francisco, CA, USA; ²London School of Hygiene & Tropical Medicine, London, UK; ³University of Cape Town, Cape Town, ⁴The Aurum Institute, Johannesburg, South Africa. e-mail: ali.khaki@ucsf.edu

Background: Xpert MTB/RIF ("Xpert"), an automated nucleic acid amplification test, is now widely implemented within national tuberculosis programs in over 115 countries. While diagnostic accuracy is well documented, anticipated improvements in patient outcomes have not been described.

Design/Methods: We performed an individual participant data (IPD) meta-analysis of four randomized controlled trials (RCTs) from the Southern African region investigating the impact on early mortality among tuberculosis suspects screened using Xpert compared with sputum smear microscopy. We utilized both one- and two-stage methods to account for individual and cluster-level trial designs, and Huber-White sandwich

estimators for multiple centers. Analyses were adjusted for age and gender, and were stratified by HIV infection.

Results: In four trials involving 8,567 patients Xpert was not associated with a decrease in overall 3-month mortality (odds ratio [OR] 0.91 [95%CI 0.68-1.20], $P = 0.50$) or in HIV-positive persons (OR 0.86 [95%CI 0.66-1.13], $P = 0.29$). Similar results were found for 6-month mortality (three RCTs, $n = 8,142$). In time-to-event analysis Xpert was not associated with a decreased hazard of death among all (hazard ratio [HR] 0.82 [95%CI 0.64-1.05], $P = 0.11$) or HIV-negative participants (HR 0.81 [0.46-1.41], $P = 0.45$), but was associated with decreased mortality among HIV-positive participants (HR 0.75 [95%CI .59-0.96], $P = 0.02$). Heterogeneity among trials was minimal (Chi-square test, $P = 0.55$, $I^2=0.0\%$).

Conclusion: In this large multi-country IPD meta-analysis, Xpert was associated with decreased mortality among HIV-positive patients. Although our preliminary analyses are potentially limited by informative censoring and/or unmeasured confounding, our study represents, to our knowledge, the first randomized evidence that novel TB diagnostics decrease risk of death.

OA-410-05 A pilot proficiency testing program for Xpert® MTB/RIF using dried tube specimens

K Klein,¹ K Degruy,² C Hatcher,² H Alexander² ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: xim0@cdc.gov

Background: Use of the Cepheid Xpert MTB/RIF assay has expanded rapidly since the World Health Organization's initial recommendation in 2010. However, proficiency testing (PT) material for this assay is not widely available. The U.S. Centers for Disease Control and Prevention (CDC) piloted a voluntary, cost-free PT program using Dried Tube Specimens (DTS) to assist testing sites in monitoring the performance of Xpert MTB/RIF testing.

Design/Methods: Inactivated DTS were prepared at CDC using selected isolates of rifampicin (RIF)-susceptible *Mycobacterium tuberculosis* (*M. tuberculosis*), RIF-resistant *M. tuberculosis*, and non-tuberculous mycobacteria. Panels composed of 5 DTS samples per round were shipped at ambient temperature to designated country coordinators and then distributed to enrolled testing sites. Participating sites conducted Xpert MTB/RIF testing per enclosed instructions and submitted test results to the country coordinator using a standardized electronic form. Country coordinators collated and submitted results to CDC for review. Participating sites were provided unscored PT reports after each round. Between March and December 2013, 4 PT rounds were conducted.

Results: Enrollment increased from 103 sites from 6 countries in the first round (March 2013) to 222 sites from 10 countries in the fourth round (December 2013), for a total of 648 panels provided.

Results were returned electronically submitted for 475 (73.3%) or 648 panels. The mean proportion of responding sites achieving 100% concordance with expected results over all rounds was 66.7% (range 62.3-70.8%). Among 163 sites with any discordant result, the number of discordant results per site in a single panel ranged from 1 to 5. Unsuccessful tests (i.e., error, invalid, or no result) were responsible for 78 (42.6%) of the total 183 discordant results in all 4 rounds. Of the 105 discordant test results, 39 (37.1%) were false negative *M. tuberculosis*, 37 (35.2%) were indeterminate RIF resistance, 11 (10.5%) were false negative RIF resistance, 11 (10.5%) were false positive RIF resistance, and 7 (6.7%) were false positive *M. tuberculosis* results. **Conclusion:** DTS PT panels are critical for monitoring Xpert MTB/RIF testing performance as part of a comprehensive quality assurance program that includes routine quality indicator monitoring, supervisory visits, and when necessary, corrective action. To facilitate quality improvement, future PT rounds will include performance scores and follow-up for those sites not achieving satisfactory scores.

15. When waves trump paper: the triumph of e-technology

OA-411-05 Patient networking for TB Care using mobile technology: care of 'I Decide' mApplication

T Kizhakkeparampil Thomas,¹ S Kumar,² J Yakubu,² S Pulibanti² ¹Olive Touch Health Care Services, Thrissur, ²School of Public Health, SRM University, Chennai, India. e-mail: ceomarg@gmail.com

Background and challenges to implementation: Patient Knowledge and ability to communicate with care providers has been found to be important in enabling patients to continue the treatment without default. It has been found gaps in the knowledge flow regarding disease and treatment which work as barrier in treatment. Patient to Patient Learning is an important element in treatment of TB. The drop outs is an important problem even today and the social stigma on the disease continue to be an important problem. Thus we have piloted a project where peer networking and learning is activated with the help of mobile phone. This project as part of a bigger project developed a mobile application which enables patients to interact and network with their peers and care providers to resolve many of the health issues. **Intervention or response:** We have developed a mobile application which enables learning, interactions and problem solving with the help of mobile phones. The application facilitate patient networking, getting feedback from the providers on the various adverse health effects and raising questions about various problems that patients have during the treatment. Mobile phone is provided with application installed to 100 TB patients who were defaulters to find out if the knowledge dissemination and mobile real-time tracking and net-

working facility help in strengthening the treatment and the treatment outcome. This found very much useful for the patients as well as the various stakeholders involved in TB care.

Results and lessons learnt: The study suggests that peer networking and connectivity with the care providers enhance confidence in patients and the DOT providers and this help in minimizing the default. The problems could be resolved faster and with clarity and this make patients on a better side in their ability to resolve treatment blocks. The communication facility at times of adverse effect helps in managing them more effectively and disseminating the solutions to larger mass.

Conclusions and key recommendations: Peer networking and opportunity to network with the treatment stakeholders can build confidence among patients and can strengthen the TB and the ultimate treatment outcome. Mobile phones could be a good way to network faster with all stakeholders with clarity of information care process. The care outcomes could be strengthened by strengthening the patient connectivity with all stakeholders. Technology can facilitate a cost effective networking.

OA-412-05 A sustainable model of effective private provider engagement via e-health and free TB drugs, Mehsana District, Gujarat, India, 2014

P Dave,¹ P Nimavat,¹ K Patel,¹ B Vadera,² K Rade,² P Dewan,³ A Sreenivas,² N Kulshreshta⁴ ¹Ministry of Health & Family Welfare, Gandhinagar, ²World Health Organization Country Office for India, New Delhi, ³Bill & Malinda Gates Foundation, New Delhi, ⁴Ministry of Health & Family Welfare, New Delhi, India. e-mail: dr.vadera@gmail.com

Background: Private providers (PP) in India manage 1 in 8 TB patients in the world, and are believed to account for 1 million of the 3 million 'missing' TB case notifications globally. Prior solutions have yielded modest, incremental increases in TB case notification. We developed a model to leverage e-health advances and using free anti-TB drug vouchers to attract PP TB notifications, reduce patient out-of-pocket expenses, and improve the quality of TB care at scale.

Intervention: Gujarat State has a large PP presence, with >18,000 members registered with the Indian Medical Association. In largely rural Mehsana district (pop. 2.1m), all PP and chemists were mapped & prioritized for engagement based on speciality and TB drug sales. A call centre receives TB notification and issues immediate e-vouchers for anti-TB drugs as per national standards, which patients redeem at private chemists. Notified patients are visited by program staff for contact assessment and offer of HIV & diabetes comorbidity screening. Patients receive adherence support, reminders, self-reporting via call centre, and active follow-up by call centre and then program staff of non-reporting or missed refills.

Results: From 1 August '14 to 31 March '15, out of 440 total PP, 180 were targeted and 81 (45%) notified;

similarly, of 159 chemists who stocked anti-TB drugs, 80 (50%) redeemed e-vouchers. Total TB case notification rate (annualized) doubled, relative to the same quarter one year earlier. This included 1493 from public sector, and 1582 from PP; public TB notification remained stable. In eight months, 4098 patient months of vouchers (USD\$30 thousand) were issued and redeemed. Initial treatment cohort ($n = 220$) show 79% patients completed treatment or continued on treatment at end of 6 months under PP.

Conclusions: This unique model demonstrated that in rural areas with well-staffed TB programs, PP's in India can be engaged effectively at scale, with e-health support and modest additional resources. With notification, treatment and support as per national standards can be extended to patients. Similarly, PP quality can be monitored and improved. Needed enhancements include modern adherence monitoring and free TB diagnostic services for PP.

OA-413-05 E- and m-Health solutions for national TB programmes to track missing cases

S Achanta,¹ J Jaju,¹ C Chatla,¹ R Samyukta,² M Parmar,¹ KS Sachdeva,³ A Sreenivas¹ ¹World Health Organization Country Office for India, New Delhi, ²State TB Cell, Hyderabad, ³Central TB Division, New Delhi, India. e-mail: achantas@rntcp.org

Background: Pre-treatment loss to follow-up (PLFU) of TB patients, hinders tuberculosis control efforts globally. Cohort analysis of cases detected by Revised National TB Control Programme (RNTCP) in Telangana, India show that nearly 2000 smear positive cases appear in Lab registers consistently quarterly but are not recorded in TB patient registers, a log of patients registered for treatment under the programme. Feedback on treatment initiation is either missed or delayed of patients who are referred for treatment to other TB units after diagnosis, often outside the district or State. Current monitoring practices fail to trace these patients and the Lab diagnostic cohort is neither validated nor reported. In view of the global concern of 'missed cases' from India and Government's mandate to notify all diagnosed and treated TB cases; it is significant that programme addresses challenges associated with notifying diagnosed cases, tracing PLFU patients, and initiating early treatment. To address these challenges, an e- and m-Health module has been devised by RNTCP in Hyderabad, Telangana to 1) identify the diagnostic cohort 2) decrease PLFU during the TB diagnostic pathway.

Intervention: Lab technicians enter smear results and demographic details of smear positive TB cases into electronic-Lab registers which are linked through a central server. Feedback on the date of starting treatment is exchanged electronically and auto SMS/IVRS system tracks them for early treatment initiation. Data on patient referrals and their feedback is compared from 30 microscopic centers in Hyderabad, before and after this intervention

Results: There were 750 smear positive patients diagnosed during April-June 2013 and 708 patients during

April-June 2014, which could be reported as a diagnostic cohort of TB patients. Feedback on treatment initiation of referred out patients was received for 424 of 689 (61 %) in 2013 and 563 of 645 (87 %) in 2014 after introducing e-Lab register. Electronic feedbacks were obtained within a range of 2-7 days. Pending feedbacks and eventual PLFUs dropped from 39 % to 13 %

Conclusions: The e-Lab register and auto SMS/IVRS system improves patient tracking, reduces PLFU and identifies a diagnostic cohort for TB case reporting. Innovative technological solutions are needed to track missing TB cases and improve TB case notification

Table: Number of feedbacks received of patients referred out for treatment initiation and registration before and after introduction of the e-Lab register in 30 Microscopy centers of Hyderabad, Telangana

Patients	Before Intervention April-June (2013)		After Intervention April-June (2014)	
Sputum positive patients diagnosed in the microscopy centers (A)	750		708	
Sputum positive patients of (A) referred out (B)	689		645	
	Referred <i>n</i>	Feedback received <i>n</i> (%)	Referred <i>n</i>	Feedback received <i>n</i> (%)
Patients of (B) referred for treatment to TB units within the same district	451	262 (70)	405	348 (92)
Patients of (B) referred for treatment to other districts	231	162(58)	233	215 (86)
Patients of (B) referred for treatment to other States	7	0	7	0
Total	689	424 (61)	645	563 (87)

TB = tuberculosis.

OA-414-05 99DOTS: monitoring and improving TB medication adherence using mobile phones and augmented packaging

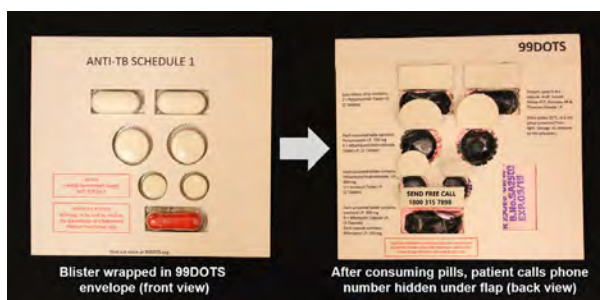
A Cross,¹ M Kumar,² P Soren,² K Rade,³ A Sreenivas,³ S Kumar,^{3,4} B Thomas,⁴ P Dewan⁵ ¹Microsoft Research India, Bangalore, ²Innovators In Health, Patna, ³World Health Organization, Country Office for India, Delhi, India; ⁴Arcady Group, Richmond, VA, USA; ⁵Melinda Gates Foundation, Delhi, India. e-mail: across@microsoft.com

Background and challenges to implementation: A critical challenge in tuberculosis treatment is to ensure that patients adhere to the full course of medication. In India, use of Directly Observed Therapy (DOT) in the public sector has been associated with high treatment success. However, direct observation introduces challenges for patients and providers, who need to undertake frequent travel throughout the course of treatment. It is also challenging for program managers to detect and respond to missed doses in an accurate and timely way.

Intervention or response: A low-cost approach for monitoring and improving TB medication adherence, called 99DOTS, was deployed in a public-sector program in Samastipur district, Bihar, India. Each anti-TB blister pack is wrapped in a custom envelope (pictured), which includes a hidden phone number that is visible only when a dose is dispensed. After taking the medication, patients make a free call to hidden phone number, yielding high confidence that the dose was “in-hand” and has been taken. Initially, patients undergo normal DOTS supervision and providers assist in making the call. Over time, adherent patients can take custody of their drugs and make calls with lesser supervision, while still permitting remote monitoring of each dose. In addition to compiling a real-time dosing history for each patient, 99DOTS enables a wide range of reminders, alerts and follow-ups.

Results and lessons learnt: From August, 2014 to January, 2015, 49 patients initiated treatment under 99DOTS. Of these, 31 showed 100% adherence, 16 patients showed 85-99% adherence and 2 patients showed 75-85% adherence. A total of 1791 doses were logged via calls to 99DOTS. Most doses were observed by providers; however, small-scale experience with self-administration (5 patients) and family observation (6 patients) showed adherence of 94% and 91%, respectively.

Conclusions and key recommendations: 99DOTS empowers patients, providers, and treatment programs, supporting health system efficacy and efficiency. Adherent patients can take independent custody of their drugs and confirm consumption without physical observation, which simultaneously reduces the burden on providers. Program managers gain real-time information on adherence, enabling more customized and more efficient patient supervision and support. 99DOTS may be especially applicable as India switches from thrice-weekly to daily regimens, as it enables daily monitoring without daily observation.



OA-415-05 GxAlert SMS improves DR-TB patient enrollment and management in Nigeria

K Jimoh Agbaiyero,^{1,2} L Ekblad,^{1,2} M Benezet,² J Takle,³ C Macek³ ¹Abt-Health Finance and Governance Project, Abuja, Nigeria; ²Abt Associates, Bethesda, MD, ³SystemOne, Boston, MA, USA. e-mail: kehindeagbaiyero@yahoo.com

Background and challenges to Intervention: Nigeria is a WHO high-burden drug-resistant TB (DR-TB) country that relies on GeneXpert MTB/RIF machines to diagnosis DR-TB at multiple clinical locations. However, reporting TB testing results is a lengthy process due to a continued reliance on paper records and slow data transit systems. Quality of results data is often poor and subsequent program management decisions are not always timely or focused on priority needs.

Intervention: In pursuit of cost-effective technologies to improve healthcare responses to DR-TB by the Nigerian Tuberculosis and Leprosy Control Program (NTBLCP), Abt Associates and SystemOne developed an innovative mobile-based solution that sends GeneXpert diagnostic results to key health system actors instantly. GxAlert is configured on GeneXpert systems by installing a modem from a local telecom that sends encrypted data sent to the secure web-based GxAlert database in real time. The system then sends the results in an SMS alert to program decision makers at the state and national TB program, shortening the new-case reporting period from months to seconds.

Results and lesson Learnt: The proportion of DR-TB patients enrolled for treatment based on GxAlert messages received from 35 GeneXpert facilities jumped to 85% in March, 2015 from only 20% enrolled in April 2014. SMS or text message alerts are sent to TB State program manager and National Program DR-TB enrollment officer upon GeneXpert confirmation of a *M. tuberculosis* + Rif+ case to speed treatment initiation. Weekly reports of all new TB+ cases are both emailed and sent by SMS to local health officials to ensure better connection between diagnosis, enrollment and treatment. Faster, better quality data on MDR-TB portion of total TB indicators are now reported with minimal error or effort.

Conclusions and key Recommendations: The use of GxAlert SMS notification of GeneXpert testing suggests a scalable model for sustainability: Installation is done once and in-country. Technology is kept simple as local telecom modems are readily available and affordable for connectivity. In Nigeria, GxAlert has the potential to strengthen surveillance of DR-TB, TB in children, speeding response and improving programmatic decision making for faster enrollment of patients in treatment programs. Based on these results, a national rollout of GxAlert was formally launched by the honorable Minister of Health of Nigeria on World TB Day 2015.

OA-416-05 57 Zone: using social media in China to empower TB patients for treatment success

X Lin,¹ X Xu,² Z Yu,¹ W Zhang,¹ Z Huang,³ I Ling,² G Nie,¹ A Innes⁴ ¹Yunnan Center for Disease Control and Prevention, Kunming, Yunnan Province, ²FHI 360 China, Kunming, Yunnan Province, ³57 Zone, Kunming, Yunnan Province, China; ⁴FHI 360 Asia Pacific Regional Office, Bangkok, Thailand. e-mail: ainnes@fhi360.org

Background: China's Yunnan Province has a high TB burden with increasing numbers of complicated retreatment and drug-resistant cases. Interviews with TB patients in Yunnan show that not knowing the correct treatment course and poor compliance are common barriers to treatment success. Effective patient-doctor communication for treatment adherence is limited by understaffed TB clinics. At the same time, many TB patients are open to taking responsibility for their disease and are motivated to be cured.

Intervention: In December 2013, multi-drug resistant (MDR) TB patients in Yunnan established a social media group called 57 Zone using QQ, a popular social network and mobile app in China with over 830 million users. Through 57 Zone, patients and their family caregivers have instant, virtual access to peer educators and clinicians, asking questions about TB medications, adverse drug effects, proper nutrition, and psychosocial concerns. QQ managers were identified at the launch of 57 Zone and given clear roles and responsibilities to deliver online services in a friendly, timely and professional manner. These QQ managers disseminate key TB messages daily, follow online discussions, and organize activities to encourage experience sharing among patients.

Results: As of March 2015, 57 Zone had more than 300 members, 90% of whom are current or former patients and family caregivers. More than 100 members actively participate in discussion each day, with conversations covering tips on navigating the TB system; coordination of follow-up visits with TB doctors and face-to-face peer counselling at TB hospitals; and emergency fund raising for patients who need money to continue treatment. 57 Zone patients express a strong sense of community, connectivity, and moral support for each other. Improved patient-doctor relationships have also been formed through monthly 1-hour consultation sessions and information exchange online. TB-HIV patients now participate in 57 Zone, and the social network has also expanded to include members in rural Zhenxiong County (which has the highest TB notification rates in Yunnan) and Xinjiang Province (with the highest TB prevalence in China).

Conclusions: 57 Zone is among the first social networks in China created by patients for TB and MDR-TB. Social networking can give patients instant, virtual access to education and support, a powerful adjunct to routine communication during follow-up visits.

OA-417-05 Tuberculosis case finding at pharmacies in Tanzania using trained pharmacists and an electronically monitored referral system

F Mhimbira,^{1,2,3} J Hella,^{1,2,3} B Mutayoba,⁴ B Doulla,⁴ E Mahongo,³ J Minde,⁴ L Fenner^{1,2,3} ¹Swiss Tropical and Public Health Institute, Basel, ²University of Basel, Basel, Switzerland; ³Ifakara Health Institute, Bagamoyo, ⁴Ministry of Health and Social Welfare, Dar Es Salaam, Tanzania. e-mail: fmhimbira@gmail.com

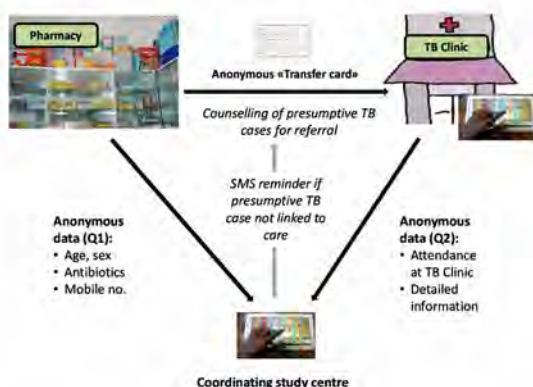
Background: Introducing new tuberculosis (TB) diagnostics is critical, but additional interventions are needed to bring patients suspected with TB to care. There is evidence that presumptive TB patients use un-prescribed antibiotics to relieve their symptoms. We aimed to set up and evaluate a referral system at pharmacies to detect TB cases who were missed or delayed by the routine health care system.

Methods: We established an electronic referral system using android tablet computers at five pharmacies in a densely populated area of the Ilala District, Dar es Salaam (Buguruni Health Center). Pharmacists were trained to refer any customers who reported coughing (any duration) or any other TB related symptom. Anonymous referral cards were given and an automatic follow-up SMS reminder were sent to customers who did not report to a within three and five days. TB Diagnosis was either done by sputum microscopy, chest X-ray or based on clinical findings. In addition, a control population of consecutive TB patients diagnosed through the routine care system was also recruited. The study started in November 2014 and will last for 12 months.

Results: Until March 2015, the pharmacies referred 118 presumptive TB patients. The median age was 37 years (Interquartile range [IQR]: 28-43), and 82 (70%) were men. Apart from coughing, 75 (63.6%) patients reported excessive night sweats, and 69 (58.5%) weight loss. The most commonly purchased antibiotics at the pharmacies were amoxycillin (52 customers, 44 %) and ampiclox in 36 (31%) customers. Overall, 103 (87%) of the referred customers reached the TB diagnostic center, of these 89 (86%) came within 3 days. Out of 103, 77 (74%) had TB investigation results, of which 29 (37%) were diagnosed with TB and started on treatment. Smear microscopy diagnosed 16 (55%) of TB patients, and the remaining 12 (41%) were diagnosed based on clinical or radiological features. Coughing of 4 weeks or more was reported in 26 (90%) of the TB patients. Compared to TB patients referred by pharmacies, routinely diagnosed TB patients tended to have longer range of duration of cough (1-16 vs. 0-50 weeks).

Conclusion: We successfully demonstrated the feasibility that presumptive TB cases visiting pharmacies to purchase antibiotics can be referred to a TB diagnostic center. If this low-cost case finding strategy could be scaled-up, it may have a huge impact on TB control by increasing early TB diagnosis and thus reduce transmission in the community.

Figure Intensified case finding using trained pharmacists and an electronically monitored referral system: schematic presentation of the patient referral flow from pharmacies to a tuberculosis diagnostic center and data management (Q, questionnaire).



OA-418-05 Novel package of integrated mobile applications reduce time to treatment initiation for patients with MDR-TB

J Farley,^{1,2} J McKenzie-White,^{3,4} S Seiguer,⁴ M Naicker,¹ L Isherwood,⁵ F Olsen,⁵ S Candy,⁵ W Stevens⁵ ¹Jhpiego South Africa, Pretoria, South Africa; ²Johns Hopkins University School of Nursing, Baltimore, MD; ³Johns Hopkins University, Baltimore, MD; ⁴Emocha Inc., Baltimore, MD, USA; ⁵National Health Laboratory System, Johannesburg, South Africa. Fax: (+1) 410 955 7733. e-mail: jfarley1@jhu.edu

Background: Like rapid diagnostic technology, mobile health (m-health) has the power to revolutionize TB care. We set out to test whether the time from TB suspicion to treatment initiation could be reduced to 5 days or less to meet the National Strategic Plan for TB-HIV in South Africa utilizing an m-health application-based platform. We describe the initial implementation of a package of mobile applications, developed by emocha Mobile Health, Inc., that is designed to register, link, refer and document initiation.

Design/Methods: Prospective, descriptive study of rapid identification and linkage to care for TB suspects registered between March 20, 2015 and April 20, 2015 in Ugu District, KwaZulu Natal, South Africa. Specimen data and results matching from the National Health Laboratory System (NHLS) were completed using both barcodes from clinical specimens and South African identification number.

Results: We enrolled 586 TB suspects through the application. Of these, 336 (57%) were matched with NHLS results.

Results were available via the application for the ordering clinics in less than 40 hours. Thirty-three (10%) were positive for drug-susceptible TB; 3(0.9%) were identified as rifampicin-resistant patients and 16 (5%) were inconclusive and required repeat testing. For MDR-TB patients, the average time from registration in the application to initial contact by the tracer was 1.65 days and time from registration to treatment initiation was 3.55 days. Of the 250 suspects unmatched with NHLS results, 129 patients (51.6%) did not have a barcode entered into the NHLS data system. The

remaining 121 (48%) of unmatched patients were entered into the application, but either leaked, contaminated, inadequate or otherwise untestable specimens, which were rejected at the lab.

Conclusions: These data demonstrate that the time from TB suspicion to treatment initiation can be reduced to 5 days or less for MDR-TB patients using a package of mobile applications seamlessly communicating through an integrated platform with the NHLS system. Matching of results between the lab and the application was perfect when barcodes were recorded within the lab system and when specimens were of adequate quality for processing. Integrating technologic advances with skilled human resources can increase efficiency and improve time to treatment initiation.

16. From bench to treatment

OA-419-05 Fluoroquinolone use delays tuberculosis treatment despite immediate mycobacteriological tests

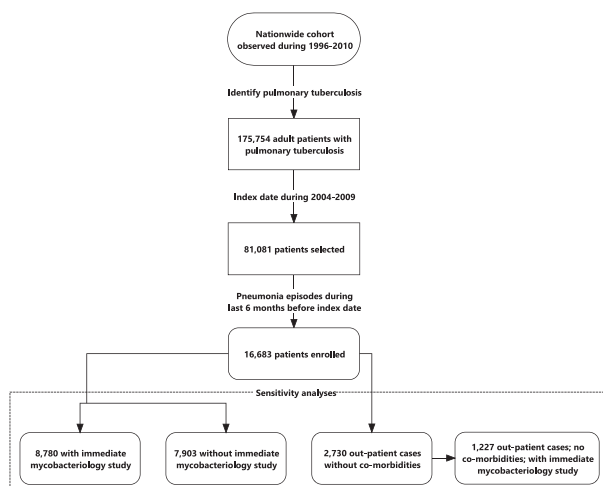
J-Y Wang,¹ C-H Lee² ¹National Taiwan University Hospital, Taipei, ²Wanfang Hospital and School of Medicine, Taipei Medical University, Taipei, Taiwan. Fax: (+886) 2 2358 2867. e-mail: jywang@ntu.edu.tw

Background: Empirical use of a fluoroquinolone (FQ) for pneumonia can mask tuberculosis (TB). This study aimed to investigate if immediate mycobacteriology study, including mycobacterial culture and *Mycobacterium tuberculosis*-nucleic acid amplification test (MTB-NAA) can reduce delays in anti-TB treatment.

Methods: Adult pulmonary TB patients presenting as pneumonia were identified from the National Health Insurance Research Database of Taiwan. Those with a prescription of FQ ≥ 7 days on the first consult for pneumonia were classified as the FQ group. Factors influencing the interval between pneumonia and anti-TB treatment were evaluated using linear regression analysis.

Results: Of 16 683 patients identified, 2051 (12.3%) were in the FQ group. The time to anti-TB treatment was longer in the FQ group than in the non-FQ group (63.0 ± 47.1 vs. 49.4 ± 47.6 days, $P < 0.001$). By multivariate analysis, prescription of FQ ≥ 7 days was associated with delayed anti-TB treatment (beta: 16.50 [14.39-18.61]). In sensitivity analyses, prescription of FQ ≥ 7 days remained a significant factor in (1) patients with mycobacteriology study done on the first consult for pneumonia, (2) out-patients without co-morbidity, and (3) patients meeting both criteria.

Conclusion: Empiric use of FQ for ≥ 7 days delays anti-TB treatment even when mycobacteriology study is prescribed on the first visit for pneumonia.



OA-420-05 In-patient wards as a source of missed pulmonary tuberculosis cases: a case study in Ethiopia

D Assefa Lemma,¹ G W Desalgn,¹ E Klinkenberg^{1,2} ¹KNCV Tuberculosis Foundation, Addis Ababa, Ethiopia; ²RESEARCH, KNCV Tuberculosis Foundation, Haiguer, Netherlands. e-mail: dawita8246@gmail.com

Background: Ethiopia is one of the ten countries contributing to the ⁴United States Agency for International Development 4% of estimated missed cases globally in 2013. The national TB program enhanced community TB service implementation and scaled up the use of new technologies and tools to ensure that people with TB are promptly identified and treated. However, there might be areas where cases of tuberculosis are being missed due to low degree of clinical suspicion or diagnostic difficulties, for example in the hospital wards which may illustrates possible problems of case finding. Our aim was to assess whether there are undiagnosed pulmonary TB (PTB) cases in the inpatient wards of hospitals.

Design/Methods: A cross sectional design was employed to review medical records and conduct structured interviews with medical inpatients from June 10 – Sept 30, 2014. All patients without TB diagnosis in the inpatient medical wards of one large hospital were evaluated for signs and symptoms of PTB and for all one morning sputum sample was collected for smear microscopy (LED) and molecular testing (GeneXpert®). Multivariate analysis was conducted to assess factors associated with missed TB cases.

Results: A total of 300 inpatients (40.6% female) were enrolled in the study. The median duration of sickness was 30 days [IQR 14 - 240]. The median BMI was 21.5 [IQR 20 - 22.6]. Of the inpatients, 102 (34%) had no documented HIV status, while 37/198 (18.7%) were HIV positive with a median CD4 count of 176 [IQR 52 - 400]. A total of 10 (3.3%) PTB cases were identified as *M. tuberculosis* by GeneXpert of which one was smear positive. This is more than 10 times higher than in the general population. And, of the identified cases 8 (80%) reported

a cough (any duration), while 6 (60%) of them had at least three symptoms of PTB. None of the identified cases reported history of contact with a PTB patient. Co-morbidity was observed in two tuberculosis cases, one was HIV positive and one had diabetes mellitus.

Table History of other chronic illness and Xpert positivity

Xpert result	History of other chronic illnesses					Total
	Chronic bronchitis	Diabetes Mellitus	HIV positive	No history of chronic illness	other	
Positive	0	1 (10%)	1 (10%)	8 (80%)	0	10
Negative	3 (10%)	37 (12%)	30 (10%)	131 (45%)	89 (30.7%)	290
Total	3	38	31	139	89	300 (100%)

Conclusion: All identified PTB cases in the inpatient ward had at least one common symptom of PTB while their medical record showed no evaluation for PTB. The index of suspicion by clinicians should be improved. This, together with the use of new technologies could assist the tuberculosis case finding strategy.

OA-421-05 Diagnostic barriers among newly diagnosed pulmonary TB patients in Kyrgyzstan: patient delay

C Zhumalieva,¹ A Estebesova,^{2,3} M Ryspekova,¹ D Madybaeva,⁴ A Tursynbayeva,^{5,6} N Usenbaev,¹ C Kamarli,⁷ S Verver⁸ ¹Department of State Disease Prevention and Sanitary-Epidemiological Surveillance, Bishkek, ²KNCV Tuberculosis Foundation Country Office, Bishkek, Kyrgyz Republic; ³Open Society Foundations, Public Health Program, New York, NY, USA; ⁴AFEW in Kyrgyzstan, Bishkek, Kyrgyz Republic; ⁵KNCV Tuberculosis Foundation Regional Office, Almaty, ⁶Central Clinical Hospital of the Medicine Department of the President Administration Affairs, Almaty, Kazakhstan; ⁷United States Agency for International Development, Health and Education Office, Bishkek, Kyrgyz Republic; ⁸KNCV Tuberculosis Foundation, The Hague, Netherlands. e-mail: aida.estevesova@gmail.com

Background: Kyrgyzstan has a tuberculosis (TB) notification rate of 102/100 000 in 2013, and WHO estimates the TB incidence 141/100 000 population (WHO, 2012). Very little is known about delay in diagnosis and risk factors related to patients in the country and the Central Asia region. The objective of this study was to assess patient related factors contributing to delay in presenting to the health system.

Design/Methods: We included all new adult (>18 years) TB patients, both smear positive and negative, drug-sensitive and drug-resistant, starting treatment in selected sites in Kyrgyzstan during April–June 2014. Two largest urban areas and four rayons in the North and South of the country were selected for the study. Data was collected from medical records and structured interviews were conducted with TB patients.

Results: Among 416 patients fulfilling the selection criteria 383 were interviewed (92%). Delay between first onset of symptoms and first visit to facility varied

between 0 and 207 days, with a median and mean of 28 and 36 days, respectively. Only half the patients visited a state facility as a first step while almost one third (29%) visited a pharmacy first. 70% of patients had more than 14 days delay between onset of symptoms and first visit to a state facility. The following factors were significantly associated with delay over 14 days in multivariate analysis: being migrant (OR 2.6, 95%CI 1.3-5.3), living in rural area (OR 2.5, 95%CI 1.3-4.6) vs. urban, having any symptom (OR 3.7, 95%CI 1.7-7.5) vs. no TB symptoms and having no knowledge of symptoms (OR 1.9, 95%CI 1.2-3.3). Non-symptomatic patients had probably less delay since they were detected by screening. **Conclusion:** A mean patient delay of one month is unacceptably high and interventions should be designed to improve care seeking behavior in the country, especially among migrants and patients in rural areas. Advocacy on TB symptoms is needed. Interventions are needed to involve pharmacies in referral for TB care.

OA-422-05 Genetic determinants of the pharmacokinetic variability of isoniazid and rifampicin in Malawian adults with pulmonary tuberculosis

A McCallum,^{1,2,3} A Schipani,² A Owen,² H Mwandumba,^{1,4,5} S Ward,⁵ S Khoo,² G R Davies,^{2,3} D Sloan^{1,4,5,6} ¹Department of Medicine, College of Medicine, University of Malawi, Blantyre, Malawi; ²Institute of Translational Medicine, University of Liverpool, Liverpool, UK; ³Institute of Infection and Global Health, University of Liverpool, Liverpool, UK; ⁴Malawi-Liverpool-Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, Blantyre, Malawi; ⁵Liverpool School of Tropical Medicine, Liverpool, UK; ⁶Liverpool Heart and Chest Hospital, Liverpool, UK. e-mail: andrewmccallum@doctors.org.uk

Background: Anti-tuberculosis therapy (ATT) has concentration-dependent activity against *Mycobacterium tuberculosis*. Inter-individual variability in the pharmacokinetics of ATT may be associated with emergence of drug resistance. We evaluated the contribution of host genetic factors to this variability.

Design/Methods: 174 Malawian adults with pulmonary tuberculosis were assessed for single nucleotide polymorphisms (SNPs) in genes previously reported to have functional significance for the clearance of isoniazid and rifampicin; NAT2, SLCO1B1, AADAC and CES1. 14-21 days after commencing first-line ATT, patients returned for plasma sampling at 2 and 6 hours post-dose. Drug concentrations were measured by liquid chromatography / tandem mass spectrometry and non-compartmental techniques were used to calculate the area under the concentration-time curve (AUC). The effect of individual genotypes and inferred NAT2 acetylator phenotype on isoniazid and rifampicin exposure was assessed by multivariate linear regression.

Results: Plasma AUCs for isoniazid and rifampicin varied up to 20-fold between patients, despite weight adjusted dosing. Fast NAT2 acetylator phenotype (by a 6-SNP panel or single rs1495741 tag-SNP) was associated with

a significant reduction in isoniazid exposure ($P < 0.05$). The tag-SNP was in a linkage disequilibrium block with the 6 NAT2 SNPs assessed ($D' = 0.62$). However, genetic variability at either of two SNPs of the SLCO1B1 gene did not explain any of the variability in rifampicin AUCs. This contrasts with other sub-Saharan African studies, in which variant alleles on rs4149032 significantly reduced rifampicin exposure. Rs4149032 variant allele frequency was also much lower (0.32) in this Malawian population than previously described from South Africa (0.70). AADAC and CES1 SNPs did not explain inter-individual variability in AUCs for either drug.

Conclusion: The finding that assignment of NAT2 phenotype by a single tag-SNP is associated with isoniazid exposure may be used to simplify future genomic analysis of clinical pharmacology studies. The absence of a relationship between SLCO1B1 mutations and inter-individual rifampicin variability in Malawi suggests that pharmacogenetic determinants of rifampicin exposure may vary between African populations.

OA-423-05 Assessment of the sustained anti-tuberculosis activity of clofazimine after stopping treatment in mice

R Swanson,^{1,2} N Ammerman,^{1,3} J Adamson,¹ C Moodley,¹ A Dorasamy,¹ S Modley,¹ L Bester,⁴ J Grosset^{1,3} ¹KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, ²University of KwaZulu-Natal, Durban, South Africa; ³Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁴University of KwaZulu-Natal, Westville, South Africa. e-mail: nicole.ammerman@gmail.com

Background: In recent years, the anti-leprosy drug clofazimine has shown promising activity for the treatment of tuberculosis (TB), having demonstrated both potent bactericidal and treatment-shortening activity in different experimental models and in patients. Clofazimine has peculiar pharmacokinetic and pharmacodynamic properties, including a very long half-life, massive accumulation in tissues and lack of early bactericidal activity. Interestingly, clofazimine can remain in the body for weeks after stopping treatment at levels above the minimum inhibitory concentration (MIC) for *Mycobacterium tuberculosis*. Based on this, we hypothesized that clofazimine contributes sustained antimicrobial activity after the cessation of TB treatment. **Design/Methods:** To address our hypothesis, we conducted an experimental chemotherapy study in a mouse model of TB. BALB/c mice were aerosol-infected with *M. tuberculosis* and treated with the first-line anti-TB drug regimen with or without clofazimine for 1 or 2 months. After stopping treatment, sustained antimicrobial activity was evaluated by monitoring bacterial re-growth in the lungs and spleen up to 8 weeks post-treatment. The clofazimine concentration in the serum, lungs and spleen was determined at each time point.

Results: Clofazimine levels in the serum remained above the MIC for *M. tuberculosis* for 2 or 4 weeks after stopping treatment that was administered for 1 or 2 months, respectively. In mice treated with the clofazimine-containing regimen, the bacterial regrowth in the

tissues was delayed for at least 2 or 4 weeks after stopping the 1- or 2-month treatment regimens, respectively. In mice that did not receive clofazimine, bacterial regrowth began immediately after stopping treatment.

Conclusion: Clofazimine does contribute antimicrobial activity after treatment cessation. This is likely due to the constant release of bound clofazimine from the tissues into the serum, where free clofazimine can exert antimicrobial activity. Thus clofazimine's unusual pharmacokinetics may in fact be beneficial features of the drug, although more work is needed to optimize both the dose and duration of its use in TB treatment.

OA-424-05 Pharmacokinetics of first-line anti-tuberculosis drugs in children with tuberculosis with and without HIV coinfection

A Kwara,^{1,2} A Enimil,^{3,4} H Yang,⁵ F Gallani,^{1,2} A Dompok,³ A Orstin,³ L Wiesner,⁶ S Antwi^{3,4} ¹The Miriam Hospital, Providence, RI, ²Warren Alpert Medical School of Brown University, Providence, RI, USA; ³Komfo Anokye Teaching Hospital, Kumasi, ⁴Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; ⁵University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; ⁶University of Cape Town, Cape Town, South Africa. Fax: (+1) 401 793 4704. e-mail: akwara@lifespan.org

Background: Given the concern that the high frequency of low plasma peak concentration (C_{max}) of the antituberculosis (anti-TB) drugs among children may be associated with poor treatment outcomes, the World Health Organization (WHO) recently recommended higher dosages of the first-line anti-TB drugs for children. We investigated the pharmacokinetics (PK) of the first-line anti-TB drugs in children who were mostly prescribed revised dosages.

Design/Methods: Children aged 3 months to 14 years old with tuberculosis on first-line therapy for at least 4 weeks had blood samples collected at pre-dose, 1, 2, 4, and 8 hours post-dose. Drug concentrations were determined by validated liquid chromatography mass spectrometry methods and PK parameters calculated using noncompartmental analysis. Factors associated with C_{max} below the target range of each drug were examined using univariate and multivariate analyses.

Results: Of the 62 children, 32 (51.6%) were male, 29 (46.8%) were younger than 5 years old and 28 (45.2%) had HIV coinfection. The median (IQR) plasma C_{max} was 4.8 (3.7–6.4) µg/mL for isoniazid, 6.3 (3.5–8.8) µg/mL for rifampin, 28.6 (21.8–35.6) µg/mL for pyrazinamide and 1.9 (0.9–3.1) µg/mL for ethambutol. Compared with published therapeutic ranges, low plasma C_{max} was observed in 10/62 (16.1%), 40/62 (64.5%), 10/59 (16.9%) and 30/59 (50.8%) for isoniazid, rifampin, pyrazinamide and ethambutol, respectively. None of the factors evaluated significantly influenced isoniazid C_{max}. Lower rifampin dose was associated with rifampin C_{max} < 8 µg/mL. Younger age, lower body weight, shorter height, lower weight-for-age z-score, lower height-for-age z-score, and smaller head circumference were associated with pyrazinamide C_{max} < 20

µg/mL and ethambutol C_{max} < 2 µg/mL. Children with HIV coinfection were also more likely to have low ethambutol C_{max}. In the multivariate analysis, younger age (odds ratio, 1.23; *P* = 0.023) and lower rifampin dose (odds ratio, 1.28; *P* = 0.004) were associated with low rifampin C_{max}. Shorter height (odds ratio, 1.05; *P* = 0.011) was associated with low pyrazinamide C_{max}. Shorter height (odds ratio, 1.04; *P* = 0.009) was associated with low ethambutol C_{max}.

Conclusion: Despite the use of revised drug dosages, low rifampin and ethambutol C_{max} were common among Ghanaian children with TB. These findings suggest that higher rifampin and ethambutol dosages than currently recommended are needed to achieve target C_{max} in children.

OA-425-05 Tuberculosis among individuals presenting with community-acquired pneumonia to an emergency room at a referral hospital in Gaborone, Botswana

J Gersh,¹ Z Feldman,² E Greenberger,¹ H Friedman,^{3,4} A Chandra,⁵ T Lere,⁶ M Haas,^{3,4,7,8} A Ho-Foster^{3,4} ¹University of Washington, Seattle, WA, ²University of Colorado, Boulder, CO, USA; ³Botswana U Penn Partnership, Gaborone, Botswana; ⁴University of Pennsylvania, Philadelphia, PA, USA; ⁵University of Botswana, Gaborone, ⁶Ministry of Health, Gaborone, Botswana, ⁷University of Colorado, Denver, CO, ⁸Denver Public Health, Denver, CO, USA. e-mail: jillgersh@gmail.com

Background: Delays in diagnosing Tuberculosis (TB) are associated with increased transmission and worsened outcomes. Overlap in the clinical presentation of TB with conditions such as community-acquired pneumonia (CAP) can contribute to diagnostic delays. Identifying opportunities to diagnose TB earlier has the potential to improve outcomes. Our primary objective was to determine the frequency of TB among patients presenting with CAP at a large referral hospital in Gaborone, Botswana.

Methods: We performed a retrospective cohort study of adults presenting with confirmed (defined as new chest radiograph findings) or presumed (no chest radiograph obtained) CAP from April 2010–October 2011 to the Emergency Department (ED). This cohort was matched to the National Botswana Tuberculosis Registry to identify individuals subsequently diagnosed with TB. We assessed demographic characteristics, time to TB diagnosis, clinical outcomes and performed logistic regressions to identify factors associated with a diagnosis of TB.

Results: We identified 1305 individuals presenting with CAP and of those, TB was subsequently diagnosed in 64 (4.9%). 63% (*n* = 40) were diagnosed with TB within 15 days of their presentation for CAP and 88% (*n* = 56) presented within 90 days. The median time to TB diagnosis after CAP presentation was 11 days (IQR 5–43 days). 39% were AFB sputum smear positive, 27% were smear negative and 34% were unknown. 48% of those later diagnosed with TB were admitted to the hospital, compared to 56% without TB (*P* = 0.286). HIV

status could be determined in 84% of those with TB compared to 68% of those without TB ($P = 0.005$). Of these, 87% were HIV-TB and 87% were HIV positive without TB ($P = 0.94$). There were no differences in vital signs, respiratory symptoms, weight loss, night sweats, or history of TB. Older individuals were significantly less likely to be diagnosed with TB within 90 days [OR for one year increase in age 0.977, 95%CI (0.957, 0.997)]. Individuals with known HIV status were more likely to be diagnosed with TB in 90 days than those with unknown HIV status [OR 3.36, 95%CI (1.51, 7.48)].

Conclusion: Subsequent presentation with TB is common among individuals presenting with CAP at our ED, suggesting that TB may be present at the time of CAP presentation. Given the lack of distinguishing clinical factors between pulmonary TB and CAP, all adults presenting with CAP should be evaluated for active TB in Botswana.

OA-426-05 Rapid turnaround leads to better care: designing country solutions for effective data exchange

J Takle¹ ¹Global Connectivity, Inc., Boston, MA, USA. e-mail: jeff.takle@globalconnectivity.co

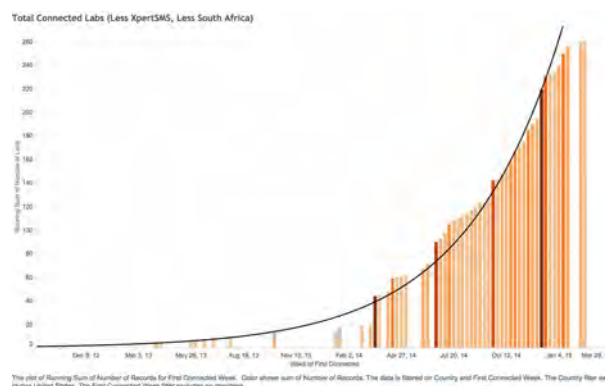
Background and challenges to implementation: Historically, lab services have been a major bottleneck due to slow information transfer from the labs to the broader healthcare system. Connectivity solutions for the GeneXpert and other diagnostic devices hold the potential to exchange diagnostic data directly into the health system within a few seconds of diagnosis, rather than days or weeks later, and studies suggest this rapid turnaround of data leads to higher enrollment rates onto care. Implementation poses new challenges with management of modems, SIMs, data plans, and related services. Challenges persist with inconsistent power and network availability, and limited computer skills.

Intervention or response: Solutions for connectivity emerged from 2012-2015 that enable the GeneXpert® and devices from Alere, Abbott, and others to rapidly transmit results. They rely on simple USB modems and SMS/2G/3G networks to move information and have largely been designed to operate in the developing world context. These systems can exchange results into EMRs, LMIS, and other databases. They can auto-alert patients and doctors via SMS text when results are ready; they can auto-populate the existing Excel-based reports used by NTLPs, donors, and projects; and, they enable alerts when machines exceed acceptable error rates. Connectivity decisions are increasingly made at the NTLP level, which streamlines implementation and enables more efficient procurement, cartridge management, and module replacement.

Results and lessons learnt: Connectivity solutions are in place today at over 500 labs in 23 countries, covering >5 million patient results, and those networks continue to grow rapidly. More than 100 000 text message alerts are helping enroll patients into appropriate care. Errors are measured and error rates are dropping as a result. Data is

being exchanged more freely from labs to many health information systems. Lessons: Plan and implement at the national level. Connectivity presents immediate results and reduces commodity waste.

Conclusions and key recommendations: In addition to improving the linkage to care, this approach demonstrates an ability to reduce diagnostic errors and stock-outs, yielding considerable return on investment for a relatively modest investment in connectivity. Donors and MOHs should consider building connectivity into implementation plans.



This plot of Running Sum of Number of Records for First Connected Week. Color shows sum of Number of Records. The data is stored on Country and First Connected Week. The Country filter is set to United States. The First Connected Week filter excludes no reports.

17. TB & NCD co-morbidity

OA-427-05 Glycemic control and risk of tuberculosis among diabetic patients: a cohort study

P-H Lee,¹ H Fu,² T Lai,³ H-H Lin² ¹Centers for Disease Control, Taipei, ²Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, ³Department of Medical Research, Mennonite Christian Hospital, Hualien, Taiwan. e-mail: leepinhui@gmail.com

Background: Diabetes increases the risk of developing active tuberculosis (TB). However, it remains unclear whether improving glycemic control in diabetic patients could lower the risk among these populations.

Methods: We conducted a cohort study of participants from the community-based integrated health screening survey in northern Taiwan from 2005 to 2008. The baseline information of demographics, behavioral risk factors, and fasting plasma glucose was obtained from the survey. The baseline status of diabetes was determined through linking the health survey database to the national health insurance database using the individual unique identifier. Diabetes was defined by the prescription of oral hypoglycemic agents or insulin for more than 28 days. The cohort was followed up for the development of active tuberculosis, which was defined by the presence of TB-related ICD-9-CM code (010-018) plus the prescription of ≥ 2 anti-TB drugs for 28 days or longer. We divided the population into three groups based on diabetes status and the level of glycemic

control: (1) no diabetes, (2) diabetes with good control: fasting plasma glucose ≤ 130 mg/dL, and (3) diabetes with poor control: fasting plasma glucose >130 mg/dL. We used Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between different glycemic control group and incident TB.

Results: Among the 116 893 eligible participants, 388 incident TB cases developed during follow-up. The TB incidence per 100 000 person-years was 68.6 (95%CI: 68.6–83.7) in those without diabetes, 106.6 (50.8–162.5) in diabetic patients with good control, and 169.9 (125.4–214.4) in diabetic patients with poor control. After adjusting for age, sex, tobacco smoking, alcohol use, body mass index, frequency of outpatient visit utilization, and medical comorbidities, we found that diabetic patients with poor control had significantly increased risk of TB (adjusted HR=1.80, 95%CI: 1.34–2.40) than those without diabetes. On the other hand, good glycemic control in diabetic patients lowered the risk of TB (adjusted HR=0.85 compared with non-diabetic individuals, 95%CI: 0.50–1.47).

Conclusions: Fasting plasma glucose predicted the risk of TB regardless of diabetes status. Good glycemic control could potentially reverse the risk of TB among diabetic patients.

OA-428-05 Screening for diabetes mellitus in tuberculosis patients: who should be prioritized?

R Koesoemadinata,¹ S Mcallister,² N Rahmadika,¹ P Santoso,¹ R Ruslami,¹ P Hill,² R Van Crevel,³ B. Alisjahbana¹ ¹Faculty of Medicine Universitas Padjadjaran, Bandung, Indonesia; ²University of Otago, Dunedin, New Zealand; ³Radboud University, Nijmegen, Netherlands. e-mail: craspati@yahoo.com

Background: Diabetes Mellitus (DM) is a known risk factor for tuberculosis (TB) disease and also treatment failure of TB. Screening for DM among TB has been recommended by The WHO. However, in resource limited settings, screening may not be feasible for every TB patient. This study aims to define characteristics of TB patients that have a greater association with DM to allow for more directed screening.

Design/Methods: As part of the TANDEM program (www.tandem-fp7.eu) on TB and DM in different countries, a cross sectional study was done between February–December 2014. Presumptive TB cases were recruited from DOTS Clinic in Hasan Sadikin Hospital and 30 Primary Health Clinics in Bandung City, Indonesia. Patients underwent history taking, physical examination, chest X-ray, and sputum examination for smear and culture for *Mycobacterium tuberculosis*. Those who were found to have active pulmonary TB were eligible for inclusion and screened for DM using a structured questionnaire and laboratory HbA1c test. Patients without history of DM with two laboratory HbA1c results $>6.5\%$ were defined as definite DM, while for patients with history of DM, laboratory HbA1c test only done once and their DM medication were

recorded. We analyzed data collected using Chi-square test and independent T-test (mean comparison test).

Results: From a total of 253 eligible TB patients screened for DM, we found 52 (20.6%) with TB-DM, of whom, 41 (78.8%) were previously known DM and 11 (21.2%) were newly diagnosed. TB-DM patients were significantly older than TB-only patients (mean 51.2 vs. 38.8 years; $P < 0.001$), had a higher mean body mass index (BMI) (22.2 vs. 18.1; $P < 0.001$) and were more likely to have hypertension (30.1% vs. 6.0% $P < 0.001$). However, fewer TB-DM patients presented with anemia (55.1% vs. 72.5% $P = 0.018$). GeneXpert® MTB/RIF was examined in 6 TB-DM patients and 21 TB-only patients. Rifampicin resistance was found to be higher in TB-DM patients (33.3% vs. 19.1%; $P = 0.46$), but not statistically significant.

Conclusion: There was a greater proportion of known DM found, therefore physicians should be recommended to ask history of DM to every TB patients. Screening for DM should be prioritized for pulmonary TB patients who are older, have higher BMI, non-anemic, and with hypertension prior to the treatment of TB.

OA-429-05 High burdens of medical co-morbidity and drug toxicity on the Category II retreatment regimen in Malawi

D Cohen,^{1,2} K Mbendera,³ W Malwafu,⁴ S Greenwood,⁵ E Joekees,^{2,5} L Corbett,^{1,6} G R Davies,⁷ S B Squire² ¹Malawi Liverpool Wellcome Clinical Research Programme, Blantyre, Malawi; ²Liverpool School of Tropical Medicine, Liverpool, UK; ³Malawi National Tuberculosis Control Program, Lilongwe, ⁴College of Medicine, University of Malawi, Blantyre, Malawi; ⁵Royal Liverpool University Hospital, Liverpool, ⁶London School of Tropical Medicine & Hygiene, London, ⁷University of Liverpool, Liverpool, UK. e-mail: danbcohen@yahoo.com

Background: The WHO category II retreatment regimen is widely used but poorly evaluated. Data are lacking about the safety of the drug regimen, and outcomes are consistently reported to be poor with treatment success rates varying from 27–83%. However, reasons for poor clinical outcomes are unclear particularly in settings where the prevalence of drug resistance is low. The aim of this study was to investigate if any clinical factors are associated with unsuccessful outcome in patients being retreated for TB.

Design/Methods: A prospective cohort of patients starting standard WHO Category II retreatment regimen was recruited at a central hospital in Blantyre, Malawi. Patients were evaluated for respiratory co-morbidity (CT thorax and pulmonary function testing); anaemia; renal impairment; diabetes; and ART failure. Systematic screening for drug toxicity included baseline and month-2 audiology, renal function, and clinical evaluation.

Results: Of the 158 patients who were recruited, 57% had TB confirmed on sputum smear, culture or GXP. The prevalence of medical co-morbidities was high: 131/158 (83%) of patients were HIV positive, of whom 96 (73%) were already on ART. Of the 63 patients on ART for

>year, 24 (38%) had an HIV viral load >5000 copies/ml. Chronic lung disease was found in 88% on CT thorax, including scarring in 80%, bronchiectasis in 61%, COPD in 22%, and destroyed lung in 19%. Spirometry revealed restrictive deficit (FVC <80% predicted) in 60%, and obstructive deficit (FEV1 <70% predicted) in 7% of patients. Anaemia (Hb <10g/dL) and renal impairment (CrCl <90%) were also common (34% and 45% respectively). Only 3% had HbA1C >6.5%. During the first 2 months of treatment ototoxicity (change of ≥ 10 db at 2 frequencies or ≥ 20 db at 1 frequency) was seen in 32%. Nephrotoxicity (25% decrease in CrCl or 1.5 fold increase in Cr) was seen in 15%. The rate of self-reported peripheral neuropathy was 40%. Drug induced liver injury developed in 4%, and 1 patient had rash requiring treatment interruption. **Conclusion:** The burdens of co-morbidity and drug toxicity in this cohort of patients on Category II regimen were extremely high. If outcomes are to be improved in TB retreatment, there is an urgent need to address the impact of other co-morbid medical conditions including chronic lung disease and ART failure, and the serious toxicities associated with treatment such as renal injury and ototoxicity.

OA-430-05 Tuberculosis and diabetes in Southern Uganda

S Annette¹ ¹RESEARCH, Mulago-Mbarara Teaching Hospital, Kampala, Uganda. e-mail: daizyjulian@yahoo.com

Background: To determine the impact of diabetes on the rates of tuberculosis in a region where both diseases are prevalent.

Design/Methods: Data from a population-based cohort of patients with pulmonary tuberculosis undergoing clinical and mycobacteriologic evaluation (isolation, identification, drug-susceptibility testing, and IS6110-based genotyping and spoligotyping) were linked to the 2010 National Health Survey (ENSA2010), a national probabilistic, polystage, stratified, cluster household survey of the civilian, noninstitutionalized population of Uganda.

Results: From March 2010 to March 2012, 581 patients with *Mycobacterium tuberculosis* culture and fingerprint were diagnosed, 29.6% of whom had been diagnosed previously with diabetes by a physician. According to the ENSA2010, the estimated prevalence of diabetes in the study area was 5.3% (95%CI 4.1–6.5). The estimated rates of tuberculosis for the study area were greater for patients with diabetes than for nondiabetic individuals (209.5 vs. 30.7 per 100 000 person-years, $P < 0.0001$).

Conclusion: In this setting, the rate of tuberculosis was increased 6.8-fold (95%CI 5.7–8.2, $P < 0.0001$) in patients with diabetes due to increases in both reactivated and recently transmitted infection. Comorbidity with diabetes may increase tuberculosis rates as much as coinfection with human immunodeficiency virus (HIV), with important implications for the allocation of health care resources.

OA-431-05 Diabetes in patients with tuberculosis in Africa: to test or not to test?

N Boillat Blanco,^{1,2,3} L T Minja,³ C Schindler,¹ R Kaushik,⁴ S Gagneux,¹ C Daubenberger,¹ K Reither,¹

N Probst-Hensch¹ ¹Swiss Tropical and Public Health Institute, Basel, ²University and University Hospital, Lausanne, Switzerland; ³Ifakara Health Institute, Dar Es Salaam, ⁴Hindu Mandal Hospital, Dar Es Salaam, Tanzania. e-mail: noemie.boillat@chuv.ch

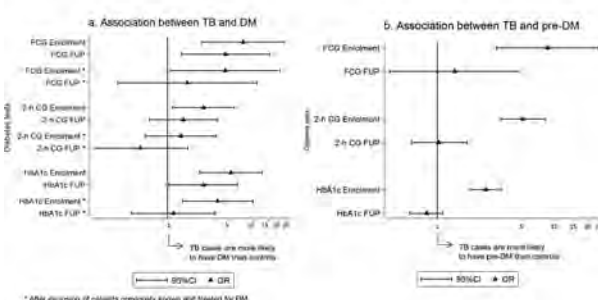
Background: Diabetes mellitus (DM) increases the risk of active tuberculosis (TB) while, on the other side, TB, as an infectious disease, tends to lead to hyperglycemia. It is therefore important to identify DM in TB patients but the most efficient algorithm for DM screening among TB patients, particularly in low resource settings, has to be established. We prospectively compared healthy controls with new TB patients over 5 months follow-up using the 3 recommended DM screening strategies in Dar es Salaam, Tanzania.

Design/Methods: Consecutively recruited adults with new active TB were included in a longitudinal case-control study between July 2012 and June 2014. Healthy volunteers matched to TB patients for sex and age, free of acute infection and without past history of TB, were enrolled in the same recruitment area. Screening for HIV was done at enrolment. All participants underwent three tests for the diagnosis of DM (fasting capillary glucose (FCG), 2-hours capillary glucose (2h-CG) and glycated hemoglobin (HbA1c; Roche Cobas Integra)) at enrolment and after at least five months of TB treatment. The association between TB and DM was assessed using logistic regression after adjustment for age, HIV status and socioeconomic status.

Results: Overall, 539 TB patients and 496 healthy controls were included. At enrolment, DM prevalence was significantly higher in TB cases compared to controls using any DM diagnostic test and irrespective of HIV status (Figure). None of the patients newly diagnosed with DM was treated. A significant association between newly diagnosed DM and TB was no longer found after 5 months of TB treatment with any of the screening tests (enrolment vs. follow up (adjusted (a)OR(95%CI): FCG 4.7(1.1-20.7) vs. 1.7(0.3-11); 2-h CG 1.42(0.6-3.7) vs. 0.5(0.1-1.7); HbA1c 3.9(1.5-10) vs. 1.2(0.4-3.6)) (Figure). DM and pre-DM diagnosed at enrolment with FCG and 2-h CG were associated with adverse TB outcome (lost to follow up-death-failure), aOR (95%CI) 2.3(1-4.9) and 2.3(1.2-4.3), respectively.

Conclusion: In this African setting with low DM prevalence, hyperglycemia seems to be the result rather than the cause of TB, as it was no longer present after 5 months of TB treatment. While screening for an underlying DM, particularly with HbA1c, at the time of TB diagnosis has no clinical utility, testing for the presence of transient hyperglycemia with FCG may be relevant for the success of TB treatment.

Figure. Longitudinal evolution of the association between a.) tuberculosis and diabetes and b.) tuberculosis and pre-diabetes, adjusted for age, HIV status and socioeconomic status.
Abbreviations: DM: diabetes mellitus; TB: tuberculosis; FUP: follow-up; FCG: fasting capillary glucose; 2-h CG: 2-hours capillary glucose; HbA1c: glycated hemoglobin.



OA-432-05 Sputum culture conversion of diabetes/tuberculosis patients compared to age, sex and disease-matched patients without diabetes in Virginia

S Heysell,¹ D Staley,² D Dodge,² S Keller,² E Houpt,¹ J Moore² ¹University of Virginia, Charlottesville, VA, ²Virginia Department of Health, Richmond, VA, USA. e-mail: scott.heysell@gmail.com

Background: Diabetes (DM) complicates TB treatment including a prolonged time to sputum culture conversion and increased risk of death compared to non-DM/TB patients. Since 2013 in Virginia, recommendations have been in place to perform early therapeutic drug monitoring and dose correction for isoniazid and rifampin after 2 weeks of therapy for DM/TB patients. Further effort has been made to screen those without known DM by HgbA1c.

Methods: A retrospective study of the state TB registry was performed for patients initiating treatment in 2013-2014. DM/TB patients undergoing early TDM were compared to non-DM/TB patients by 1:1 matching on age (± 10 years), gender and sputum smear status. Subjects were included if their pretreatment sputum culture was positive and excluded if they had extrapulmonary TB, other immunosuppressing conditions, HgbA1c $\geq 6.5\%$ (if not previously known to have DM), or any first-line drug resistance. DM/TB and matched non-DM/TB patients were then assessed for the time to sputum culture conversion.

Results: 373 patients started treatment, of which 60 were DM/TB. 19 DM/TB patients met study criteria, including 10 (53%) men and 16 (84%) smear positive, and were compared to 19 matched non-DM/TB patients. DM/TB patients mean age was 61.5 years [± 13.6] compared to non-DM/TB controls of 58.7 [± 15.7] ($P = 0.57$). In DM/TB, the isoniazid mean C2hr (daily dosing) was 2.5 $\mu\text{g/ml}$ [± 1.8] and 12 (66%) were in range for dose increase, rifampin mean C2hr was 8.4 $\mu\text{g/ml}$ [± 6.8] and 8 (47%) in range for dose increase, and rifabutin C2hr of 0.57 $\mu\text{g/ml}$ in one subject (within the expected range thus no dose increase). Mean time to sputum culture conversion in DM/TB patients was 36.0 days [± 21.9] compared to non-DM/TB of 58.8 days

[± 34.6] ($P = 0.02$), despite the majority of DM/TB having cavitory disease.

Conclusions: Early therapeutic drug monitoring for DM/TB may shorten the time to sputum culture conversion compared to age, gender and disease matched non-DM/TB patients. These findings warrant further controlled study.

OA-433-05 Associations between tuberculosis and hyperglycaemia in Zambia, Southern Africa

S L Bailey,^{1,2} S Floyd,^{2,3} J Yudkin,⁴ P Godfrey-Faussett,² H Ayles^{1,2} ¹Zambart, Lusaka, Zambia, ²LSHTM TB Centre and Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, ³LSHTM TB Centre and Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, ⁴University College London, London, UK. e-mail: slbailey@doctors.org.uk

Background: Hyperglycaemia is known to be associated with active tuberculosis (TB), though to date few relevant studies have originated from Southern Africa. The strength of the association may differ in Southern Africa due to high HIV prevalence and a high prevalence of poorly-controlled diabetes mellitus (DM). A set of studies in Lusaka, Zambia aim to determine the association between hyperglycaemia and active TB in this location; determine if HIV modifies this association; determine the contributions of DM and stress-induced hyperglycaemia to hyperglycaemia among newly-diagnosed TB cases, and determine the diagnostic accuracy for DM of measures of hyperglycaemia used at the time of TB diagnosis compared to a gold standard.

Methods: A case-control study among adult TB cases and population controls in Lusaka defines active TB disease as the outcome and hyperglycaemia (random blood glucose (RBG) $\geq 11.1\text{mmol/L}$) as the exposure of interest. HIV status is defined by serological result. Multivariable logistic regression is used to explore associations. A study of diagnostic accuracy compares RBG, fasting blood glucose (FBG) and glycated haemoglobin (HbA1c) measured at the time of TB diagnosis to the gold standard for DM diagnosis, defined as FBG measured 12 weeks after TB treatment commencement, after stabilisation of TB disease.

Results: The prevalence of hyperglycaemia among 3131 TB cases was 1.3% and among 6977 controls was 1.5%. Overall, the adjusted odds of active TB was 1.42 (95%CI 0.78-2.58) times higher among those with hyperglycaemia compared to those without. The corresponding adjusted odds ratio among those with HIV was 5.34 (95%CI 1.21-23.62, $P = 0.03$) and among those without HIV was 1.00 (95%CI 0.49-2.02). Among 362 participants of the diagnostic accuracy study, only 46%, 50% and 38% of those with hyperglycaemia measured by RBG, FBG and HbA1c respectively at the time of TB diagnosis were confirmed to have DM. RBG, FBG and HbA1c showed similar test sensitivity, specificity and positive and negative predictive values for the diagnosis of DM at the time of TB diagnosis.

Conclusions: Overall, no evidence of association between hyperglycaemia and active TB was found in this study population, though among those with HIV there was strong evidence of an association. A relatively low proportion of hyperglycaemia measured at the time of TB diagnosis was due to DM. HbA1c showed no greater test accuracy for DM diagnosis at the time of TB diagnosis than FBG or RBG.

OA-434-05 Exploring the association between TB and diabetes

F Pearson,¹ M Pearce,² R McNally,² N Unwin,³ J Critchley¹
¹St Georges University of London, London, ²Newcastle University, Newcastle-Upon-Tyne, UK; ³University of West Indies, Cave Hill, Barbados. e-mail: fpearson@sgul.ac.uk

Background: Many studies have found an increased risk of PTB amongst those with Diabetes Mellitus (DM), however, evidence on whether the association is specific to disease sub-types or is bi-directional remains sparse. This study assesses rates of TB, PTB and EPTB amongst those with DM, Type 1 DM (T1DM) and Type 2 DM (T2DM) comparative to those without. It also assesses the converse (DM rates among those with prior TB episodes) to investigate association bi-directionality.

Methods: Retrospective cohort analyses were completed using UK primary care data collated prospectively between 2003 and 2009 in The Health Improvement Network database. Individuals in the dataset were classified as either exposed to or unexposed to TB, PTB, EPTB, DM, T1DM or T2DM. The incidence rate ratio (IRR) and 95% confidence intervals (95% CI) were then calculated amongst each exposure group for outcomes of interest (TB, PTB, EPTB or DM, T1DM, T2DM) using negative binomial regression.

Results: TB risk was raised amongst individuals with DM (IRR 1.50 (95%CI 1.27-1.76) P value < 0.001), T1DM (IRR 1.46 (95%CI 1.10-1.92) P -value 0.008) or T2DM (IRR 1.54 (95%CI 1.30-1.82) P value < 0.001) compared to those without. The risk of EPTB amongst those with T1DM was also increased compared to those without (IRR 2.09 (95%CI 1.19-3.66), P value 0.010). DM risk was raised amongst those who had a prior episode of TB (IRR 5.65 (95%CI 5.19-6.16) P value < 0.001), PTB (IRR 5.74 (95%CI 5.08-6.50) P value < 0.001) or EPTB (IRR 4.66 (95%CI 3.94-5.51) P value < 0.001) compared to those with no TB history. T1DM risk was raised amongst those with prior TB (any sub-type) (IRR 5.49 (95%CI 5.02-6.02) P value < 0.001) or EPTB (IRR 0.84 (95%CI 0.35-2.03) P value < 0.001) compared to those with no TB history. T2DM risk was raised amongst those who had prior TB (IRR 2.21 (95%CI 1.68-2.91) P value < 0.001), PTB (IRR 5.38 (95%CI 4.73-6.12) P value < 0.001) or EPTB (IRR 4.36 (95%CI 3.65-5.22) P value < 0.001) compared to those with no TB history.

Discussion TB risk was increased in those with DM and DM risk raised substantially amongst those who had a prior TB episode. We are not aware of other studies with sufficient power to assess the risk of DM among those

with prior TB. As DM prevalence increases, consideration of the specificity and directionality of these associations will become important to improve disease control and TB treatment outcomes amongst those with co-morbid disease.

18. TB in children: diagnosis, prevention and best practice

OA-435-05 Underdetection of TB exposure among children admitted to a tertiary hospital in Botswana

T David,^{1,2} A Steenhoff,^{1,3,4,5} L Mazhani,¹ A Ho-Foster,^{3,4} T Mazhani,^{1,2} T Arscott-Mills^{3,5,4} ¹University of Botswana, Gaborone, ²Botswana Ministry of Health, Gaborone, ³Botswana-U Penn Partnership, Gaborone, Botswana; ⁴University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, ⁵The Children's Hospital of Philadelphia, Philadelphia, PA, USA. e-mail: pascaldav@yahoo.co.uk

Background: In a high tuberculosis (TB) setting, such as Botswana, an important risk factor to assess in each child is whether they have a "TB contact" at home. We aimed to determine the proportion of TB exposure detection by clinicians as compared to the study team, in children admitted to Princess Marina Hospital (PMH), in Gaborone Botswana. In secondary analysis, we sought to determine the difference between TB exposure detection in two time periods – the pre-intervention and post-intervention phases of the study.

Design/Methods: This was a single center, prospective cross sectional study. Participants were children (0-13 years) admitted to pediatric medical, surgical or any neonatal ward at PMH during the pre-intervention and the post-intervention phases of the study. The intervention was a feedback session to clinicians which gave them results of their TB exposure direction compared to the study and an educational handout describing how to adequately assess TB exposure. An investigator interviewed caregivers using a standardized form to determine whether a child had been exposed to a TB contact. To determine TB exposure detection in "by clinicians", the investigator then reviewed the child's in-hospital medical record to assess whether a TB household exposure was recorded in the medical records. The proportion of TB exposure detected was compared between "clinicians" and the study team using McNemar's chi2 test for proportions.

Results: A total of 736 (81%) and 170 (19%) participants were enrolled in the pre and post-intervention phases respectively. Overall, the study detected TB exposure in 39/906 (4%) of participants compared to 15/906 (1.7%) by clinicians, P < 0.001. Pre-intervention, TB exposure was detected in 22/736 (3.0%) participants by the study compared to 6/736 (0.9%) by clinicians (P < 0.0001); a 3-fold difference. Post-intervention, TB exposure was detected in 17/170 (10%) participants by the study compared to 9/170 (5%) by clinicians (P = 0.005); a 2-fold difference.

Conclusion: TB exposure detection was lower in clinicians in both phases of the study confirming that this important exposure is being missed in this setting. TB exposure detection may be improved by implementing standardized tools such as was used by the study team to screen for TB.

OA-436-05 Focused Point-of-Care Ultrasound (FASH) for diagnosis of childhood tuberculosis

S B  lard,^{1,2,3} E Banderker,⁴ W Isaacs,³ L Bateman,³ J Munro,³ T Heller,² M Grobusch,² H Zar³

¹Charit  -Universit  tsmedizin Berlin, Berlin, Germany;

²Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands; ³Red Cross War Memorial Children's Hospital, and MRC Unit on Child & Adolescent Health, Cape Town, ⁴Red Cross War Memorial Children's Hospital, Cape Town, South Africa. e-mail: sabinebelard@yahoo.de

Background: Pulmonary tuberculosis (PTB) is the commonest presentation of TB disease in children. The incidence of extrapulmonary disease (EPTB) in children presenting with symptoms of PTB has not been well studied. This study aimed to investigate focused point-of-care ultrasound for diagnosis of EPTB (FASH) in children presenting with suspected PTB.

Design/Methods: Children with suspected PTB enrolled into a prospective cohort study of novel diagnostics in Cape Town, South Africa, underwent a clinician-performed FASH examination to detect pericardial, pleural or ascitic effusion, abdominal lymphadenopathy, or focal hepatic or splenic lesions. Ultrasound scans were reviewed by a senior pediatric radiologist. Children were categorized as confirmed TB (microbiologically diagnosed), possible TB (clinical diagnosis only) or NOT TB (improvement on follow-up in the absence of TB treatment). The primary objective was to describe FASH findings of EPTB. Funding: NIH RO1 HD058971, MRC South Africa.

Results: 125 enrolled children with suspected PTB underwent FASH; of these 34 (27%), 70 (56%) and 21 (17%) had confirmed, possible, and no TB, respectively; 23 (18%) children were HIV-infected and the median age was 43 months (IQR 21; 88). Agreement on the sonographic diagnosis between the clinician performing FASH and the radiologist reviewing the scans was 97%. On presentation 38 (30%) children had at least one FASH finding compatible with active EPTB; 5 (4%) children had multiple FASH findings. Within the confirmed, possible and NO TB categories, 10/34 (29%), 25/70 (36%), and 3/21 (14%) children had at least one FASH finding, respectively. The presence of FASH findings was lower in HIV-infected compared to HIV-uninfected children (4/23 (17%) versus 34/102 (33%), respectively). Pleural effusion was most common (20 (16%)), followed by abdominal lymphadenopathy (15 (12%)), pericardial effusion (7 (6%)), focal splenic lesions or ascites (4 (3%)), each, and focal hepatic lesions (1 (<1%)).

Conclusion: Around a third of children with confirmed or possible PTB had sonographic features of EPTB.

FASH is a promising, quick, non-invasive, radiation-free imaging tool for visualizing features of EPTB at the point-of-care with potential to improve diagnosis and management of childhood TB.

OA-437-05 Piloting upfront Xpert   MTB/RIF testing on various specimens under programmatic conditions for the diagnosis of TB and DR-TB in a paediatric population

N Raizada,¹ K S Sachdeva,² S Swaminathan,³

A Sreenivas,⁴ S Kulsange,¹ C Boehme,¹ C Paramasivan¹

¹FIND, Geneva, Switzerland; ²Central TB Division, New Delhi,

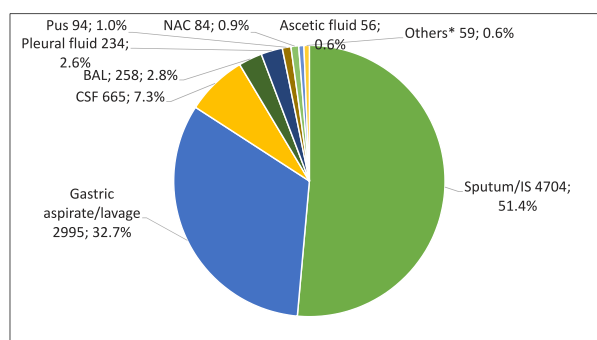
³NIRT, Chennai, ⁴WHO, New Delhi, India. e-mail:

drneerajraizada@gmail.com

Background: India accounts for one-fifth of the global (Tuberculosis) TB incidence. While the exact burden of childhood TB is not known, TB remains one of the leading causes of childhood mortality in India. Bacteriological confirmation of TB in children is challenging due to difficulty in obtaining quality specimens, in the absence of which diagnosis is largely based on clinical judgement. Xpert   MTB/RIF (here after referred as Xpert), a tool with a quick turn-around time, which simultaneously detects TB and rifampicin resistance, offers a promising solution to these TB diagnostic challenges. In line with 2013 WHO recommendations a pilot project was undertaken under the Revised National TB Control Programme of India (RNTCP) in four major cities offering upfront Xpert testing to all types of presumptive paediatric TB and DR-TB cases. The objectives of the project were to assess feasibility aspects of routine upfront Xpert testing for paediatric TB diagnosis, evaluate Xpert performance on different types of paediatric specimen and assess the diagnostic yield of Xpert on different types of specimen.

Methods: Upfront Xpert testing was offered to all paediatric (0-14 years) presumptive TB cases (both pulmonary and extra-pulmonary) seeking care at public and private health facilities in the project areas covering 4 major cities of India.

Figure: Various types of specimens tested on Xpert MTB/RIF n = 9149



*Others = cervical aspirate, peritoneal fluid, tracheal aspirate, abscess, synovial fluid, bone, chyle fluid, nasal aspirate, pleural biopsy, thoracic swab, ET secretion, pericardial fluid

Results: Overall 8370 paediatric presumptive TB & presumptive DR-TB patients were tested during 8

months of project implementation. Total 9149 specimens were tested, of which 4445 (48.6%) were non-respiratory specimens. Overall, Xpert gave 9083 (99.3 %) valid results. Of the 8143 presumptive TB cases enrolled, 517 (6.3%, CI 5.8-6.9) were bacteriologically confirmed. TB detection rates were two fold higher on Xpert as compared to smear microscopy. Further, a total of 60 rifampicin resistant TB cases were detected under the project.

Conclusion: The pilot demonstrated the feasibility of extending Xpert testing to non-sputum specimens from children with a very high proportion of interpretable results. With more than a two fold increase in TB case detection over smear microscopy and detection of significant numbers of rifampicin resistant TB cases, the study demonstrates the utility of offering upfront Xpert testing to paediatric presumptive TB and DR-TB patients under programmatic conditions.

OA-438-05 Bacteriological response to treatment in children with intrathoracic tuberculosis

E Walters,¹ M Van Der Zalm,¹ A-M Demers,¹ C Bosch,¹ H S Schaaf,¹ M Palmer,¹ R Gie,² A Hesselning¹ ¹Desmond Tutu TB Centre, Stellenbosch University, Cape Town, ²Tygerberg Hospital, Cape Town, South Africa. Fax: (+27) 021 938 9719. e-mail: ewal@sun.ac.za

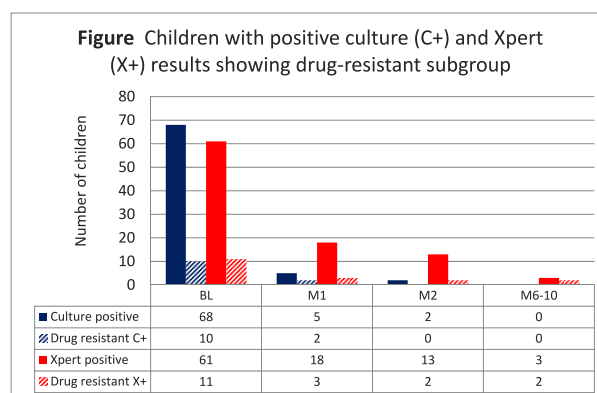
Background: Children with drug-susceptible (DS) intrathoracic tuberculosis (TB) generally respond well to 6 months' standard WHO-recommended therapy. However, assessing response to treatment is largely based on clinical improvement in the absence of bacteriological confirmation in paucibacillary disease. The bacteriological response to treatment in children with confirmed TB has not been characterized.

Design/Methods: We enrolled children <13 years of age routinely presenting with suspected intrathoracic TB to Tygerberg and Karl Bremer hospitals, Cape Town, South Africa, from April 2012 - April 2015. Children were eligible if ≥ 1 of prolonged cough/wheeze, fever or poor growth, or any duration of cough with 1 of a) close contact with known TB index case, b) reactive Mantoux, or c) chest radiograph compatible with intrathoracic TB were present. Study investigations included a minimum of 2 respiratory samples (gastric aspirate, sputum, induced sputum or nasopharyngeal aspirate) and one stool sample for smear microscopy, liquid mycobacterial culture and Xpert MTB/RIF. Hain MTB DRplus on positive cultures was done to determine susceptibility to INH and RIF. TB investigations from other routinely collected samples were also included. In children with Xpert or culture confirmed TB, respiratory sampling was repeated at 1, 2 and 6 months following treatment initiation.

Results: Culture results were available for 391/421 children (median age 15 months); 52 (13%) HIV-infected and 200 (51%) male. 172 (44%) children started TB treatment (clinical decision to treat). 81/172 (47%) were confirmed by either culture or Xpert: 68/172 (40%) were

culture positive for *Mycobacterium tuberculosis*; 60/172 (35%) Xpert positive and 12/172 (7%) smear positive for acid-fast bacilli. 11/81 (14%) had INH and/or RIF resistance. Xpert remained positive in 22% and 15% of children at months 1 and 2 respectively, compared to 6% and 2% for culture (Figure).

Conclusion: We observed a rapid decline in the proportion of children with positive bacteriology in the first month after treatment initiation. Xpert remained positive for longer than culture, in both DS and drug-resistant cases. The clinical relevance of persistent positive Xpert results in children receiving TB treatment up to 10 months requires further study. The use of clinical and bacteriological markers of response to therapy requires investigation in children, especially in view of planned paediatric TB treatment shortening trials.



OA-439-05 Implementation of a multi-level intervention to improve isoniazid preventive therapy for child TB contacts in South Africa

K Du Preez,¹ L Du Plessis,¹ J Caldwell,² V Azevedo,² E Mhlope,³ A Hesselning¹ ¹University of Stellenbosch, Cape Town, ²City Health, Cape Town, ³United States Agency for International Development TB Program, Johannesburg, South Africa. e-mail: lienkiduplessis@gmail.com

Background: Isoniazid preventive therapy (IPT) is effective in preventing tuberculosis (TB) in children following TB exposure. Despite global recommendations, gaps persist at multiple levels of the IPT delivery cascade. We previously (2010) showed a screening rate of 46%, IPT initiation rate of 58% and completion rate of 13% in children < 5 years of age.

Design/Methods: We assessed the impact of a multi-level intervention to improve IPT delivery in 3 health clinics in Khayelitsha, Cape Town, during 2013/4. Clinics were selected by stratified random selection according to TB caseload. The intervention included 1) HCW training, 2) supported implementation of paper-based IPT registers, and 3) client focussed health education. Audits for pre- and post-intervention periods (Quarter 1, 2013/4) were completed to measure the impact.

Results: A total of 264 infectious adult TB cases (pre-audit) and 306 (post-audit) were identified from the electronic TB register; 248 (94%) and 297 (97%) folders were available for review, respectively. During the pre-

audit, 236/248 (95%) TB cases had documentation of child contacts; only 47/72 (65%) of documented eligible child contacts were screened; 39/47 (83%) of screened contacts started IPT/TB treatment. Table 1 describes comparisons between pre- and post-audit for key variables, overall and by clinic. Following the intervention, names of child contacts were more likely to be recorded in the adult folder [OR 4.9 (95%CI 0.9-49.8), $P = 0.032$], and contacts were more likely to be started on treatment after screening [OR 6.1 (95%CI 1.1-60.5) $P = 0.015$]. During Q1 2014, 121 contacts were documented to start IPT in the IPT registers, an additional 63 (52%) to the 58 identified through the audit. The additional children were linked to extra-pulmonary exposures ($n = 11$), to exposures proceeding the audit period ($n = 17$), and to source cases from other clinics ($n = 35$).

Conclusion: Our pre-intervention data already indicate remarkable improvement in IPT delivery since previous audits through all levels of the IPT delivery cascade, likely due to emerging prioritisation of IPT by routine services. A multi-level intervention resulted in substantial additional improvements in IPT delivery. A large remaining gap is the drop-out between contact identification and screening, requiring a better understanding of processes at this level. Insight into this key area at the community level could inform more targeted interventions in future.

OA-440-05 Diagnostic yield of Xpert® MTB/RIF assay and *Mycobacterium tuberculosis* culture on respiratory and non-respiratory specimens among Kenyan children

S Rinn,^{1,2} E Click,³ K McCarthy,³ W Mchembere,⁴ E O Okeyo,⁴ J Orwa,⁴ S Musau,⁴ K Cain^{3,4} ¹Harvard Medical School, Boston, MA, ²Boston Children's Hospital, Boston, MA, ³U.S. Centers for Disease Control and Prevention - Division of TB Elimination, Atlanta, GA, USA. ⁴Kenya Medical Research Institute - Center for Global Health Research, Kisumu, Kenya. e-mail: rinn.song@childrens.harvard.edu

Background: Microbiological confirmation of tuberculosis (TB) among young children is challenging because obtaining the required specimens (gastric aspirate or induced sputum) is invasive and requires specifically trained personnel. Even when collected, diagnostic yield of culture for *Mycobacterium tuberculosis* is relatively low. The objective of our study was to assess the yield of *M. tuberculosis* culture and the Xpert® MTB/RIF assay on multiple respiratory and non-respiratory specimens among children with high clinical suspicion for TB.

Methods: In an ongoing study in Kisumu, Kenya, children under 5 years suspected of having TB were enrolled based on history of prolonged symptoms despite standard therapy (cough >4 weeks, fever >1 week, malnutrition > 3 weeks) and presence of parenchymal abnormalities on chest radiograph. Per enrolled child, two of the following specimens were tested by *Mycobacteria* Growth Indicator Tube culture for *M. tuberculosis* and Xpert MTB/RIF assay: nasopharyngeal aspirate, induced sputum, gastric aspirate, string test, stool, and urine; one blood specimen was tested by TB culture.

Results: As of March 2015, among 189 enrolled children (median age 27 months, interquartile range 14-45 months; 25% co-infected with HIV) with final culture results available, 24/189 (12.7%) children had confirmed TB based on at least one specimen positive on Xpert MTB/RIF or culture. Among the 24 children with confirmed TB, the number with at least one culture or one Xpert MTB/RIF positive by specimen type was as shown in the table. The combination of 2 nasopharyngeal aspirates and 2 stool specimens diagnosed 18/24 (71%) children using culture and 15/24 (63%) children using Xpert MTB/RIF.

Conclusions: In this cohort, nasopharyngeal aspirates and stool show promise as alternative specimens to gastric aspiration or induced sputum collection for diagnosis of TB in young children using culture and Xpert MTB/RIF. Neither specimen requires hospitalization and both could be obtained at lower levels of the health care system in high-burden settings to improve TB diagnosis in young children.

Table:

Specimen type	Positive TB Culture		Positive Xpert MTB/RIF	
	%	n	%	n
Gastric aspirate	78	18/23	43	10/23
Nasopharyngeal aspirate	67	16/24	46	11/24
Induced sputum	63	12/19	42	9/21
String test	40	8/20	35	8/23
Stool	22	5/22	48	11/23
Urine	9	2/22	19	4/21
Blood	6	1/18	N/A	N/A

OA-441-05 Risk factors for tuberculosis disease in pediatric TB contacts identified during a TB Reach contact tracing project in Swaziland

P Swamy,¹ R Golin,^{1,2} P Ustero,^{1,2} K Ngo,¹ J Glickman,² B Mzileni,² M Hlatshwayo,² A Mandalakas¹ ¹Global TB Program, Department of Pediatrics, Baylor College of Medicine and TX Children's Hospital, Houston, TX, USA; ²Baylor College of Medicine Children's Foundation-Swaziland, Mbabane, Swaziland. e-mail: swamy@bcm.edu

Background: Early detection of pediatric tuberculosis (TB) continues to be a significant challenge in TB-HIV high-burdened settings like Swaziland. Swaziland has a TB case detection rate of 38% with 15% child TB case notification. As limited evidence exists, identification of risk factors for TB disease among child contacts could inform preventive interventions in Swaziland and similar high burden settings.

Design/Methods: Supported via WHO TB REACH funding, Baylor College of Medicine Children's Foundation - Swaziland (BCMCF-SD) implemented standardized contact tracing in partnership with 7 local TB clinics. Cough monitors performed contact tracing of index cases (IC) receiving anti-TB treatment (ATT). The aim of this intervention was to improve TB case detection and promote Isoniazid preventive therapy (IPT) uptake. While adult contacts were assessed, our intervention

prioritized child contacts (<15 years of age per WHO reporting standards) and HIV-affected households. Contacts were screened for TB symptoms, HIV status, relationship and sleep proximity to IC, household death, and miner in the home. Data was collected regarding diagnostic testing (GeneXpert, smear, culture, CXR) and treatment initiation (ATT or IPT). Utilizing this dataset, our study aimed to focus on child TB contacts as often pediatric TB is underreported. This program provides a unique opportunity to evaluate risk factors associated with TB disease in child contacts living in a high TB-HIV burdened, resource limited setting.

Results: Of 2589 ICs, 1547 reported a child contact, yielding a total of 4438 child contacts (2.86 child contacts/IC). 67 cases of child TB were diagnosed (1510 cases/100 000 child contacts) of which 17 had bacteriologic confirmation, and 50 clinically diagnosed. TB was diagnosed 8 times more in child contacts with a positive TB symptom screen (RR=7.90, CI 4.15-15.04) and 9 times more in HIV-infected contacts (RR=8.97, CI 5.29-15.20). Child contacts were likelier to have TB if they were <5 years of age, child of an IC, and shared a bed with an IC. TB was not associated with contacts' gender, recent household death, and miner in the home. **Conclusion:** High TB incidence among child contacts emphasizes the need for comprehensive contact tracing programs. TB symptom screening and reported HIV-infection are strong predictors of TB among child contacts. If resource-limited, the cost-effectiveness of contact tracing programs may be improved by prioritizing HIV-affected households with younger children.

Figure 1 Characteristics of Pediatric TB Contacts

Characteristics	Contacts w/ RTT <15 years of age	Contacts NOT w/ RTT <15 years of age	Relative Risk [95% CI]	P-value
Overall [n(%)]	671 (5.1%)	4341 (97.8%)	N/A	N/A
Mean Age (years, SD)	5.1 (4.8)	7.1 (5.1)	2.67 (1.42-5.00)	0.0014
Categories of Age [n(%)]				
<5 years	37 (5.5%)	1563 (36.0%)	Referent	N/A
5-9.99 years	13 (1.9%)	1486 (34.2%)	Referent	N/A
10-14.99 years	17 (2.5%)	1293 (29.8%)	1.50 (0.73-3.07)	0.27
Gender [n(%)]				
Female	38 (5.2%)	2167 (49.9%)		0.71
Male	29 (4.2%)	2174 (49.9%)		
Sleep Proximity [n(%)]				
Different House	19 (2.8%)	1694 (39.0%)	Referent	N/A
Same House	19 (2.8%)	1477 (34.0%)	1.21 (0.64-2.29)	0.56
Same Room	16 (2.4%)	950 (21.9%)	1.77 (0.92-3.38)	0.081
Same Bed	12 (1.7%)	219 (5.0%)	4.94 (2.41-10.12)	<0.001
Relationship to IC [n(%)]				
Child	14 (2.0%)	1514 (34.9%)	1.90 (1.16-3.06)	0.006
Other	13 (1.9%)	2827 (65.1%)	Referent	
TB Symptom Screen [n(%)]				
Positive	56 (8.6%)	1671 (38.5%)	7.90 (4.15-15.04)	<.0001
Negative	11 (1.6%)	2670 (61.5%)	Referent	
Reported HIV Status [n(%)]				
Positive	17 (2.5%)	44 (1.0%)	8.97 (5.29-15.20)	<.0001
Negative	13 (1.9%)	505 (11.5%)	Referent	
Unknown	18 (2.7%)	3220 (73.6%)	Referent	

OA-442-05 The power of visual data across a multinational integrated pediatric HIV-tuberculosis program

R Puttagunta,^{1,2,3} K Ngo,^{1,2,3} A Mandalakas^{1,2,3} ¹Baylor College of Medicine, Houston, TX, ²TX Children's Hospital, Houston, TX, ³Global TB Program, Baylor College of Medicine and TX Children's Hospital, Houston, TX, USA. e-mail: rputtagunta@gmail.com

Background: The global tuberculosis (TB) burden from pediatric cases (<15 years) is estimated to be 4-20%. Among people living with HIV, TB accounts for almost a quarter of all deaths, yet there is a paucity of data related to TB-HIV co-infection in children. Given their developing immune system, children are more likely to

develop active disseminated disease compared to adults following infection with TB. In addition, the paucibacillary nature of childhood TB makes confirmation of disease difficult. Though availability of new technologies like GeneXpert MTB/RIF and updated guidelines from the World Health Organization (WHO) have improved diagnosis and treatment of pediatric TB cases, many obstacles still exist in effectively implementing recommended services. Given the complexity of diagnosing childhood TB, it is important to evaluate the feasibility of implementing WHO guidelines and recommendations related to TB care particularly in resource poor settings. **Intervention:** The Global TB Program of TX Children's Hospital and Baylor College of Medicine has developed a comprehensive approach to integrating, monitoring and evaluating TB best practices within the Baylor International Pediatric AIDS Initiative (BIPAI) network of pediatric HIV clinics that spans six sub-Saharan African countries.

Results: Fourteen TB indicators were identified and incorporated into the standardized medical record. The indicators were stratified by age and treatment history and cover a broad range of TB care components including preventive and diagnostic services, drug resistance, and treatment in relation to HIV. To improve interpretation of data and the efficiency of operations, a graphical tool was developed for the generated TB indicator data. Each indicator was visually represented by bar, line or pie charts. On a quarterly bases each clinical site is able to generate summary statistics with accompanying visual aids independently to evaluate their performance and make appropriate quality improvement decisions.

Conclusions: The identification and implementation of these 14 indicators required clinical site buy-in, regular training, and reconciling differing country guidelines and current professional guidelines. After addressing barriers in implementation and quality data entry, clinical sites are better able to make practical interpretations of WHO TB guidelines for program monitoring and evaluation.

19. Tobacco: economics and illicit trade

OA-443-05 Preference for buying cigarettes in packs or loose: a cross-sectional study among male smokers in Chennai city

P Saravanan,¹ M K Parangimalai Diwakar² ¹Sri Venkateswara Dental College and Hospital, Chennai, ²Ragas Dental College and Hospital, Chennai, India. Fax: (+91) 442 453 6059. e-mail: poornis@yahoo.com

Introduction: Amongst the 1.1 billion people who smoke worldwide, 182 million live in India, representing the second largest group of smokers in the world after China. India is a party to the World Health Organization's Framework Convention on Tobacco Control, which states that countries shall endeavor to prohibit sales of loose cigarettes, which are more affordable for minors. The Government of India, in the proposed amendments of Cigarette and Other Tobacco Products Bill 2015 (COTPA) has also suggested the same. With conflicting evidence

of the effectiveness of ban on sale of loose cigarettes as a tobacco-use control advocacy, this study was contemplated to assess the preferences of male smokers in Chennai over buying cigarettes in packs or in loose.

Methods: The present study was done among current male smokers of cigarette who were above 18 years of age and who reported to the dental outpatient department and consented to participate in this study. Data collection was done using a single-examiner administered closed ended questionnaire. The questionnaire consisted of two parts – the first part gathered information regarding their smoking dependence based on the Fagerstrom Test for Nicotine Dependence Questionnaire and the second part dealt with questions regarding their preference of buying cigarettes, the most common place where they bought the cigarette and also the places where they preferred to smoke.

Results: 73.4% of the male current smokers who participated in this study were low or moderately dependent. 94.5% of the participants preferred buying cigarettes in loose – mostly in singles (67.3%), two's (23%) and more than two's (4.5%). Those who preferred buying in packs cited reasons that they bought in pack due to their travel plans or if they felt difficulty in the availability of cigarette brand of their choice. Almost all the participants (98.3%) preferred buying cigarettes in the street vendors rather than supermarkets and also tend to smoke the cigarette in and around the same area of purchase. Most of them seem to associate their smoking habit with consumption of snacks and beverages.

Conclusion: Though a ban of the sale of loose cigarettes would nevertheless discourage smoking; adequate implementation of this ban by authorities would pose challenges in the form cigarette companies manufacturing packets with fewer cigarettes and the street vendors still trying to illegally sell loose cigarettes at a premium.

OA-444-05 Raising taxes on tobacco products by effective advocacy with government officials

R Mahajan¹ ¹Government of India, Mumbai, India. e-mail: drrupeshmahajan@gmail.com

Background and challenges to implementation: As per WHO, increasing the retail price of tobacco products through higher taxes is the single most effective way to decrease consumption and encourage tobacco users to quit. Comparative to other states of India, in Maharashtra taxes on tobacco products was less (Cigarettes - 20% & Bidi - 5%). In year 2012, state government increased the tax on Bidi to 12.5% but in couple of days that tax was rolled back to 5% again due to the political pressure and Bidi industry lobbying. Before the 2013 state budget session, under the National Tobacco Control Program (NTCP), initiative was taken to raise the taxes on tobacco products through the affective advocacy with the State Finance department and the Finance minister.

Intervention or response: To raise tobacco products tax in the state, initiative was launched under NTCP, involving civil society. In the month October 2012, State

consultant approached to Chief Secretary of the state and requested to form State Level Coordination Committee as per the guidelines which was formed by the government in November 2012. In the month of December, WHO India office organised two day conference on tobacco taxation. Using this opportunity, NTCP State consultant had meeting with principal secretary Finance and tobacco taxation was discussed with him. After the SLCC formation, SLCC's first meeting was called in January 2013, tobacco taxation issue was discussed in detail in the meeting and taxes in the other state was brought in the notice of Principal Secretary, Finance and Chief Secretary. In the SLCC's review meeting, meeting Chief Secretary again asked the finance to consider the raise in the taxes in coming budget session. Simultaneously, civil society organised meetings with the State Finance Minister focusing the agenda of tax raise, who responded positively. State Finance Minister was very keen on banning the Gutkha in the state and after the advocacy he was very much interested in tobacco products tax raise.

Results and lessons learnt: In state budget 2013, taxes on Cigarettes gone up to 25% from the existing 20% and on Bidi gone up to 12.5% from the existing 5% and financed department also promised about increasing taxes regularly every year on tobacco products. Sensitization is the key.

Conclusions and key recommendations: Sensitising higher government officials with effective advocacy can yield the positive results in tobacco control. Involvement of stakeholders is important.

OA-445-05 Advocacy at the top level resulted in tax increase on tobacco products in Madhya Pradesh

B Sharma¹ ¹Free Launcher, Indore, India. e-mail: silkdrops@rediffmail.com

Background and challenges to implementation: Tobacco consumption is quite prevalent in Madhya Pradesh state of India, 40 percent people consume tobacco in one form or other in the state. A large population consuming tobacco belongs to below poverty line. In a state like Madhya Pradesh where infant mortality and maternal mortality rate is quite high it was difficult to convince policy makers to take initiative for tobacco control as most of them were not considering tobacco control as an issue, for them tobacco control can be done only by awareness. Studies shows that tax increase is the most effective way for tobacco control.

Intervention or response: Continues sensitization of policy makers like finance minister, finance secretary, health secretary, commissioner food and drug, nodal officer was done at state level in which a factsheet on tax on tobacco products in other states was shared with them. The issue of tax increase on tobacco products was also raised during state tobacco control committee meeting. One to one contact was made with elected representatives to convince them about the importance of tax increase. Chief Minister and Health Minister were

motivated to give their message for tobacco control which has resulted in increased political will and getting support of elected representatives and other important stakeholders. Governor was also oriented on various issues of tobacco control. Other important stakeholders were involved through their capacity building.

Results and lessons learnt: Major decision was taken by state government and Value Added Tax (VAT) on all forms of tobacco product increased from 13 to 27%. The VAT amendment bill was passed by state assembly on March 2014 and notification passed in April 2014.

Conclusions and key recommendations: Top level advocacy is very effective in bringing major policy changes for tobacco control in the state. Regular Capacity building and awareness of elected representatives and other important stakeholders is important in increasing tax on tobacco products.

OA-446-05 India's single cigarette economy: a back of the envelope assessment of its volume and size

R Thakur,¹ P Lal,² A Pandey² ¹World Health Organization-Randstad, Shimla, ²International Union Against Tuberculosis and Lung Disease South East Asia Office, New Delhi, India. Fax: (+91) 177 262 7601. e-mail: ravindermph@gmail.com

Background: Sale of single cigarettes is an important factor to the spread of the tobacco epidemic globally. Single cigarette sale is associated with greater accessibility to minors and youth as it lowers immediate cost of purchase. It also provides perverse benefits for vendors and lowers the operating margins for cigarette companies. Singles stand to undermine public health effect of tax and distort fiscal policy and administration of tax.

Methods: In February 2014, a survey identified three prominent vendors of 10 cities. Through participant observation and end of day interviews, the sale of cigarettes in pack or single sticks, brands, their price and volumes sold in a single day were recorded and validated. Percentages and means were used to analyse and aggregate the survey data and simple back-of-the-envelope methods were used to arrive at broad results.

Results: There are currently no legal provisions that restrict sale of single cigarettes in India and other developing countries. We estimate that about 89.7% of all cigarettes are sold as single sticks. Depending on the segment (size, and filter or non-filter) retailers' have margins per single cigarette sold within every city. There are small variations in the price of sale of pack and singles across the country. The net worth of the single cigarette market is Rs 35.9 billion (or 0.598 bn USD, 1 USD= 60). The single cigarette economy is nearly 30 percent of the revenues from cigarette taxes (Rs 121.33 billion or USD 2.02 bn in 2012-13). This is the price which the consumers pay but is not captured through tax and therefore pervades in an informal economy. The widespread existence of the single cigarette market buffers for any significant increase tax which is passed

on to the consumer which defeats the public health goals and fiscal rationale of taxing cigarettes.

Conclusion: Tracking price of single cigarette is an efficient measure of raising taxes on cigarettes (in the absence of any other rationale) on a sustained annual basis by the Government of India, and can help achieve the desired goals of garnering revenues and meeting public health objectives. We repeated the survey in 2015 and found that the volumes and revenues have increase. We are in the process of data validation and will present the trends in sale of single cigarette in India (2013-14 and 2014-15). We will also deliberate upon practical implications of excise and VAT increase on retail price of cigarettes.

OA-447-05 Socio-economic and environmental determinants of tobacco products consumption: a case study of Pakistan

N Arshad,¹ B Wasim,² A K Chandio³ ¹The Network for Consumer Protection, Islamabad, ²Federal Bureau of Statistics, Islamabad, ³Ministry of Health, Islamabad, Pakistan. e-mail: naureenarshad@hotmail.com

Background: Pakistan is the sixth most populous country with highest tobacco consumption among South East Asian region. Every year around 110 000 tobacco related deaths occur in Pakistan. 40 % of male and 9% of female are smoker and this number is growing. The most prevalent mode of tobacco use is cigarette smoking whereas other products of tobacco like Paan, Gutka and Naswar are very eminent. So far this is the only study which has used Household level data from HIES (2010-11) to calculate the percentage of tobacco consumption expenditure at national level. The objective of the study is to investigate the demographic and social determinants of tobacco use and calculated the percentage of tobacco consumption expenditure.

Design/Methods: Secondary data analysis of HIES (2010-11). Dependent variables includes Tobacco consumption expenditure and Demographic and dummy variables were created to assess the impact of tobacco consumption at the household level. Statistical analysis of the data was done in SPSS 16. Descriptive and multiple regression analysis was done by using least square model.

Results: Percentage expenditure on tobacco consumption in rural areas is 1.36 % and 0.96% in urban settings. The highest consumption expenditure of 2.98% is observed in rural Sindh, whereas the lowest 0.52% is observed in urban areas of Khyber Pakhtunkhwa province. Expenditure on smoke-able products is higher than non-smoke able tobacco product in Pakistan. Spending on tobacco is higher in HH with average age group equal or more than 35 years i.e. 1.44%. Tobacco consumption expenditure is more in male and divorced individuals. Higher tobacco spending observed in HH with three or more adult male members, more employed males and HH with per capita income ranging from 3500 to 5000 per month. Multiple regression analysis showed significant negative correlation with average years of schooling and per capita income. Lack of environmental factors such as poor drinking and toilet facility and non-availability of gas

and electricity have significant negative association with tobacco consumption expenditure

Conclusion: Higher HH spending per month is observed in males in rural areas, illiterate, divorced and with poor living condition. The tobacco control efforts should be targeted towards low socioeconomic, rural and marginalized communities.

OA-448-05 A closer look at 'illicit' white cigarettes

H Ross,¹ N Vellios,¹ K Clegg Smith,² J Cohen² ¹University of Cape Town, Cape Town, South Africa; ²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: nicolevellios@gmail.com

Objective: To better understand the phenomenon of Illicit White cigarettes: how they are defined, both by the tobacco industry and other sources, their presence at various markets, brand proliferation, prices, manufacturers, location of manufacturing facilities, trademark ownership and compliance with tax and warning labels laws.

Methods: A review of scientific articles, news articles, online trademark registries and customs' and tobacco industry documents was the primary data source for the definitions, market presence, brand proliferation, manufacturers and trade mark owners. The data from the John Hopkins Bloomberg School of Public Health's Tobacco Pack Surveillance System (TPackSS) provided additional information on the manufacturers, prices and compliance with local tax and warning label laws

Results: We identified 82 Illicit White brands and 54 Illicit White manufacturers that operate at least 83 production facilities. A specific Illicit White brand is generally sold in a country either legally or illegally. Among the 35 Illicit White brands in the TPackSS database, two thirds had neither the correct health warning nor the required tax stamp at least in one country, and about 87% of illegal Illicit Whites were purchased outside large retailers. Both government agencies and Transnational Tobacco Companies (TTCs) report an upward trend in the market presence of illegal Illicit Whites, particularly in the European Union. One third of the manufacturers are located in the Free Zones of Russia, Cyprus and UAE. Some TTCs are also involved in the production of Illicit White cigarette brands. The trademark ownership is very complex with multiple owners dividing the global market into geographical segments and registering different features of a brand.

Conclusions: Similar to TTC brands, Illicit White brands are sold both legally and illegally, and a portion of them are distributed without paying the proper taxes. Illicit cigarette trade is not going to be solved by eliminating Illicit Whites, because the majority of illicit cigarette still consist of TTCs brands. The illicit cigarette trade can be addressed by adopting the WHO Protocol to Eliminate Illicit Trade in Tobacco Products and implementing the global tracking and tracing system.

OA-449-05 Pricing strategies for electronic nicotine delivery systems: gateway or deterrent?

C Cherukupalli¹ ¹Johns Hopkins University, Baltimore, MD, USA. e-mail: rajeevrc2063@yahoo.com

Background: As an evolving and growing product category with a projected US\$ 2 billion global market, ENDS pose challenges for regulation and taxation. The main argument to tax e-cigarettes is that higher prices deter use. The main argument against taxing them is that if e-cigarettes help current smokers quit smoking, higher prices discourage substitution and experimentation – especially relevant considering the tripling of use by teenagers in the US within two years. Pricing data on ENDS, and comparisons to combustible cigarettes have both been lacking in discussions of recommendations on tax and price regulations.

Design/Methods: A systematic review of internet retail sites and manufacturers' websites was done to establish product categories and price points at which ENDS are sold. Company and industry analyst reports were analyzed to understand pricing strategies and cost structures. Retail prices were also compared with wholesale prices listed on a prominent wholesale trade website.

Results: Retail prices for ENDS in the United States in 2015 varied fundamentally by whether ENDS products are disposable (US \$ 2 to US \$11) or refillable (\$ 25 to \$ 200), a much larger price variation than for combustible traditional cigarettes (US\$ 4.75 to US\$ 12.50 in 201). Price listings were frequently found to be accompanied by rebates and discounts of up to 50% over listed prices. Wholesale prices for importers of products were up to 350% cheaper than retail prices, indicating a considerable markup on product cost.

Conclusion: Refillable ENDS have both a fixed cost and a variable cost associated with repeated use and a significant premium over traditional cigarettes. By contrast, disposable e-cigarettes – including brand variants of refillable ENDS – are available at prices comparable to cigarette pack prices. Four phenomena – the marketing of starter kits, presence of disposable variants of refillable brands, large discounts, and comparisons of lifecycle cost savings of ENDS and traditional cigarettes – underscore active price competition and company strategies to encourage experimentation by potential users. Globally, a large supplier base with low unit prices suggests that price competition can keep ENDS cheap in several markets. This points to a future role of pricing regulations as an important complement to regulating ENDS.

OA-450-05 Smokeless tobacco consumption among adolescents: a global epidemiological perspective

I Agaku,¹ L Ayo-Yusuf² ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Sefako Makgatho Health Sciences University, Pretoria, South Africa. e-mail: WGN9@CDC.GOV

Background: Smokeless tobacco (ST) products can lead to tobacco addiction, disease, and death. The cultural differences in global adult tobacco use suggest that adolescents' tobacco use may also vary across cultures. We assessed ST use among adolescents in 57 countries during 2007-2010 using school-based surveys.

Design/Methods: Data were analyzed for 57 countries for which nationally representative data were available, using the 2007-2010 Global Youth Tobacco Surveys (for 55 countries); the 2009 US National Youth Tobacco Survey, and the 2008-2009 Canada Youth Smoking Survey. Number of countries by World Health Organization (WHO) region were: Africa, AFRO ($n = 11$); Eastern Mediterranean, EMRO ($n = 9$); Europe, EURO ($n = 11$); the Americas, AMRO ($n = 14$); South-East Asia, SEAR ($n = 8$), and Western Pacific, WPRO ($n = 4$). Analyses were restricted to persons aged 13-15 years in each country. Current ST use was defined as past 30-day use of chewing tobacco, pinch, snuff, dip, or snus. Data were weighted and analyzed by sex, WHO region and World Bank national income categories. Cross-country dispersion in ST use was assessed with the Coefficient of variation (CV).

Results: ST use varied widely among countries ($CV=0.62$); overall prevalence ranged from 1.1% in Montenegro to 16.4% in Congo. Prevalence by WHO region was: AFRO (median = 7.4%; range=5.4% to 16.4%); EMRO (median = 5.1%; range=1.6% to 12.6%); EURO (median = 2.0%; range=1.1% to 6.9%); AMRO (median = 5.3%; range=1.8% to 9.8%); SEAR (median = 6.3%; range=2.8% to 9.4%), and WPRO (median = 5.1%; range=2.1% to 8.7%). Prevalence by national income category was: low-income countries (median = 6.2%; range=2.5% to 16.4%), lower-middle-income countries (median = 6.2%; range=2.0% to 14.4%), upper-middle-income countries (median = 4.7%; range=1.1% to 11.3%), and high-income countries (median = 3.4%; range=1.8% to 9.8%). Overall ST prevalence exceeded 10% in 5 countries – 4 in AFRO and 1 in EMRO regions. Girls' ST use equaled or exceeded that of boys' in 10 low and middle income countries.

Conclusion: While the limited number of countries assessed may not be representative of each region, these findings suggest that region-specific patterns of ST use exist, with higher ST use observed in low and middle income countries, particularly in the AFRO and SEAR regions. Evidence-based interventions outlined in the WHO MPOWER package, such as raising tobacco taxes, and warning about the dangers of tobacco use, may prevent and reduce ST use among adolescents.

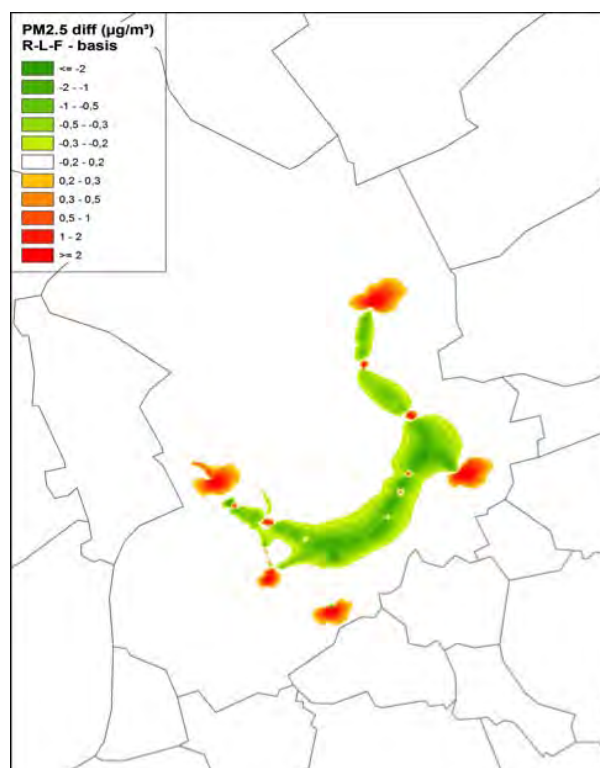
20. IAP, pneumonia, asthma and chronic lung disease

OA-451-05 Does 'Ringland' improve air quality and health in Antwerp? Health impact assessment of a predicted air pollution change by covering the Antwerp Ring Raod

D Van Brusselen¹ ¹University of Ghent, Ghent, Belgium. e-mail: daan.vanbrusselen@hotmail.com

Background and challenges to implementation: In Antwerp, the plans for an expansion of the existing ring road have initiated widespread resistance over a 10-year period. This resistance raised awareness about air quality, gave rise to detailed air quality research in the city, and stimulated bottom-up development of alternative solutions. The thinktank 'Ringland', a collective of urban planners and scientists, advocates covering the entire ring road. The 'Ringland' plan involves turning the Ring essentially into a tunnel, in order to reduce noise and air pollution, creating 384 hectares of open space on top of the ring, available for development of public parks and buildings. We conducted a health impact assessment (HIA) to quantify long term differences in mortality and cardiovascular/pulmonary outcomes of the predicted PM_{2.5} and NO₂ reduction in an Immision Frequency Distribution Model (IFDM) – street canyon model of 'Ringland'.

Intervention or response: The HIA consisted of three steps: 1) Calculation of an air pollution reduction scenario, using an IFDM-street canyon model. 2) Review of the medical literature and selection of the health outcomes to be evaluated. 3) Calculation of the health impact.



Results and lessons learnt: A clinically relevant reduction of PM_{2.5} and NO₂ was calculated within a 1500 meter buffer of the Ring Road. The calculated reduction of PM_{2.5} was associated with an expected annual decrease of 21 deaths (CI 7 to 41) in the population of Antwerp. 1710 (+570) life years could be gained by Ringland. In 430 schools in the 1500 meter buffer around the Ring Road a significant improvement of lung function was calculated among children aged 10 to 18 years by the reduction of NO₂ and PM_{2.5}. Differences in lung cancer mortality and the incidence of acute myocardial infarction were significant, but low for the calculated air quality improvement.

Conclusions and key recommendations: 'Ringland' could significantly improve air quality. The decrease of PM_{2.5} was associated with a relevant mortality reduction and an increase in life expectancy. The decrease of NO₂ and PM_{2.5} was associated with an improved lung function development in school children, which is linked to long term respiratory and other health benefits. The impact of air quality improvement on cardiovascular health has to be evaluated in combination with noise reduction and the effect of green space.

OA-452-05 Change over time in peak expiratory flow among workers exposed to polyvinyl chloride dust

H Lawin,¹ P Ayelo,¹ V Hinson,¹ J Kagima,² B Fayomi¹

¹University of Abomey Calavi, Cotonou, Benin; ²Egerton University, Nakuru, Kenya. e-mail: hervelawin@yahoo.fr

Background: Occupational exposure to polyvinyl chloride (PVC) may cause lung disease, including occupational asthma according to anecdotal reports. This study is to evaluate the variation of PEF over a workweek in nonsmoking workers and without previous asthma exposed to PVC dust.

Design/Methods: We conducted a cross-sectional study among 42 operators with exposure to PVC dust (filling hoppers to feed extrusion machines) and 23 employees without exposure to PVC dust in a plant producing PVC pipes in West Africa. A pre-tested questionnaire was administered and PEF was measured using a portable peak flow meter after a day off (day 1), day 3 and at the end of the week (day 6).

Results: The two groups did not differ by age or BMI. Dyspnea was more prevalent in exposed workers (52%) than controls (13%) ($P = 0.002$). PEF decreased more significantly in exposed workers than controls (−8% vs. −3% on day 3 and −10% vs. −5% on day 6, both $P = 0.004$). The exposure duration did not affect the PEF variability in the exposed groups.

Conclusion: The decrease of PEF over the workweek in workers exposed to PVC dust is consistent with occupational asthma although standard measures to diagnose occupational asthma were not used. This result reinforces the needs to prevent excessive exposure to PVC dust.

OA-453-05 Asthma control rates in Burundi: a preliminary study of 183 cases

F Ndikumwenayo¹ ¹Centre Hospitalier Universitaire de Bujumbura, Bujumbura, Burundi. Fax: (+257) 22 23 22 68. e-mail: ndikumwenayo@yahoo.com

Background: Level of asthma control is not known in Burundi. A first study was conducted for determining the level of asthma control and risk factors of asthma symptoms in adult patients according to GINA classification.

Methods: A prospective, descriptive and preliminary study was done on asthma patients seen in University Hospital center of Bujumbura during 12 months. GINA criteria were used for determining level control of asthma and risk factors.

Results: It was included 183 asthmatic patients, the average age was 45.39 ± 7.19 years, with 2.3 of sex ratio. Those patients were not different from age or gender ($p \leq 0.10$). The beginning of asthma symptoms was under 50 years of age in 85.39% ($p \leq 0.001$), particularly in women group ($p \leq 0.001$). According comorbidities, allergic rhinitis was found in 60.7%, GERD in 18%, HIV in 6%, and diabetes mellitus in 4.4%. Asthma was controlled in 12.6%, partly controlled in 35% and uncontrolled in 52.4%. Factors of the lack of asthma control were: unconscious therapeutic noncompliance (RR = 1.78, 95%CI [1.11 to 2.86]), non-using of inhalator spacer (RR: 12; 95%CI [6.45 to 22.34]) and lack of basic treatment (RR 2.26; 95%CI [1.06 to 5.06]), inadequate patient education and fears about side effect. Aggravating factors were viral infection, tobacco smoke, occupational and domestic environment.

Conclusion: Control asthma is a common target. Therefore, many patients are looking forward to improving their asthma control. Many actions may be done for relieving asthma in Burundi. Key words: Asthma, level, control

OA-454-05 Sequelae following successful treatment of multidrug-resistant tuberculosis patients under the national programme in India

R Singla,¹ M Mallick,¹ N Singla,¹ S Munjal¹ ¹National Institute of Tuberculosis & Respiratory Diseases, New Delhi, India. Fax: (+91) 1 126 517 834. e-mail: drrupaksingla@yahoo.com

Background: India has highest number of multi-drug resistant tuberculosis (MDR-TB) patients in the world. However, there is paucity of data about the residual sequelae at the successful completion of treatment of MDR-TB patients under national programme. The current study was aimed to evaluate occurrence and severity of residual sequelae among MDR-TB patients following successful completion of their treatment.

Design/Methods: 46 MDR-TB patients were sequentially enrolled in Delhi, India at the completion of their successful two years of treatment under the national programme. They were evaluated clinically; radiologically by X-ray chest; and by complete pulmonary

function tests (PFT) including spirometry, lung volume and diffusion capacity measurements. The quality of life (QOL) was evaluated by Seattle Obstructive Lung Disease Questionnaire (SOLDQ).

Results: 44/46 (95.6%) patients were left with persistent symptoms with 40/44 (90.9%) among them having dyspnoea as a prominent symptom. 38/46 (82.6%) patients had residual advanced lesions on chest X-ray. Out of 46 patients, 42 could perform PFT. Among these 41/42 (97.6%) patients were left with abnormal pulmonary functions; 19/42 (45.2%) patients had severe impairment in PFT as per European Respiratory Society guidelines; 27/42 (64.3%) had mixed obstructive and restrictive pattern; 4/42 (9.5%) had pure obstructive pattern; 24/42 (57%) patients had reduced diffusion capacity. With increase in severity of chest X-ray abnormalities there was increase in pulmonary function impairment and decrease in QOL score, especially related to physical function. Patients had residual reduced mean SOLDQ scores: Physical function 49%, Emotional factor 51.6%, Coping skills 60% and Treatment satisfaction 52.1%.

Conclusion: Under the national programme for the management of MDR-TB in India, following successful bacteriological cure of MDR-TB patients, significant number of patients under study had residual clinical symptoms, radiological sequelae and impaired lung functions leading to poor QOL. In addition to achieving bacteriological cure, there is a need under national programme to focus on management of post treatment sequelae and improving quality of life of the successfully treated MDR-TB patients.

OA-455-05 Is monitoring CO₂ an acceptable surrogate for rebreathed air volume assessment?

C Morrow,¹ W Bryden,² C Call,² R Wood¹ ¹University of Cape Town, Cape Town, South Africa, ²Zetech, Paris, France, e-mail: carl.morrow@hiv-research.org.za

Aim: To determine the validity of using CO₂ monitoring as a surrogate for rebreathed air. This relationship has been queried in the context of personal CO₂ monitoring and the development of Rebreathed Air Volume assessment.

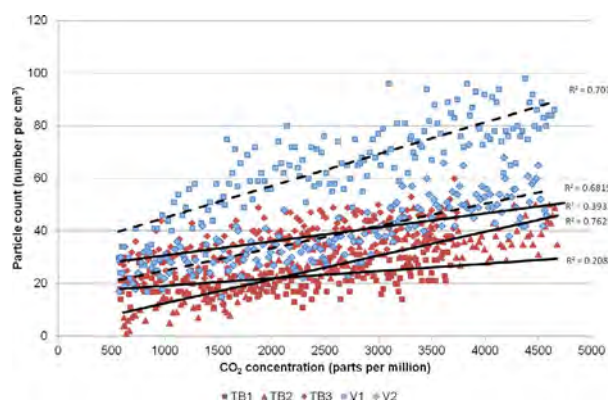
Methods: CO₂ release and particle accumulation from untreated patients actively infected with pulmonary tuberculosis (PTB) and TB screen-negative volunteers were individually monitored in a 1.45 m³ clean room. Participants were dressed in Tyvec suits and booties to reduce nonrespiratory particle sources. After participants entered the room, the air was cleaned by HEPA filtration at 300 Air Changes per Hour (ACH). Participants then sat in the room under conditions of 0.1 ACH and breathed normally (occasional coughing was allowed as needed) for the first of 30 minutes or until the surrounding air reached 4000 parts per million above ambient CO₂ concentration. During this time CO₂ concentration and aerodynamic particle size were monitored at 10 second intervals. Actual size of TB bacilli is approximately 2 µm, but the aerodynamic size is

considerably smaller, allowing easy infiltration into the lungs. Only particles of 1.114 to 2.458 µm aerodynamic size are therefore presented here

Results: Preliminary results from 3 patients and 2 volunteers are presented. The Figure shows a compelling association between increases in CO₂ concentration and expired particle load. This relationship was stronger for smaller particles, becoming random with larger particles (>2.5 µm) owing to low numbers. Further study subjects will allow for more refined analysis of factors associated with this observed relationship.

Conclusion: Preliminary results show evidence to support the utility of carbon dioxide monitoring as a surrogate for rebreathed air volume. Final results will open up a new agenda for more detailed investigations into the infectivity of the air we breathe.

Figure The association between carbon dioxide concentration and expired particles for both untreated, active PTB patients (TB1 to 3) and TB screen-negative volunteers (V1 and 2) in a clean room environment. Only particles in the aerodynamic size range 1.114–2.458 µm are presented here.



OA-456-05 High burden of respiratory morbidity among individuals treated for recurrent tuberculosis in Southern Africa

J Metcalfe,¹ S Makumbirofa,² R Penaloza,¹ T Vu,¹ P Hopewell¹ ¹University of California San Francisco School of Medicine, San Francisco, CA, USA; ²Biomedical Research and Training Institute, Harare, Zimbabwe. Fax: (+1 415 695 1500. e-mail: john.metcalfe@ucsf.edu

Background: The natural history of patients successfully treated for tuberculosis (TB) in high HIV-burden countries is poorly characterized.

Design/Methods: We recruited and followed consecutive individuals with history of prior TB treatment recruited from outpatient clinics in Harare, Zimbabwe. At 12-18 months post-treatment completion, we collected detailed demographic, socioeconomic, respiratory symptom, HIV, microbiologic, and radiographic data; we performed spirometry, endurance shuttle walk testing (ESWT), and accelerometry.

Results: From November 2011 to August 2014, 447 individuals were recruited at time of TB treatment initiation and followed for a median of 1.1 years (IQR

0.98-1.9 years). Median age of the cohort was 37 years (IQR 29-44), 59% were male, and 70% were HIV-positive; 25% had initial culture-confirmed TB, 19% had culture-confirmed rifampicin-resistant TB, and 56% had no microbiologic evidence of TB. At final follow-up, 11% had died and 6% were lost to follow-up. Among those undergoing respiratory studies ($n = 183$), 61% reported continued respiratory symptoms (score > 5 on CAT), 67% had obstruction or restriction on spirometry, 11% desaturated below 90% on ESWT. Mean (SD) for duration walked during ESWT was 10.4 minutes (SD 2.5 minutes). Overall, 69% had abnormalities on chest radiograph, with 23% having abnormalities across 25% of lung fields or greater.

Conclusion: Despite successful treatment, considerable respiratory morbidity exists among TB and DR-TB patients; in particular among HIV-positive participants and those without microbiologic confirmation of TB.

OA-457-05 The Cooking and Pneumonia Study: successful implementation of electronic data capture in rural Malawi with source document verification from the UK

W Weston,¹ K Mortimer,¹ J Smedley¹ ¹Liverpool School of Tropical Medicine, Liverpool, UK. e-mail: williamweston@gmail.com

Background: The Cooking and Pneumonia Study (CAPS) is a village-level cluster randomised controlled trial assessing the effectiveness of an advanced cook-stove intervention in preventing pneumonia in children under 5 in rural Malawi (www.capstudy.org). Each child is visited at their home every 3 months to collect information using an electronic Case Report Form (eCRF) on a smartphone. Here we report our experience of electronic data capture (EDC) in rural Malawi with remote Source Document Verification (SDV) (the process of evaluating the consistency of the data in the eCRF with the source data in the source documents) in the UK.

Design/Methods: Every 3 months fieldworkers capture digital images of the health passport (a booklet owned by the child where health workers make a record of any health related event) of each CAPS participant ($n = 9289$) using the camera in the smartphone and enter data from the health passport (including a study-specific 'CAPS sticker' shown in the Figure) into an eCRF. If an episode of pneumonia is recorded in the health passport, the fieldworkers transcribe the data from the CAPS sticker (severity, symptoms and signs, and outcome) into the eCRF. We conducted SDV of pneumonia data (occurrence, severity and 8 clinical indicators) recorded in the eCRF, the health passport and the CAPS sticker remotely from the UK. Microsoft Access was used to visualise each recorded pneumonia episode with the data from the eCRF and digital images of the health passport and CAPS sticker.

Results: 585 episodes of pneumonia had been recorded in the master database by 1/2/2014. Of these, 538 had a finding of pneumonia in the health passport and 240 in the CAPS sticker. 547 (94%) episodes of pneumonia

were supported by at least one source document. All digital images of the health passports and CAPS stickers were clear and legible.

Conclusion: EDC using eCRFs on smartphones is feasible in rural Malawi. This methodology has facilitated high quality data collection. Capturing digital images of source documents in the field allows SDV to be conducted efficiently and remotely without requiring additional field visits. We recommend these approaches for future work in similar settings. Acknowledgements CAPS is funded by the Medical Research Council, Wellcome Trust and UKAid (Joint Global Health Trials scheme).

This child is participating in the COOK STOVE AND PNEUMONIA STUDY: (CAPS)

ID Number: _____

Each time the child is diagnosed with pneumonia please use this sticker to document your assessment by writing in the information or ticking the appropriate box.

PNEUMONIA EPISODE				
DATE REVIEWED				
NAME AND CADRE				
PNEUMONIA CLASSIFICATION				
PNEUMONIA	☐	☐	☐	☐
SEVERE PNEUMONIA	☐	☐	☐	☐
VERY SEVERE PNEUMONIA	☐	☐	☐	☐
SYMPTOMS				
Cough	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Difficult breathing	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Fast breathing (60-110/min; 50-60/min; 40-50/min)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Chest indrawing	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Stridor	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Respiratory Rate (please write breaths per minute)				
Temperature (please record temperature)				
Danger Signs	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
X ray (please write result in health passport)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Pulse oximetry (please write result)	%	%	%	%
Malaria test (please check positive or negative if done)	☐ Positive ☐ Negative	☐ Positive ☐ Negative	☐ Positive ☐ Negative	☐ Positive ☐ Negative
OUTCOME				
TREATMENT AND SENT HOME	☐	☐	☐	☐
ADMITTED	☐	☐	☐	☐
REFERRED TO DISTRICT HOSPITAL	☐	☐	☐	☐
DEATH	☐	☐	☐	☐

Figure 1: CAPS sticker

OA-458-05 Obliterative bronchiolitis: a common cause of chronic lung disease in older adolescents with vertically acquired HIV

J Rylance,¹ S Desai,² A Nair,² G Mchugh,³ J Metcalfe,⁴ H Mujuru,⁵ K Kranzer,⁶ R Ferrand^{3,6} ¹Liverpool School of Tropical Medicine, Liverpool, ²King's College Hospital NHS Foundation Trust, London, UK; ³Biomedical Research and Training Institute, Harare, Zimbabwe; ⁴University of California San Francisco, San Francisco, CA, USA; ⁵University of Zimbabwe, Harare, Zimbabwe; ⁶London School of Tropical Medicine and Hygiene, London, UK. e-mail: jamie.rylance@lstmed.ac.uk

Background: Vertically HIV-infected children have a high burden of chronic lung disease that is not well-characterised. We prospectively investigated the spectrum of HRCT abnormalities and lung function indices in HIV-infected children with (non-tuberculous) chronic respiratory disease.

Methods: HIV infected older children and adolescents (aged 6-16 years) on antiretroviral therapy for at least 6 months were systematically recruited from an HIV clinic in Harare, Zimbabwe. Assessment included clinical examination, spirometry and chest radiography (CXR).

Patient with previous *Pneumocystis jirovecii* pneumonia and asthma were excluded. Subjects with chronic symptoms, CXR or spirometric abnormalities were referred for high resolution CT (HRCT).

Results: Thirty-nine participants (female=14 [36%]; median age=11.8 [range 6.8 – 16.4 years] and median age at HIV diagnosis=6.1 [IQR 3.7 – 8.6] years) had HRCT, spirometry and clinical assessment. The median CD4 count was 354 (IQR 200-717) at diagnosis and 641 (IQR 413-775) at enrolment. Thirty patients produced satisfactory spirometric traces. Ten (26%) patients desaturated on exercise. Fifteen (38.4%) patients had been treated for tuberculosis. HRCT was abnormal in 34 (87.2%). Decreased attenuation (consistent with constrictive obliterative bronchiolitis [OB]) was present in 22/39 (56%), strongly associated with reduced FEV1 (mean z-score difference 1.10, $P < 0.001$) and associated with chronic cough (but no other symptom). Bronchiectasis (seen in 13/39 (33%) patients) was associated with breathlessness, cough as well as reduced FEV1. Thin-walled cysts (possibly indicating lymphoid interstitial pneumonia [LIP] in 1/39 [3%]) and emphysema (10/39 [26%]) were present in the minority. There was no linkage between HRCT patterns and presence of hypoxia and CD4 count at diagnosis / enrolment.

Conclusion: Chronic lung disease in children with vertically-transmitted HIV appears to be caused by constrictive obliterative bronchiolitis in over 50%; the pathogenesis of OB warrants further study. Pulmonary air cysts and ground glass opacification (consistent with LIP) are uncommon.

POSTER DISCUSSION SESSIONS

26. TART: TB risk and impact of ART

PC-914-05 Determining factors associated with occurrence of tuberculosis among adults living with HIV after initiation of antiretroviral treatment in Addis Abeba

K Kibret,¹ Alem Yalew² ¹Wollega University, Nekemte, ²Addis Ababa University, Addis Ababa, Ethiopia. e-mail: ktwu27@gmail.com

Background: Tuberculosis (TB) is a leading morbidity and mortality, and the first presenting sign in majority of people living with Human Immune deficiency Virus (PLWH). Determinants of active TB among HIV patients on anti retroviral treatment (ART) are not well described in resource limited settings. The aim of this study was to assess determinant factors for the occurrence of TB among people living with HIV after ART initiation in public hospitals and health centers in Addis Ababa, Ethiopia.

Design/Methods: A case control study was conducted from December 2011 to February 2012 in 2 public hospitals and 13 health centers in Addis Ababa. The study population consisted of 204 cases and 409 controls. Cases were adult people living with HIV who

developed TB after ART initiation and controls were adult people living with HIV who did not develop TB after ART initiation. An interviewer administered structured questionnaire was used to collect information

Results: After adjustment for potential confounders, presence of isoniazid prophylaxis (adjusted odd ratio [AOR] 0.35, 95% confidence interval [CI] 0.125, 0.69) and cotrimoxazole prophylaxis (AOR= 0.19; 95%CI: 0.06, 0.62) had protective benefit against risk of TB. In contrary, bedridden (AOR= 9.36; 95%CI: 3.39, 25.85), having World Health Organization (WHO) clinical stage III/IV (AOR= 3.40; 95%CI: 1.69, 6.87) and hemoglobin level < 10 mg/dl (AOR= 7.43; 95%CI: 3.04, 18.31) at enrollment to ART care were predictors for increased risk of tuberculosis in PLWH after ART initiation

Conclusion: Increasing coverage of isoniazid preventive therapy and cotrimoxazole preventive therapy reduced risk of TB among HIV patients who started treatment. All PLWH should be screened for TB, but for patients who have advanced disease condition (WHO clinical stage III/IV, being bedridden and having hemoglobin level < 10 mg/dl) intensified screening is highly recommended during treatment follow up

PC-915-05 High rate of late incident tuberculosis among HIV-infected patients taking long-term antiretroviral therapy in Western India

A Dravid,¹ M Kulkarni,¹ C Saraf,² S Kore,² P Bhagwat³

¹Ruby Hall Clinic, Pune, ²Precision Diagnostics and Biosciences, Pune, ³Qua Blu Consultancy Services, Pune, India. e-mail: ameer.dravid@gmail.com

Background: India has a high tuberculosis (TB) and HIV burden. As of 2014, 800 000 patients are on antiretroviral therapy (ART) in India. Due to easy access to ART, India has reported declining HIV incidence rate. However data on incident TB especially late incident TB (TB developing > 3 months after ART initiation) and its association with baseline and treatment related risk factors is sparse.

Methods: In an observational cohort of 1425 HIV infected patients following up at a private HIV clinic in Pune, western India between February 2009 and February 2015 with at least 3 months of follow-up on ART, TB screening (WHO TB symptom score) was done at every clinic visit. Sputum smear examination and radiological investigations were done in case of positive symptoms. Demographic data, CD4 count and Plasma HIV viral load was collected at entry and yearly thereafter. Isoniazid preventive therapy (IPT) was given to eligible patients. Incidence of late onset TB and 95% Poisson CIs were estimated. Cases of paradoxical worsening of baseline TB were excluded. Risk factors for late onset TB were identified using univariable and multivariable Poisson regression analysis. Multivariable model was adjusted for age, sex, baseline TB, baseline CD4, baseline haemoglobin (Hb) and virologic status (virologic success/failure).

Results: 1425 HIV patients (34.3% females) were on ART with median age 40 yrs, median baseline CD4 count 154 cells/mm³ and median (IQR) follow-up on ART 3(1.25-5) years. 36.7% patients had baseline TB. 78% patients were on Non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART while 22% were on protease inhibitor (PI) based ART. 25% patients were given IPT with ART. Overall incidence of early incident TB (within 3 months of ART initiation) and late incident TB(95% CI) was 5.9 episodes/100 person years(4.6-7.1) and 2.6 episodes/100 person years(1.77-3.41) respectively. 126 episodes of late TB were reported among 118 patients with median time to TB(IQR) of 2.38 (1.78-3.75) years. 13/126(10%) episodes of late TB were due to unmasking immune reconstitution inflammatory syndrome (IRIS). 51.6% patients were virologic failures on ART at the time of late TB while 48.4% were virologic successes. 56% of incident cases were confirmed on TB culture while drug sensitivity testing was performed in 15%. Age, male sex and baseline TB were not associated with late TB. CD4 count $\leq$ 200 cells/mm³ ($P = 0.001$) and baseline Hb $<$ 10 g/dl ($P = 0.03$) were significantly associated with late incident TB. Virologic failure on ART increased incidence of late TB (10.99 versus 1.34 episodes/100 person years, $P = 0.0001$). Use of IPT and ART together were associated with lowest TB incidence of 0.087 episodes/100 person years. There were 3 deaths because of late incident TB.

Conclusions: Incidence of late TB in patients on ART (2.6 episodes/100 person years) is higher compared to national average of 0.8 episodes/1000 person years in HIV negative population and calls for measures like combining IPT with ART in HIV patients without active TB, HIV viral load monitoring on ART, immediate switch to virologically suppressive ART on diagnosis of virologic failure and initiation of ART at higher CD4 counts.

PC-916-05 Incidence and risk factors for tuberculosis among HIV-infected children in India

A Kinikar,¹ S Khadse,¹ A Deluca,² N Gupte,² D Kadam,¹ A Chandanwale,¹ A Gupta,³ R Bollinger³ ¹Byramjee Jeejeebhoy Government Medical College & Sassoon General Hospital, Pune, ²Byramjee Jeejeebhoy Government Medical College-JHU Clinical Trials Unit, Pune, India; ³Johns Hopkins University, Baltimore, MD, USA. e-mail: aarti.kinikar63@gmail.com

Background: The risk for TB among HIV infected children may vary based on local community burden of TB and their access to HIV treatment. India has the largest burden of TB and a national program for HIV treatment of children. Defining the incidence and risk factors of TB among HIV-infected Indian children will help optimize programmatic guidelines and objectives to reduce TB-associated morbidity and mortality.

Design/Methods: This was a retrospective observational study, with data drawn from a large cohort of HIV infected children seeking care at an ART center from January 2000 to December 2014 at Sassoon General Hospital in Pune, India. Free ART under the National

program was rolled out in 2004 and new ART treatment guidelines were introduced in 2013. The TB incidence rate estimates were calculated using Poisson assumptions. Univariable and multivariable Poisson regression analysis was done to assess independent risk factors for Incident TB.

Results: At baseline median age was 10 years. A total of 321 children were put on anti TB treatment. Between 2000 and 2014, TB incidence among 6017 HIV infected children $<$ 18 years was 10.8/1000 person-years (95%CI, 9.7 – 12.0). Compared to children with WHO Stage I HIV disease, children with WHO Class Stage IV were at greater risk for TB (aIRR 6.2, 95%CI: 4.2–9.2 ; $P < 0.001$). TB incidence was also lower for those on ART at registration vs. those who were not (2.7 and 13.1; respectively aIRR 0.30, 95%CI: 0.17-0.51; $P < 0.001$). At CD4 count of $<$ 250 the TB incidence was 13.9/1000 py with aIRR of 1.47 (CI 1.0 – 2.12; $P < 0.05$). Kaplan-Meier estimates of time to TB show that over 10% of our pediatric population contracted TB during the study period. Median time to TB was 3.61 years and IQR was (2.25-4.96) after registration.

Conclusion: The incidence of TB in children seeking care at our ART center is higher than other South Asian countries in a setting of higher background burden of TB disease. Our study results show that 1 in every 10 HIV infected child developed active TB disease over time. Frequent TB screening and preventive therapy should be considered for those most at risk of developing TB disease in order to reduce incidence, which for this population includes those with low CD4 cell counts, not on ART treatment, and at a late clinical stage classification.

PC-917-05 What drives the TB epidemic in Kenya: county TB profile

J Kiarie,¹ D Mibei,¹ B Langat,¹ A Ronoh,¹ D Nyangahu,¹ R Muthee,¹ E Mailu¹ ¹Kenyan Ministry of Health, Nairobi, Kenya. e-mail: jckiarie@gmail.com

Background: Tuberculosis is a disease of public health importance that contributes the high burden in terms of morbidity and mortality in Kenya. It is established that HIV/AIDS is the leading driver of Tuberculosis. It has been noted though that there is a mismatch between the trends of TB and HIV. HIV alone therefore might not explain the currents and pattern of TB distribution. The main objective of this study was to determine other risk factors for TB disease in the different Counties in Kenya. Findings from this study will trigger the initiation of appropriate evidence-based County specific interventions

Design/Methods: Secondary data was used in this study. Key variables that have been proposed as possible risk factors for TB from other studies were obtained from each County and analyzed using regression and ANOVA models using Ms Excel and SPSS software. There was clustering of the Counties according to the case notification level into two categories; high and low which was then used to compare predictors based on the

two categories. The percentage of urban population in a county was used to measure urbanization and area per facility in square kilometers was used to estimate facility accessibility. A multiple linear regression was then used to identify factors that could be associated with CNR variations in different counties

Results: Counties in Kenya have significant variation in HIV prevalence and TB CNR. Results showed that in addition to HIV prevalence ($P=0.00$), Urbanization ($P=0.007$), HDI, Population density ($P=0.041$) and Poverty ($P=0.003$) were significant predictors. Facility accessibility ($P=0.008$) was significantly associated with TB CNR on its own but it was not found to be a predictor. Poverty was found to be negatively associated with TB CNR. Population per health workforce, number of TB facilities, literacy level and fully immunized level were not significantly associated with TB CNR. The variation of HIV prevalence, the various factors and TB CNR in the various Counties shows that different factors are Key in the different Counties

Conclusion: There is need to align efforts in the fight against TB to all risk factors if the fight against TB is to be won in Kenya and further dissect the approaches according to risks by county. Also, further research needs to be done to determine the risk factors for TB in Counties with high poverty levels.

PC-918-05 Epidemiology of tuberculosis among HIV-positives in Nepal

S Sah,¹ G Bhatta,² S Verma³ ¹National Tuberculosis Center, Thimi, Bhaktapur, ²RESEARCH, SAARC Tuberculosis and HIV/AIDS Center, Thimi, Bhaktapur, ³SAARC Tuberculosis Center, Thimi, Bhaktapur, Nepal. Fax: (+977) 1 663 0706. e-mail: sujitmph12@gmail.com

Background: Globally, tuberculosis (TB) is the most common opportunistic infection and leading cause of mortality in people living with the human immunodeficiency virus (PLHIV), contributing 1 in 5 of these deaths. Tuberculosis is a public health problem of importance in Nepal with an estimated incidence of 156 per 100 000 population. The estimated prevalence of HIV among people aged 15-49 years was 0.23% in 2013. The HIV epidemic is concentrated to key populations. People living with HIV are 29 times more likely to develop TB disease as people without HIV. TB-HIV activities had been implemented in 43 districts out of total 75 districts in Nepal. However, the proportion of TB patients in Nepal who had an HIV test result recorded in the TB register dropped from 25% in 2012 to 11% in 2013. Therefore, this study aims to find out TB epidemiology among People Living with HIV (PLHIV) in Nepal.

Design/Methods: This is the first an institutional based prospective study. This survey was conducted at 6 sites representing all five regions of Nepal from July 2012 to February 2013. The calculated sample size was 400 PLHIV registered in Pre/ART centers. The statistical test analysis was done in accordance with the distribution of data.

Results: The study reveals that 11.5% prevalence of TB was found in total examined HIV clients. Highest

prevalence rate of TB among HIV clients was found in Far-West Region (28.8%) and Eastern Region (23.1%) where migration and refugee problem is prevailing. The prevalence of TB was found higher in age group of 35-65 years and above. The prevalence of TB among enrolled HIV clients was comparatively high in male (14.4%) than in females (8.4%). TB prevalence was also found higher in illiterate clients in comparison to higher educated. Prevalence of TB among migrants was higher (14.6%) followed by spouse of migrants (11.5%) and IDUs (11.1%). The prevalence of TB was found 10.7 percent among HIV clients enrolled for ART/PART. The study reveals that 5.4%, 3.1% and 3.1% were pulmonary positive; pulmonary negative and extra pulmonary TB respectively.

Conclusion: The prevalence of TB was found significantly higher in age group of 35-65 years, high risk and illiterate groups of HIV clients. Therefore, strategy should be revised to focus on targeted interventions for migrants, spouse of migrants and IDUs and illiterate community people to avoid TB co-infection in Nepal.

PC-919-05 Antiretroviral therapy scale-up for TB reduction in rural Swaziland: how far will it take us?

B Kerschberger,¹ I Zabsonre,¹ G Mchunu,² M M Win,¹ I Ciglenecki,³ L Rusike-Pasipamire,¹ A Telnov,³ W Sikhondze² ¹Médecins Sans Frontières (Operational Centre Geneva), Mbabane, ²National TB Control Programme, Ministry of Health, Manzini, Swaziland; ³Médecins Sans Frontières (Operational Centre Geneva), Geneva, Switzerland. e-mail: benadi11@yahoo.de

Background: Timely antiretroviral therapy (ART) reduces the TB burden in people living with HIV (PLHIV). In Swaziland, integration of TB-HIV collaborative activities has been strengthened since 2009 resulting in a decline in TB notifications since 2010. Modelling studies, however, predict a rebound in population TB incidence in high HIV prevalence settings when decline in HIV incidence is delayed and immune-virological responses are not sustained. It remains uncertain whether and when this rebound effect will occur under routine program conditions.

Design/Methods: We triangulated TB and HIV programming data from the rural Shiselweni region (population 210 000) in Swaziland, from 2009-2014. Overall and age-specific first line TB drugs notifications rates were described to elaborate signs of TB case rebound. Annual population ART coverage among PLHIV and population viral load (VL) suppression rates (defined as estimated population VL <1,000 copies/ml among PLHIV) were calculated for the same time periods. Denominators for coverage and notification estimates were obtained from projections of the 2007 population census.

Results: Overall annual TB notifications declined steadily from 1304 to 424/100 000 between 2009- 2013, and were 408/100 000 in 2014. The annual decline in TB notifications ranged from -174 to -298/100 000 between 2009-2013 ($P < 0.01$), and was reduced to -16/100 000 between 2013-2014 ($P = 0.58$). TB

notifications declined in all age-groups from 2009-2014, but increased in the 20-29 (516 to 577/100 000; $P=0.07$) and in the 30-39 (1029 to 1185/100 000; $P < 0.01$) yrs old between 2013-2014. ART coverage in PLHIV increased from 19% in 2009 to 47% in 2013, and was 53% in 2014. It was lowest for the 30-39 yrs old (45%) and above average in the 20-29 yrs old (63%). For the same time periods, estimated population level VL suppression increased from 24% (2009) to 49% (2013) and was 55% in 2014.

Conclusion: Rapid ART expansion and increasing population level virologically response may have contributed to a steady decline in TB notifications. Yet an overall flattening of annual TB notifications was recorded at approximate 50% ART coverage, and annual TB notifications started to increase in the 20-39 yrs old for the first time since 2009. Yet, it remains uncertain whether this constitutes the beginning of rebound in TB notifications. Modelling studies suggest universal ART expansion strategies (treatment as prevention) for TB control in high HIV prevalence settings to avoid TB incidence rebound.

PC-920-05 Seasonal variations in tuberculosis diagnosis in antiretroviral treatment programmes in South Africa, Zambia and Zimbabwe

M Ballif,¹ S Reid,^{2,6} M Zwahlen,¹ K Stinson,^{3,8} L Fenner,^{1,4} M Fox,⁵ H Prozesky,⁷ C Chimbetete,⁹ M Egger¹ ¹University of Bern, Bern, Switzerland; ²University of North Carolina at Chapel Hill & Centre for Infectious Disease Research in Zambia, Chapel Hill, NC, USA; ³University of Cape Town & Médecins Sans Frontières, Khayelitsha, Cape Town, South Africa; ⁴University of Basel, Basel, Switzerland; ⁵Boston University, Boston, MA, USA; ⁶Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; ⁷University of Stellenbosch & Tygerberg Academic Hospital, Cape Town; ⁸Médecins Sans Frontières, Khayelitsha, South Africa; ⁹Newlands Clinic, Harare, Zimbabwe. e-mail: mballif@ispm.unibe.ch

Background: Variations in tuberculosis (TB) diagnosis across the year have been attributed to seasonal effects, winter being associated with indoor crowding, poorer access to health care, and vitamin D deficiency due to reduced sun exposure. We investigated seasonal trends in pulmonary TB (PTB) diagnosis at five antiretroviral treatment (ART) programs from three countries in Southern Africa, with different climates depending on their latitude.

Design/Methods: We included HIV-infected adults (>15 years) enrolled between January 2004 and December 2012 in five ART programs of the International epidemiological Database to Evaluate AIDS (IeDEA) consortium: Khayelitsha, Thembalethu, and Tygerberg (South Africa), CIDRZ (Zambia), Newlands (Zimbabwe). We analyzed crude monthly numbers of PTB diagnosis and of patients starting ART. As control, we used Kaposi sarcoma (KS) diagnosis, for which no seasonal effect was expected. We accounted for trends over the study period by calculating deviations of

monthly counts to yearly averages. We assessed associations between monthly deviations in number of ART enrollments, PTB diagnosis and KS diagnosis by calculating correlation coefficients.

Results: Average monthly PTB diagnosis counts were 42 (range 3-76) in South Africa, 308 (271-354) in Zambia and 6 (1-9) in Zimbabwe. Monthly variations in PTB diagnosis were seen at all sites (Figure). The strongest fluctuations were seen in Zimbabwe with PTB diagnosis peaks in October and troughs in December (+52% and -76% of monthly average, respectively). Sites in South Africa also showed marked PTB diagnosis drops in December (up to -54% of monthly average). The largest site, CIDRZ, showed milder PTB diagnosis variations. Fluctuations in PTB diagnosis paralleled changes in ART enrollment, with recurrent patterns across 2004-2012. Correlations between deviations of monthly PTB diagnosis and ART start counts from yearly averages confirmed this parallelism (coefficient range: 0.69-0.95, $P < 0.0001$ for all sites). Numbers of KS diagnosis were low at all sites, but with marked December drops, as observed for ART enrollment and PTB diagnosis.

Conclusion: Monthly variations in PTB diagnosis at ART programs in Southern Africa were observed regardless of climate, likely reflecting fluctuations in ART enrollment rather than seasonal effects. This was further supported by the similar patterns of variations seen for KS diagnosis. In South Africa and Zimbabwe, pronounced PTB diagnosis drops in December may be associated with reduced clinical activities during summer vacations.

PC-921-05 Incidence and predictors of tuberculosis among HIV-infected adults after initiation of antiretroviral therapy, Nigeria, 2004-2012

I Pathmanathan,¹ E K Dokubo,¹ S Ray,¹ D Onotu,² S Odafe,² I Dalhatu,² H Debem,² S Agolory¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²U.S. Centers for Disease Control and Prevention, Abuja, Nigeria. e-mail: ydi6@cdc.gov

Background: Nigeria had the most AIDS-related deaths worldwide in 2013 (210 000); 39% were associated with tuberculosis (TB). The World Health Organization (WHO) recommends intensified TB case-finding and treatment before treating HIV with antiretroviral therapy (ART) to prevent TB-associated morbidity and mortality, yet TB diagnosis in immunocompromised patients is challenging. We aimed to estimate incidence and characterize factors associated with TB after ART initiation in Nigeria.

Design/Methods: We analyzed retrospective cohort data from a nationally representative sample of adult (≥ 15 years) ART patients. Data were abstracted from 3496 patient records at 35 sites selected using probability-proportional-to-size sampling. Analyses were weighted and controlled for complex survey design. Subgroup domain analyses were performed on patients without baseline TB disease. A Cox proportional hazard model was used to assess factors associated with TB incidence.

Results: At ART initiation, 3350 patients (95.8%, 95%CI: 94.6%–96.9%) were not receiving TB treatment; of these, mean age was 34.9, 66% were female, and median CD4 count was 161/mL. TB incidence was 0.48 per 100 person-years (56 cases), significantly higher for patients with baseline CD4 <50/mL (adjusted hazard ratio [AHR]: 4.9, 95% CI: 1.5–15.8) compared with CD4 >200/mL, and marginally higher for patients bedridden at baseline (AHR: 4.8, 95% CI: 0.9–24.7) compared with being asymptomatic. No significant associations were observed for age, weight, employment, marital status, education, or WHO HIV clinical stage.

Conclusion: Incidence of TB after ART initiation was associated with markers of advanced HIV infection such as low CD4 and poor functional status. Study results reinforce the benefit of early ART initiation, and highlight the need for intensified TB case-finding in patients initiating ART at advanced stages of HIV disease.

PC-922-05 The impact of AIDS treatment on tuberculosis outcomes at the national level in South Africa

Z McLaren,¹ A Sharp,¹ E Brouwer,¹ A Nanoo² ¹University of Michigan, Ann Arbor, MI, USA; ²National Health Laboratory Service, Johannesburg, South Africa. e-mail: zmclaren@umich.edu

Background: Fueled by the HIV/AIDS epidemic, TB has been the leading natural cause of death in South Africa for over a decade. In 2004, the South African government initiated the national rollout of anti-retroviral therapy for AIDS that resulted in a population-level life expectancy increase of 11.3 years. The ART rollout provides a unique and unprecedented opportunity to examine the population-level impact of ART on TB-related outcomes. This study performs a longitudinal analysis that follows the evolution of outcomes before and after the introduction of ART. This is the first study to capture national-level spillover effects of ART on TB incidence for those who were not accessing ART, including HIV-negative individuals.

Design/Methods: We use data from the National Health Laboratory Service database on tuberculosis tests performed on patients in public health facilities for the period January 2004 - December 2011, which includes over 30 million test records from over 10 million patients. Culture-confirmed TB-positive cases are based on the presence of at least one positive result from TB culture or molecular testing with Xpert® MTB/RIF or line probe assays. ART rollout data come from the Department of Health. Regressions include facility-level fixed effects to control for time-invariant confounders.

Results: The overall number patients per facility rise in a linear trend, with an uptick around the time of ART accreditation at the facility. We find an increase in the number of TB tests occurring more than 90 days from the initial testing visit, which is consistent with retaining patients in TB care for longer. There is an overall increase in TB cases in the period before ART, but it levels off at

the time ART becomes available locally. The leveling-off of TB cases occurs despite the concurrent shift away from smear testing, which reduces the underdetection of HIV-positive TB cases. Our results are consistent with patterns of increased testing and retention of HIV-positive patients when ART becomes available.

Conclusion: Our results capture the important spillover benefit of ART on TB prevalence, which reduces morbidity and mortality for HIV-positive and HIV-negative South Africans alike. Improved integration between HIV and TB health programs should take spillovers into account to improve the design and cost-effectiveness of health policy.

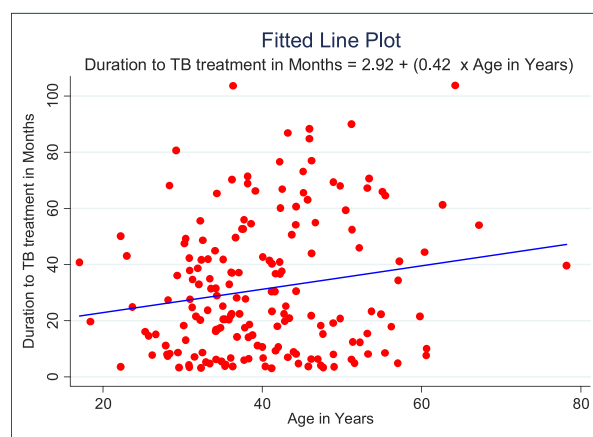
PC-923-05 Characterizing non-IRIS TB treatment among cART patients in Zambia

P Katayamoyo,¹ N Chishinga,¹ J Mukundu,¹ L Nyirenda,¹ P Kasonde,¹ A Mwango,^{1,2} M Welsh¹ ¹FHI360, Lusaka, ²Zambia Ministry of Health, Lusaka, Zambia. Fax: (+26) 021 125 7329. e-mail: pkatayamoyo@fhi360.org

Background: The development of TB among patients receiving combination antiretroviral therapy (cART) is fairly well documented. TB disease among patients on cART may be a result of poor ART adherence or HIV drug resistance that renders HIV-infected patients susceptible to TB, but generally literature may not be very clear on why this is so. This study aims to better understand and hopefully support effective interventions for TB treatment among patients receiving cART.

Design/Methods: We conducted a retrospective cross-sectional study in 12 high volume ART sites in the northern parts of Zambia between October, 2011 and September, 2012. We considered patients aged 15 years and older that developed TB after 3 months of starting cART and excluded those with immune reconstitution inflammatory syndrome (IRIS) TB. Data were extracted from patient medical charts, TB cards, TB and ART registers that included age, sex, baseline CD4 count and type of TB (pulmonary or extra pulmonary TB). Linear regression was used to determine the association between age of patients and the timing of TB treatment initiation after 3 months of receiving cART.

Figure ART duration to TB treatment versus age for cART patients



Results: There were 177 patients on cART for more than 3 months that were started on TB treatment. 96 (54.2%) were males and 153 (86.4%) had pulmonary TB. The median age was 38.4 years [interquartile range (IQR): 33.4–46.1]. The median baseline CD4 count at start of cART was 236 cells/ μ L (IQR: 147–326) and the median duration to starting non IRIS TB treatment was 23.8 months (IQR: 10.6–45.9). We found that for such patients on cART for more than 3 months, every additional year in age showed duration to starting TB treatment increased by an average of 0.42 months (Coeff. = 0.42, $P = 0.022$) (Figure).

Conclusion: Our results suggest that younger patients on cART were more likely to be at early risk of TB disease and starting treatment compared to older patients. Prospective research is recommended to better understand the implications of these findings on the control of TB disease among younger HIV-TB co-infected patients receiving cART.

27. Drug resistant TB: outcomes

PC-925-05 Shortening length of treatment in MDR-TB patients using a six-drug anti-tuberculosis regimen

Q Li,¹ X Jiang,¹ K Yang,² S Tang,¹ J Q Liang,³ K Kan,⁴ L Li,¹ I H Qiu⁵ ¹Beijing Chest Hospital, Capital Medical University, Beijing, ²Hunan Tuberculosis Hospital, Changsha, ³The 309th Hospital of PLA, Beijing, ⁴Anhui Chest Hospital, Hefei, ⁵Shandong Chest Hospital, Jinan, China. e-mail: lq0703@hotmail.com

Background: Although the course of 24 month of treatment can ensure the treatment success for the MDR-TB patients, longer treatment can bring the damage to the body and the economic burden in the MDR-TB patients so that their compliance is low and loss rate is high. The aim of research is to observe the effect and outcome of treatment using the regimens which was composed of six anti-tuberculosis drugs and shortened the length of treatment to 18 months in the MDR-TB patients.

Methods: The 251 MDR-TB patients were diagnosed and included in this study respectively in ten hospitals of China between July 2009 and July 2010. We formulated three regimens composed of 3~4 core drugs and 2 companion drugs as follows: 6ZAmMfx+XY/18ZMfx+XY (the group 1), 6RfbZAmMfx+XY/12RfbZMfx+XY (the group 2A) and 6ClrZAmMfx+XY/12ClrZMfx+XY (the group 2B), of which XY were two companion drugs selected as DST of the MDR-TB patients. 251 MDR-TB patients were randomly divided into three groups to be treated respectively using three regimens above-mentioned. The bacteriology, chest radiograph, blood, urine and so on were tested for the MDR-TB patients during and the end of course so as to evaluate the effect and outcome of treatment.

Results: 1) In 251 MDR-TB patients, the rate of acquired drug resistance was more than 86%, the numbers of drug resistance were more than 3.6, the course was more than 3.1 years, the BMI was less than 20.6, the extent of pulmonary lesion was more than 3.5 lung fields, on average. 2) In three groups of the MDR-TB patients, the sputum culture conversion were 74%, 64% and 81% in the end of intensive phase and were 78%, 79% and 75% in the end of continuation phase respectively ($P > 0.05$). 3) In the end of continuation phase, the pulmonary lesion were improved and/or absorbed in 74%, 79% and 78% of MDR-TB patients of three groups, respectively ($P > 0.05$). 4) There were 68 cases occurring adverse reaction during the treatment, of which the rate of liver injury were highest among three groups and respectively 8%, 13% and 9% ($P > 0.05$). 5) In three groups, the successful rate were 60%, 62% and 58%, mortality rate were 6%, 8% and 3%, failed rate were 19%, 14% and 17%, respectively ($P > 0.05$).

Conclusion: The effect and outcome of three treatment regimens were similar. It is suggested that two regimens composed of 4 core drugs and 2 companion drugs can shorten the length of treatment to 18 months for MDR-TB patients.

PC-926-05 Residual efficacy of levofloxacin versus moxifloxacin against fluoroquinolone-resistant *M. tuberculosis* murine infection

T Maitre,^{1,2} A Chauffour,^{1,2} C Bernard,^{1,2,3} A Aubry,^{1,2,3} N Veziris^{1,2,3} ¹Sorbonne Universités, Université Pierre et Marie Curie, Paris 6, Paris, ²Institut National de la Santé et de la Recherche Médicale, Paris, ³Assistance Publique-Hôpitaux de Paris, Paris, France. Fax: (+33) 1 4216 2127. e-mail: nicolas.veziris@upmc.fr

Background: Preliminary works, in a murine model of tuberculosis, have shown that moxifloxacin retains partial activity against fluoroquinolone resistant mutants. Levofloxacin has proven to be equivalent to moxifloxacin against drug susceptible tuberculosis and to have a better safety profile. In particular, levofloxacin prolongs less QT interval than moxifloxacin which makes it the preferred fluoroquinolone for combination with new drugs such as bedaquiline or delamanid. Our objective is to compare the in vivo activity of levofloxacin and moxifloxacin against *M. tuberculosis* strains harboring DNA gyrase mutations with various levels of fluoroquinolone resistance.

Design/Methods: We selected in vivo isogenic fluoroquinolone resistant mutants of *M. tuberculosis* H37Rv. A total of 120, 5 weeks old, BALB/c female mice were intravenously infected with 106 *M. tuberculosis* GyrA (A90V) or GyrB (E540A and A543V) mutants. Treatment for one month started one day after infection with 66 mg/kg moxifloxacin or 50 mg/kg levofloxacin given orally every 6 hours, 5 days-a-week. Antibiotic dosings were chosen in order to obtain pharmacokinetic parameters equipotent to 800 mg/day of moxifloxacin and 1000 mg/day of levofloxacin in humans.

Results: Moxifloxacin prevented mortality of mice infected with E540A, A543V GyrB mutants (MIC = 0.5

mcg/ml) and GyrA A90V mutant (MIC = 2 mcg/ml). Levofloxacin prevented mortality of mice infected with E540A GyrB mutant (MIC = 0.5 mcg/ml), reduced mortality of mice infected with GyrB A543V mutant (MIC = 1 mcg/ml) but not of mice infected with GyrA A90V mutant (MIC = 4 mcg/ml). CFU are pending.

Conclusion: High-dose levofloxacin is less active than high dose moxifloxacin against *M. tuberculosis* fluoroquinolone resistant mutants. Moxifloxacin should be preferred against XDR tuberculosis.

PC-927-05 Amplification to rifampicin resistance by not addressing isoniazid mono/polyresistance under India's MDR-TB programme

M Parmar,¹ K S Sachdeva,² S Balakrishnan,¹ A Amar Shah,^{1,2} M Ghedia,^{1,2} F Sayyed Imran,^{1,2} R Ramachandran,¹ A Sreenivas¹ ¹World Health Organization Country Office for India, New Delhi, ²Central TB Division, Ministry of Health and Family Welfare, New Delhi, India. e-mail: parmarm@searo.who.int

Background: Globally, India has world's highest burden of multidrug-resistant tuberculosis (MDR-TB) with ~3% in new, 12-17% in previously-treated TB cases. Among the later, pooled results of various sub-national DRS showed that other than R, any resistance to H (60-80%) was invariably associated with any poly-resistance to first line drugs (SH-23%, SHE-6%, HE-2%). Rapid scale-up of Programmatic Management of Drug resistant Tuberculosis (PMDT) continues in India with priority accorded to diagnosis and management of MDR-TB and XDR-TB. Early cohorts (2007-2010) of patients failing first line treatment and offered phenotypic DST (HRES) in 19 labs and LPA (HR) from 2009, revealed ~20% patients with mono/poly resistance to first line drugs other than R and were treated with standard first line intermittent regimen without modification under India's Revised National TB Control Programme (RNTCP). We studied its impact on treatment outcomes and resulting amplification of drug resistance.

Methods: Retrospective cohort analysis of treatment outcomes among TB cases with mono/poly resistance to first line drugs other than R, registered under RNTCP, treated with standard programme regimen and results of subsequent DST in cases who failed treatment, was done. Data on initial DST patterns, TB treatment outcomes and repeat DST in failures of standard programme regimen were extracted from programme records. Data was cleaned and validated before analysis.

Results: 8848 TB patients with mono/poly resistance to first line drugs were identified from lab records, whose treatment outcomes on standard programme regimen and subsequent DSTs could be traced. Overall failure rate to standard first line regimen ranged from 24-67%, of whom 35-64% amplified to R resistance on repeat DST with not much variation among new and previously treated patients. (Table 1).

Conclusion: Half of the patients with mono/poly drug resistance to first line drugs other than R, treated with standard first line intermittent regimen under failed

treatment and nearly half of them amplified to R resistance. Appropriate DST guided treatment regimen of mono/poly resistant TB cases and daily FDC based regimen for drug sensitive TB cases need to be systematically introduced under RNTCP with capacity building and resource allocations to generate evidence on improvement in treatment outcomes for all forms of TB and averting amplification of DR TB. This will have a crucial role in achieving the goals of End TB Strategy.

Table 1: Treatment outcomes of mono and poly resistant TB cases (other than R) treated with standard first line anti-TB regimen under RNTCP:

DST Pattern		Success	Failure	Amplification to R resistance
H Mono (LPA)	n= 6426	53%	24%	41%
SHE	n= 323	16%	67%	53%
HE	n=100	31%	54%	64%
SH	n=611	25%	54%	52%
SE	n=68	24%	49%	46%
H Mono (Phenotypic DST)	n= 819	31%	49%	40%
S Mono	n= 442	26%	49%	35%

PC-928-05 High efficacy of the Peruvian XDR-TB regimen for culture conversion in programmatic conditions

V Alarcon,^{1,2} D Vargas,³ J Cabrera,^{1,2} D Vela Trejo,^{1,2} R Espinoza,^{1,2} J Diaz,^{1,2} J Cornejo,^{1,2} A Mendoza,¹ A Valentina Antonieta,¹ A Mendoza-Ticona² ¹Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis, Lima, ²Peruvian National Tuberculosis Programme, Lima, ³Hospital Nacional Hipólito Unanue, Lima, Peru. e-mail: mendozalberto@hotmail.com

Background: XDR-TB cases have a high rate of fatality. Peru reports around 90 cases every year. In 2012, according to WHO guidelines, Peru began to treat XDR-TB with WHO's fifth group drugs: linezolid, imipenem/clavulanic acid completed by thioridazine and susceptible drugs according to a proportion of DST assay and moxifloxacin and capreomycin. Objective: To evaluate the efficacy of XDR-TB regimen for culture conversion in XDR-patients in their first six months of therapy.

Methods: Between May 2012 and December 2014, 56 XDR-TB patients (older than 15 years of age, culture-positive at diagnosis, with at least six months of treatment with monthly culture results) were evaluated through operational information. The average time and the proportion of culture conversion during the first six months were determined.

Results: Out of 56 patients, 52% were male; the age average was 34 years. The average for culture conversion was 2.1 ± 1.2 months. At the first month, 41% patients converted their culture and 100% during the first five months, (Figure).

Conclusion: The regimen based on linezolid, carbapenem/clavulanic acid and thioridazine was highly effective for culture conversion in XDR-TB patients in Peru during their first six months of treatment. The introduction of new drugs such as bedaquiline must be evaluated according relation between security and efficacy.

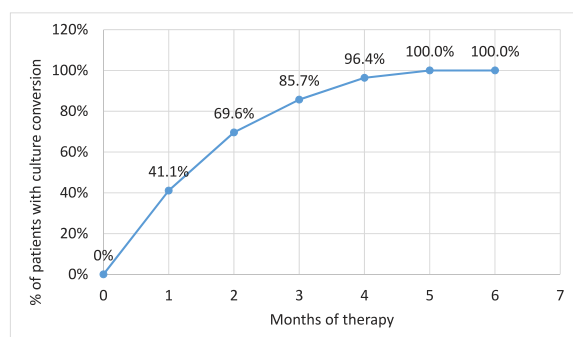


Figure. Culture conversion in XDR-TB patients treated with fifth group drugs and thioridazine, Peru

PC-929-05 Isoniazid, even at low dose, exerts some anti-tuberculosis activity against isoniazid-resistant *Mycobacterium tuberculosis* in mice

R Swanson,^{1,2} N Ammerman,^{1,3} C Moodley,¹ A Dorasamy,¹ A Tapley,^{1,4,5} J Grosset,^{1,3} C Rodrigues,⁶ D Almeida^{1,3} ¹KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, ²University of KwaZulu-Natal, Durban, South Africa; ³Johns Hopkins University School of Medicine, Baltimore, MD, ⁴Howard Hughes Medical Institute, Chevy Chase, MD, ⁵University of California San Francisco School of Medicine, San Francisco, California, USA; ⁶P.D. Hinduja National Hospital, Mumbai, India. e-mail: nicole.ammerman@gmail.com

Background: Multidrug resistant tuberculosis (MDR-TB) is defined as TB due to *Mycobacterium tuberculosis* that is resistant to both isoniazid (INH) and rifampicin, key first-line drugs in TB treatment. Resistance to INH can occur at relatively low levels such that the minimum inhibitory concentration (MIC) for *M. tuberculosis* is below the steady-state plasma concentration of INH after a high dose (15-20 mg/kg daily compared to the standard dosing of 5 mg/kg/day). Thus, high-dose INH is often included as part of a second-line regimen for the treatment of MDR-TB, despite that its effectiveness has not been clearly demonstrated either clinically or experimentally. The objective of this work was to evaluate the impact of low-, standard-, and high-dose INH in a mouse model of INH-resistant TB.

Design/Methods: BALB/c mice were infected with the following *M. tuberculosis* strains: wild-type, INH-susceptible H37Rv (MIC: 0.03 µg/ml); INH-resistant (low-level) H37Rv with inhA promoter mutation (MIC: 0.25-0.5 µg/ml); INH-resistant (high level) H37Rv with katG mutation (MIC: 8 µg/ml); and INH-resistant (intermediate level) LH4, a clinical isolate with the KatG S315T mutation (MIC: 2 µg/ml). Mice were treated for 4 weeks with one of the following regimens: (i) no drug control; (ii) INH at the standard therapeutic dose of 10 mg/kg (comparable to the 5 mg/kg dose in humans); (iii) INH at 5 mg/kg (half of standard dose); and (iv) INH at 20 mg/kg (double standard dose). Bacterial colony counts in the lungs were monitored throughout treatment.

Results: All untreated mice infected with any strain of *M. tuberculosis* died within 1-2 weeks after treatment initiation. In mice infected with the INH-susceptible

strain, INH at any dose had activity: static at 5mg/kg and cidal at 10 or 20 mg/kg. In mice infected with INH-resistant strains, INH at any dose prevented death during the 4 weeks of the study. Regardless of the level of INH resistance, INH at 5 or 10 mg/kg exhibited bacteriostatic activity and INH at 20 mg/kg exhibited limited bactericidal activity.

Conclusion: INH administered at low-, standard- or high-dose showed some benefit to mice infected with INH-resistant strains of *M. tuberculosis*. Based on this experiment, there appears to be some merit to administering INH, not necessarily at high-dose, in the treatment of MDR-TB, although further studies are needed to evaluate the activity of INH as part of a second-line regimen for MDR-TB treatment.

PC-930-05 Two-year survival in patients with XDR-TB from two provinces in South Africa

C Kvasnovsky,¹ M Van Der Walt² ¹University of Maryland, Baltimore, MD, USA; ²Medical Research Council of South Africa, Pretoria, South Africa. e-mail: ckvasno@gmail.com

Background: When extensive drug-resistant tuberculosis (XDR TB) was first described in 2006, outcomes were typified by high mortality. More favorable outcomes have been achieved, but mostly in settings with few HIV infected patients. We have a longitudinal dataset of XDR TB patients from the Eastern Cape (EC) and KwaZulu-Natal (KZN). The aim of this analysis is to determine 2-year survival and factors predictive of successful outcomes

Design/Methods: A retrospective cohort study of patients initiating treatment for XDR TB in these provinces from 2006-2008. HIV infected patients had access to ARVs. Data were collected from patient records. Patients with at least 2 consecutive negative sputum had achieved culture conversion. HIV patients not yet on ARVs. At onset of treatment were initiated on ARVs. At the end of the fourth month and defined as not on ARVs. Effective treatments were when a patient received at least 4 drugs to which their TB could be considered susceptible.

Results: 355 patients initiated XDR TB treatment, of which 62% were HIV-infected at treatment start, among which 59% had access to ARVs at onset. Many demographic and baseline clinical factors differed significantly between HIV-negative patients, HIV-positive on ART and HIV-positive not on ART. 50% of patients were smear-positive at onset, but significantly more so of HIV-positives on ART ($P = 0.02$). Patients were resistant to a median of 5 (range 4-6) drugs, and HIV uninfected patients significantly less ($P = 0.005$). 31% patients received effective treatment, among which the HIV-positives on ART significantly more ($P = 0.008$). After two years of treatment, 22% had achieved culture conversion, 27% patients were alive and still receiving treatment, and 10% had a favorable outcome. On multivariate analysis, predictors of favorable treatment outcomes were smear negative status at treatment start (hazard ratio [HR] 2.92, $P = 0.004$) and weight >50kg (HR 4.11, $P < 0.001$). HIV-negative patients had similar

outcomes as HIV-positive patients on ARVs. HIV-positive patients on ARVs were more likely to have favorable treatment outcomes than those patients not on ARVs. (HR 2.94, $P = 0.05$).

Conclusions: Even though many patients achieve culture conversion, 2 year survival and favorable outcomes are low. Early identification of and suitable interventions are needed for patients failing treatment to result in improved outcomes.

PC-931-05 Polymorphisms in the vitamin D receptor gene reduce the rate of sputum culture conversion in multidrug-resistant tuberculosis patients in South Africa

M Magee,¹ Y Sun,² S Shah,^{2,3} S Allana,² J Brust,⁴ Q Hui,² T Mthiyane,⁵ N Gandhi² ¹Division of Epidemiology and Biostatistics, School of Public Health, Georgia State University, Atlanta, GA, ²Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, ³U.S. Centers for Disease Control and Prevention, Atlanta, GA, ⁴Divisions of General Internal Medicine and Infectious Diseases, Albert Einstein College of Medicine, Bronx, NY, USA; ⁵University of KwaZulu-Natal, Durban, South Africa. e-mail: mjmagee@gsu.edu

Background: Vitamin D is an anti-inflammatory regulator of the T-helper 1 response to tuberculosis (TB) and also mediates the induction of the antimicrobial peptide cathelicidin. Deficiency of 25-hydroxyvitamin D and single nucleotide polymorphisms (SNPs) in the vitamin D receptor (VDR) gene may increase the risk of TB disease and decrease culture conversion rates in drug susceptible TB. Whether these VDR SNPs are found in African populations or impact multidrug-resistant (MDR) TB treatment has not been determined. We aimed to determine if SNPs in the VDR gene were associated with sputum culture conversion among a cohort of MDR TB patients in South Africa.

Design/Methods: We conducted a prospective cohort study of adult MDR TB patients receiving second-line TB treatment in KwaZulu-Natal province. Subjects had monthly sputum cultures performed. In a subset of participants, whole blood samples were obtained for genomic analyses. Genomic DNA was extracted and genotyped with Affymetrix Axiom Pan-African Array. Standard quality control procedures were applied including sex-mismatch, 95% call rate, Hardy-Weinberg Equilibrium, outlier of population structure, and minor allele frequencies higher than 5%. Generalized linear Poisson and Cox proportional models were used to determine the association between VDR SNPs (additive effect) and the rate of culture conversion.

Results: Genomic analyses were performed on 96 MDR TB subjects enrolled in the sub-study; 60% were female and median age was 35 years (interquartile range [IQR] 30-42). Smoking was reported by 21% of subjects and most subjects had HIV (81%), were smear negative (57%), and had cavitary disease (56%). Overall, 92 (97%) subjects converted cultures to negative, with median time to culture conversion of 57 days (IQR 17-114). Of 121 VDR SNPs examined, 8 were significantly

associated ($P < 0.01$) with both days to culture conversion and rate of sputum conversion in multivariable analyses. Each additional risk allele on SNP rs74085240 delayed culture conversion significantly (adjusted hazard ratio 0.42, 95% confidence interval 0.22-0.78).

Conclusion: Polymorphisms in the VDR gene were associated with time to sputum culture conversion in MDR TB patients in this high HIV prevalence setting in South Africa. Future studies are needed to investigate the functional roles of these VDR polymorphisms and their implications for treatment.

28. Drug-resistant TB: epidemiology and transmission

PC-932-05 Primary transmission of drug-resistant tuberculosis in South Fly District, Western Province, Papua New Guinea

S Hiasihri,¹ A Honjepari,¹ A Aia,² L John,² E Lavu,³ C Coulter,⁴ G Chan,⁵ D Paison² ¹Provincial Health Office, Daru, ²National Department of Health, Port Moresby, ³Central Public Health Laboratory, Port Moresby, Papua New Guinea; ⁴Queensland Mycobacterial Reference Laboratory, Brisbane, Queensland, ⁵Burnet Institute, Melbourne, Victoria, Australia. e-mail: suman.majumdar@burnet.edu.au

Background: Tuberculosis is a major public health issue in Western Province PNG. In 2013 the case notification rate for TB was 912 per 100 000 and it was the leading cause of hospital admissions and deaths. TB has placed an immense burden on a struggling health system. Adding to the challenge is the emergency and transmission of MDR-TB and XDR-TB.

Design/Methods: A retrospective cohort study using routine program data from the PMDT registers was conducted. Cases that were TB treatment naïve were identified as possible cases of primary transmission. Demographic and clinical details were collected. The DST results for MDR-TB and XDR-TB cases were reviewed to identify implications for programmatic management.

Results: There have been 216 cases of MDR-TB enrolled in care from January 2012 to December 2014. The data from the TB cohort at Daru General Hospital shows that the proportion of treatment-naïve cases enrolled in MDR-TB care increased from 31% in 2012 to over 50% in 2014. Twelve case of XDR-TB have been identified since 2012. Drug-susceptibility testing on available samples with rifampicin resistance revealed high rates of resistance to several TB drugs: pyrazinamide (56.6%), streptomycin (96%), fluoroquinolones (15%), ethionomide (99%). Demographic, clinical characteristics and interim cohort outcomes will be described.

Conclusion: Evidence of primary transmission of DR-TB, including XDR-TB strains is of concern in South Fly District, PNG. Western Province is in the process of scaling up its TB program in partnership with technical

partners and a national level taskforce to implement an accelerated response to the challenges of TB and DR-TB.

PC-933-05 Molecular characterization of MDR-TB and XDR-TB strains among tuberculosis patients in Chad

G W Ossoga,^{1,2} A Ba Diallo,² R Ngandolo,¹ A Thiam,² F Gehre,³ I Ndoeye,⁴ B De Jong,⁵ A Gaye-Diallo²

¹Veterinary and Zootechnical Research Laboratory of Farcha, N'djamena, Chad; ²Bacteriology and Virology Laboratory. CHNU Le Dantec, Dakar, Senegal; ³Medical Research Council Unit, Fajara, Banjul, Gambia; ⁴Biology Plant Department, Science and Technology Faculty, University Cheikh Anta Diop of Dakar, Dakar, Senegal; ⁵Institute of Tropical Medicine, Antwerp, Belgium. e-mail: ossogagedeon@gmail.com

Background: Tuberculosis is a public health concern worldwide particularly in Chad where culture and resistance testing were not performed regularly. We genotyped *Mycobacterium tuberculosis* complex strains from patients who presented with pulmonary tuberculosis from different cities in the country and performed resistance tests to anti-tuberculosis drugs.

Design/Methods: Sputum from different cities in Chad were collected at different microscopy centers using cetyl-pyridinium chloride between 2007 and 2012. Genetic characterization was applied using standard spoligotyping and MIRU-VNTR after culture based on Löwenstein Jensen media. We used the Genotype M. TUBERCULOSIS DRplus v.2 and the BACTEC MGIT 960 for resistance testing.

Results: The study population of 486 New and 107 retreatment cases included 224 men (72%) and 87 women (28%). The age of patients was ranged from 12 to 70 years. 311 (52.5%) strains were genotyped successfully out of which 304 (97.8%) were modern sub-lineages and 7 (2.25%) ancestral sub-lineages. Resistance tests among new cases gave 1.6% strains mono-resistant to rifampicin, 4.5% strains resistant to isoniazid and 0.96% MDR strains. For patients in retreatment, 3.8% strains were mono-resistant to rifampicin, 9.0% to isoniazid, 3.5% were MDR and 0.6% were XDR.

Conclusion: For the first time in Chad we identified XDR-TB strains and a rate of 4.5% MDR-TB strains. These resistant strains were found to be associated with the CAM family.

PC-934-05 The timeline of developing MDR-TB among contacts of MDR-TB patients, 2009-2012, Taiwan

P-C Chan,^{1,2,3} C H Liu,^{1,3} Y H Huang,¹ H Y Tsai,¹ K-F Wang,¹ P-H Lee,¹ C-H Chen¹ ¹Division of HIV/AIDS and TB, Taipei City, ²Institute of Epidemiology and Preventive Medicine, Taipei City, ³Department of Pediatrics, Taipei City, Taiwan. e-mail: pcanita.tw@cdc.gov.tw

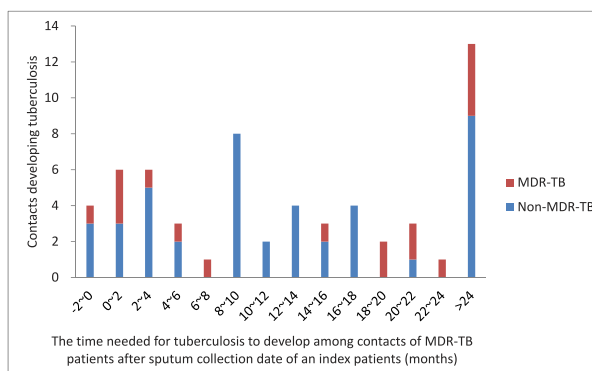
Background and challenges to implementation: Despite slowly increasing coverage of multidrug-resistant tuberculosis (MDR-TB) treatment, contacts of MDR-TB patients rarely receive preventive therapy. The manage-

ment of contacts of MDR-TB patients is challenging as the evidence base recommending best practices is very limited. Follow-up studies for development of MDR-TB among contacts of MDR-TB patients are scarce. Since April 2009, sending clinically reported MDR-TB strains to the National Mycobacteria Laboratory for confirmation before registry in Taiwan has been required. Our aim is to determine the timeline, rate and risk factors of development of MDR-TB among contacts of MDR-TB patients.

Intervention or response: We conducted a retrospective cohort study among contacts whose index cases were MDR-TB patients registered on the National web-based TB Registry between April 2009 and December 2012. All contacts were cross-linked to the National web-based TB Registry in April, 2015 to identify whether the contact developed active TB or MDR-TB during follow-up. We used the sputum collection date of an index patient related to a contact as the starting point for calculating the time needed for MDR-TB to develop among contacts. χ^2 test was used to determine risk factors for developing MDR-TB among contacts.

Results and lessons learnt: A total of 565 MDR-TB patients were registered during the study period and 550 patients (97%) had at least one contact registered in the system. During follow-up, 60 contacts (0.9%) developed active TB and 17 (0.3%) developed MDR-TB out of the 6568 contacts. Figure shows the progression of active TB among contacts; 4 contacts developed MDR-TB beyond a 2-year- follow-up (24%). After a 24 month-follow-up of contacts after index patient sputum collection, six contacts (46%) developed MDR-TB at 0-6 months; one contact (8%) at 7-12 months; one contact (8%) at 13-18 months; and five contacts (38%) at 19-24 months. Contact sharing a household with index patients were 2.8 (95% confidence interval: 1.1-7.4) times more likely to develop MDR-TB compared to those not sharing a household with index patients. Contacts of index patients with smear-positive or cavitation were 5.2 (1.5-18.1) and 3.1 (1.2-8.1) times more likely to develop MDR-TB compared to those without.

Figure. The Timeline of Developing Tuberculosis among Contacts of MDR-TB Patients



PC-935-05 Whole-genome sequencing to delineate transmission of multidrug-resistant tuberculosis in Shanghai, China: a cross-sectional study

C Yang,¹ T Luo,¹ X Shen,² J Wu,² J Mei,² K Deriemer,³ Z Yuan,² Q Gao¹ ¹Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, Institutes of Biomedical Sciences and Institute of Medical Microbiology, Shanghai Medical College, Fudan University, Shanghai, ²Department of TB Control, Shanghai Municipal Center for Disease Control and Prevention, Shanghai; ³School of Medicine, University of California, Davis, Davis, CA, USA. Fax: (+86) 021-5423-7195. e-mail: yangstoptb@gmail.com

Background: Multidrug-resistant (MDR) tuberculosis (TB) is a threat to tuberculosis elimination. MDR-TB can be acquired during inappropriate treatment and case management, or can be caused by person-to-person transmission and infection with a MDR strain. We investigated the magnitude of and risk factors for MDR-TB cases arising from recent transmission of MDR strain in China.

Design/Methods: We identified MDR TB notified in Shanghai from Jan 1, 2009 to Dec 31, 2012. We used variable number of tandem repeats (VNTR) genotyping of clinical isolates of *Mycobacterium tuberculosis* to identify clusters of TB cases with identical genotypes, followed by whole genome sequencing (WGS) of the VNTR-clustered isolates for higher resolution. We estimated the proportion of TB cases in clusters defined by WGS, calculated the pairwise genomic distances between isolates within each cluster, and used logistic regression to identify the risk factors associated with clustering. We constructed and interpreted network diagrams of the clusters derived from genotypic and epidemiological data.

Results: There were 343 patients diagnosed with MDR TB, of whom 324 (94.5%) had VNTR genotyping profiles. There were 125 (38.6%) TB cases in 45 VNTR clusters, and 122 clustered isolates were successfully sequenced. The genetic distance between the isolates of clustered cases ranged from 0-109 single nucleotide polymorphisms (SNPs). There were 38 clusters with 2-10 TB cases whose 103 (84.4%) isolates differed by 12 or fewer SNPs. Epidemiological links were identified in 56.5% of clustered TB cases, and the isolates from the epidemiologically linked TB cases were separated by 12 SNPs or less. Being a local resident versus an urban migrant (OR, 5.32, 95%CI, 3.08-9.20) and having a delayed diagnosis of at least two months (2.57, 95%CI, 1.29-5.11) were the risk factors that were significantly associated with WGS clustering. Residential communities were the most common setting of MDR TB transmission, and clustered individuals lived a relatively short distances from each other. The majority (73.7%, 28/38) of clustered MDR-TB isolates harbored compensatory mutations in the *rpoA*, *rpoB* and *rpoC* genes.

Conclusion: Recent transmission of MDR TB in the study population was high. Multiple strategies, including rapid diagnosis and effective case management, are

urgently needed to prevent the transmission of MDR-TB in China.

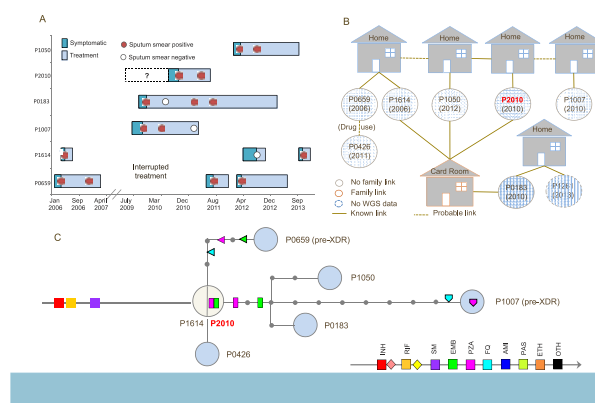


Figure Detailed investigation of cluster nine. Time of onset of symptoms, diagnosis, and treatment (A). Epidemiological network (B). Genetic distance and drug-related resistance mutations of WGS-based clusters. Each circle represents clustered patients who were infected with isolates separated by no SNPs; the size of circle indicates the number of patients; Black dots are added when patients within circles are separated by more than one SNP; Colored labels on the solid line represent drug-related resistant mutations during the transmission chains, and label within a circle represents mutations emerged within patients (C).

PC-937-05 *Mycobacterium tuberculosis* lineage is more strongly associated with MDR-TB infection than treatment history in the Republic of Georgia

N Bablishvili,¹ N Tukvadze,¹ N Bzekalava,¹ S Sengstake,² I Bergval,² S Alba,² R Anthony,² R Aspindzelashvili¹

¹National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; ²Royal Tropical Institute (KIT), Amsterdam, Netherlands. Fax: (+995) 322 910 467. e-mail: marikushane@yahoo.com

Background: A history of Tuberculosis (TB) treatment increases the risk of multidrug resistant (MDR) TB. MDR-TB may result from acquired resistance or reinfection with resistant bacteria. In the Republic of Georgia and other settings with a high burden of MDR-TB the *Mycobacterium tuberculosis* Beijing lineage is associated with MDR-TB. Typing and lineage identification of clinical isolates is usually performed retrospectively, if at all, and often reported apart from patient and drug susceptibility data. Consequently the association between *M. Tuberculosis* lineage and the MDR-TB epidemic is not fully explored.

Design/Methods: Patient treatment history, DST profiles and *M. Tuberculosis* genotype were determined for 399 diagnostic pulmonary TB samples collected at the National Center for Tuberculosis and Lung Diseases in Tbilisi, Georgia in 2012 and 2013. Association between MDR-TB, patient treatment history and strain characteristics were examined by univariate and multivariate logistic regression.

Results: Out of 74 M(X)DR TB samples identified, 63 (85.1%) were assigned to the Beijing lineage and within these group previous treatment was reported for 38

(51.4%). The Euro-American lineage dominated 248 of 399 (62.2%) strains and the Beijing lineage accounted for 140 of 399 (35.1%) strains. Cluster analysis of all 399 strains revealed two major M(X)DR-TB clusters one of which was formed entirely of Beijing M(X)DR strains. In total 42/74 (56.8%) M(X)DR-TB strains were part of a cluster. In univariate analyses individuals infected with a Beijing strain had 25-fold higher odds of being MDR-TB than individuals infected with a Euro-American strain; retreatment patients had 4-fold higher odds of being infected with an MDR-TB. Multivariate analysis confirmed that the effects of Beijing strain and retreatment were independent.

Conclusion: In our results infection with the *M. Tuberculosis* Beijing lineage is more strongly associated with multidrug resistance than treatment history. Furthermore, majority of M(X)DR cases were clustered, suggesting that the driving force of the MDR-TB epidemic in this setting is transmission. Strengthening Infection Control measures that interrupt transmission chains will therefore be expected to strongly impact the incidence of MDR-TB. *M. Tuberculosis* genotyping when combined with patient and DST information can provide clues to the dynamics of MDR-TB transmission and this type of analysis would be interesting to perform in other settings where associations may be different.

PC-938-05 Drug resistance patterns in a northeast Indian state through a line probe assay laboratory functioning in PPM mode

M Mawlong,¹ K Ranee,¹ G Singh,² M Puthenchirayil,² V Sameer,^{3,4} T Thomas,^{3,4} P Varghese² ¹Nazareth Hospital, Shillong, ²Catholic Bishop Conference of India - Coalition for AIDS and Related Diseases, Delhi, ³The Catholic Health Association of India, Secunderabad, ⁴Catholic Health Association of India, Secunderabad, India. e-mail: sameer-valsangkar@chai-india.org

Background and challenges to implementation: Access to drug susceptibility testing (DST) is limited in many regions in India and the transport of samples to regional centres implies a diagnostic and treatment delay which contributes to the rising burden of MDR TB. Early diagnosis of RIF mono-resistance and multidrug resistance is paramount to reduce treatment failure, provide a targeted intervention and reduce initial loss to follow up. Public private mix initiatives provide a sustainable model to expand the reach of DST in a universally accessible manner with minimal delay.

Intervention or response: The LPA laboratory at Nazareth Hospital, Shillong is a certified state level referral centre catering to all 7 districts in the state with a combined population of 2.65 million. The laboratory was established in the PPM mode without external funding. Resistance patterns were evaluated among samples over a period of two years from March 2013 to March 2015.

Results and lessons learnt: A total of 690 samples were processed in a mean duration of 3.75 ± 1.69 days ranging from a minimum of one day to a maximum of 20 days. 453 (65.65%) men and 237 (34.35%) of women

were tested with a mean age of 34.49 ± 14.37 years. 223 (32.32%) of the samples exhibited multidrug resistance, 47 (6.81%) exhibited INH mono-resistance and 34 (4.93%) exhibited RIF mono-resistance. 297 (43.04%) were sensitive to both drugs and results were not available for 89 (12.9%) samples. Females were significantly more likely to present with MDR (P value = 0.02).

Conclusions and key recommendations: For every two patients with MDR, one patient presents with INH or RIF mono-resistance. 10% of the sample could not be processed and some of these may have been atypical Mycobacteria. LPA provides a sensitive, cost effective approach to detect both MDR and INH or RIF mono-resistance which can be rolled out as a PPM initiative.

PC-939-05 Drug-resistant tuberculosis in Turkmenistan: results of the first nationwide survey

M Durdyeva,¹ S Tomasova,² B Karriyeva,^{3,4} M Dara,⁵ H Hoffmann,⁶ M Zignol,⁷ P De Colombani,⁸ A Dadu⁸

¹Medical University of Turkmenistan, Ashgabat, ²National Center of Infectious Diseases, Ashgabat, Turkmenistan;

³World Health Organization Temporary Adviser, Yerevan, Armenia; ⁴World Health Organization, Ashgabat, Turkmenistan; ⁵World Health Organization, Brussels, Belgium; ⁶Institute of Microbiology & Laboratory Medicine, Gauting, Germany; ⁷World Health Organization, Geneva, Switzerland; ⁸World Health Organization, Regional Office for Europe, Copenhagen, Denmark. e-mail: dad@euro.who.int

Background: The first countrywide anti-tuberculosis (TB) drug resistance survey in Turkmenistan was carried out from August 2012 to February 2013.

Design/Methods: To investigate the levels and patterns of resistance to first-line anti-TB drugs among new and previously treated pulmonary TB cases and explore the risk factors for multidrug-resistant (MDR) TB. Cross-sectional study with sampling of all 64 (100%) TB diagnostic units in the country. All consecutive patients meeting the specific criteria for survey eligibility were enrolled into the study during the data intake period. Sputum samples were transported to the National TB Reference Laboratory for bacteriological culture and drug susceptibility testing to first-line anti-TB drugs.

Results: Of the 731 patients enrolled, 561 were newly-diagnosed and 170 previously treated TB patients. MDR-TB was found in 13.9% (95%CI: 11.1-17.0) among the new patients and 37.6% (95%CI: 30.3-45.4) among the previously treated patients. History of previous anti-TB treatment was a risk factor for MDR-TB (OR: 3.66; 95%CI: 2.45-5.46). None of the socio-behavioral and demographic factors explored were found associated with MDR-TB.

Conclusion: This is the first countrywide survey of anti-TB drug resistance ever conducted in Turkmenistan. It was implemented according to international standards and provides valuable information for the future planning of effective programmatic management of drug resistant TB in the country.

PC-940-05 TB drug-resistant patterns of new multidrug-resistant TB cases in Moscow

S Borisov,¹ S Safonova,¹ E Belilovsky,¹ I Danilova¹

¹Moscow Scientific and Clinical Center for TB Control, Moscow, Russian Federation. Fax: (+7) 495 964 86 37. e-mail: belilovs.ky@gmail.com

Background: Information about TB drug-resistant patterns for different groups of patients (data about TB drugs, for which the strain of *M. tuberculosis* was resistant) is needed for planning and coordination of activities for choice and prescription of treatment regimens and chemotherapy control for multidrug-resistant TB (MDR TB) patients, including extensively drug-resistant (XDR TB) cases.

Design/Methods: Data of TB drug resistant (DR) for 82 new (NC) and 126 re-treatment (RTC) MDR-TB patients registered in 2014 in Moscow, Russia, were analyzed. According to city TB control regulations all MDR TB patients were tested on drug susceptibility to the first line TB drugs (FLD), fluoroquinolone (FqR-TB) and injectable second-line drugs (ISLDR-TB).

Results: NC and RTC included 70.7% and 77.0% men and age medians of 40.5 (IQR=31.5-56) and 40.0 (IQR=33.5-50), accordingly, $P > 0.05$. RTC patients more often than NC demonstrated resistance to all FLD, including streptomycin (S) and ethambutol (E): 38.1% vs. 24.4%, OR=1.2 (95%CI: 1.01-1.5). XDR-TB was registered among 20.7% (12.6-31.1) NC with MDR-TB and among 23.0% (16.0-31.4) RTC, $P > 0.05$. 'Pre-XDR-TB (f)', which was defined as MDR-TB plus FqR-TB cases, was more common among RTC (19.1%) than NC (8.5%): OR=1.13 (1.01-1.3). 'Pre-XDR-TB (i)', which was defined as MDR-TB plus ISLDR-TB cases, was slightly more common among RTC (22.2%, 15.3-30.5) than NC (19.5%, 11.6-29.4), $P > 0.05$. There was no statistical differences for RTC and NC in DR to levofloxacin (12.7% and 13.4%), and moxifloxacin (8.7% and 7.3%, accordingly). At the same time, 41.3% of RTC patients had TB with resistance to ofloxacin vs. 24.4% for NC: OR=1.3 (1.1-1.6). There was no statistical differences for RTC and NC in DR to amikacin (7.9% and 14.6%), capreomycin (13.5% and 6.1%, accordingly) and kanamycin, for which the very high level of DR was found for both groups of patients: 40.8% (34.1-47.9).

Conclusion: Variety of DR patterns among new and retreatment patients confirms significant role of drug susceptibility testing (DST) data for the assignment of successful regimens of MDR TB chemotherapy based on as DST results as well empirical data.

PC-941-05 Ongoing multidrug-resistant tuberculosis transmission in Ghanzi district, Botswana, 2012–2014

C Modongo,¹ D Mbatshi,¹ A Finlay,^{2,3} R Boyd,^{2,3}

J Oeltmann,³ E Click,³ P Moonan,³ N Zetola¹ ¹Botswana University of Pennsylvania Partnership, Gaborone, ²U.S. Centers for Disease Control and Prevention, Gaborone, Botswana; ³U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: afinlay@cdc.gov

Background: Ghanzi, a rural district in Botswana, is characterized by a low population density (0.4 persons/km²), a high burden of tuberculosis (TB) (>1000/100 000 population), and high prevalence of HIV among TB patients (36%). In 2008, the prevalence of MDR-TB among new and previously treated patients was 2.5% and 6.6% respectively. The Kopanyo study was designed to use molecular epidemiologic methods combined with geospatial and demographic information to identify previously unrecognized TB transmission among social networks and to identify geographic hot-spots for transmission in Botswana.

Methods: From Aug 2012 to Dec 2014, *Mycobacterium tuberculosis* isolates collected from culture-positive pulmonary TB cases reported in Ghanzi underwent drug-susceptibility testing of rifampicin, isoniazid, ethambutol and streptomycin and 24-locus mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) analysis. TB genotype clusters were defined as ≥ 2 case-patients with matching 24-locus MIRU-VNTR results. The number of clusters, cluster size and the proportion of patients in a cluster were analysed. Patients were interviewed and their clinical records reviewed to identify potential epidemiologic linkages.

Results: A total of 314 cases were reported in Ghanzi, including 11 (3.5%) with multidrug-resistant (MDR) TB. Genotyping results were available for 288 participants. In total, 86 different genotypes were identified, including 27 clusters. Median cluster size was 14 (interquartile range: 3–76). The proportion of patients included in genotype clusters was 169/288 (59%). One cluster of 9 patients included 9 (82%) of the 11 MDR-TB cases diagnosed. This was the only cluster with MDR-TB cases. Among the MDR-TB genotype cluster members, 7 (78%) belonged to the same minority ethnic group (Basarwa). Epidemiologic linkages between MDR-TB cluster members were established for 7 (78%) cases and 5 (71%) of them had no prior TB treatment. All 7 were from two communities and 4 (29%) had non-household, community-based linkages.

Conclusion: These results suggest potential MDR-TB transmission in Ghanzi. A robust public health response of community-based targeted testing for active TB and treatment is underway to identify potential undiagnosed secondary cases, including long-term follow-up of exposed contacts to monitor progression to disease.

29. LTBI testing, perceptions and epidemiology

PC-942-05 Tuberculin skin testing and QuantiFERON TB Gold In-Tube to indicate the treatment of latent tuberculosis infection in people living with HIV

J Souza,¹ M D S Evangelista,^{1,2} J P Toledo,² F Dockhorn,² A Trajman^{3,4} ¹University of Brasilia, Brasilia, Distrito Federal, ²Ministry of Health, Brasilia, Distrito Federal, ³Federal University of Rio de Janeiro, Rio De Janeiro, Rio de Janeiro, Brazil; ⁴Montreal Chest Institute, McGill University, Montreal, Quebec, Canada. e-mail: josianemaria@unb.br

Background: Human immunodeficiency virus (HIV) is one of the risk factors for infection and development of tuberculosis (TB) in people living with HIV (PLHIV), hence the importance of early identification of Latent TB infection (LTBI) and prophylactic treatment in this population. We analysed the use of the tuberculin skin test (TST) and QuantiFERON-TB Gold in-Tube (QTF-GIT) to identify latent tuberculosis infection in people living with HIV and the outcome of cases treated with isoniazid.

Method: The sample consisted of 300 PLHIV selected in eight outpatient sexually-transmitted disease public clinics in Federal District were submitted to QTF-GIT and TST, between 2011 and 2013, with follow-up until May 2014. A positive result of either test was considered as LTBI. The association of independent variables and a positive result was estimated by the adjusted odds ratio (OR) in a multivariate model using logistic regression. Wilcoxon's non-parametric test was used.

Results: The mean CD4 was 477.5cells/mm³. Eighteen patients (6%, 95%CI: 3.6%-9.3%) had LTBI, of whom 4 (1.3%, 95%CI: 0.04%-2.63%) had only a positive TST, 8 (2.7%, 95%CI: 0.8%-4.5%) had only a QTF-GIT positive test and 6 (2%, 95%CI 0.4%-3.6%) had positive results for both tests. This represents an 81.8% relative increase in LTBI detection when QTF-GIT is added to TST. The concordance between both tests was 96% ($k = 0.48$). In the follow-up, one patient was excluded who revealed a history of TB, leaving 17 patients with LTBI (5.1%), 12 (70.6%) of whom received isoniazid preventive therapy (IPT)-none of them became ill due to TB. The mean protection after the IPT was 495.4 days for QTF-GIT+ and 540 days for TST ≥ 5 mm. Two cases of pulmonary TB were identified among the patients with negative results on the QTF-GIT and TST.

Conclusion: The results revealed a low prevalence of LTBI based on the results of the TST and QTF-GIT among the PLHIV with mild immunosuppression in a scenario of low TB load. The QTF-GIT alone was more effective to detect LTBI than TST alone and had an 81% added value as an add-on sequential test. There was protection of IPT by the results of the two tests, however studies are needed to assess other risk factors and biomarkers. In addition, a longer follow-up period is needed to assess the durability of isoniazid protection

based on the result of the QTF-GIT and the assessment of the cost-effectiveness relation of using QTF-GIT among the PLHIV.

PC-943-05 Optimization of latent tuberculosis screening for new refugees in Canada

L Delmar,¹ D Fisher,¹ N Hajjar,² J Jarand,¹ S Field,¹ H Gardiner³ ¹University of Calgary, Calgary, AB, ²Refugee Health Clinic, Calgary, AB, ³Tuberculosis Services, Calgary, AB, Canada. e-mail: ljdelmar@ucalgary.ca

Background and challenges to implementation: The refugees arriving in Canada from tuberculosis (TB) endemic countries experience a higher prevalence of latent tuberculosis infection (LTBI) and are at a higher risk for TB reactivation than other migrant groups. The pre-arrival immigration medical examination aims to detect cases of infectious pulmonary TB disease but does not include screening for LTBI. Canadian guidelines recommend targeted screening and preventive treatment for LTBI as a strategy for TB control and prevention in new refugees. There is a joint partnership for LTBI screening and treatment between TB Services and the Refugee Health Clinic (RHC) in Calgary, Alberta.

Intervention or response: Patients were screened at RHC with the tuberculin skin test (TST). Those with a positive TST (10mm cut-off) received a confirmatory interferon gamma release assay (IGRA) test to improve diagnostic specificity and chest X-ray (CXR) to rule out pulmonary TB prior to physician assessment at Calgary TB Services. Only those with positive IGRA findings or abnormal CXR were clinically assessed at TB Services. A retrospective chart review of refugees screened at RHC from November 2013 to December 2014 was performed to investigate the process.

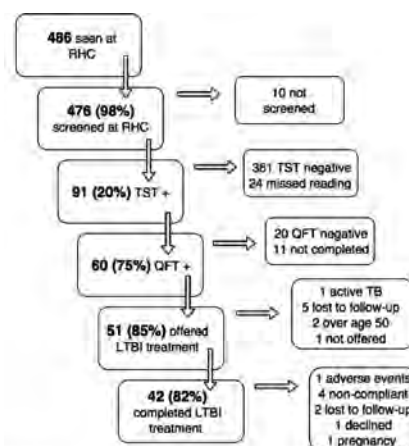


Figure 1: Flow chart of the latent tuberculosis screening process for refugees in Calgary, Canada from November 2013 to December 2014.

Results and lessons learnt: A total of 476 patients were screened with the TST at RHC and 91 were positive with the 10mm cut-off. Eighty of those patients (80/91) completed an IGRA test which confirmed 60 cases of LTBI at a concordance rate of 75% (60/80). At TB Services, 51 patients were offered a 3-month regimen of isoniazid/rifampin and the rate of treatment completion

was 82% (42/51). The median time from arrival in Canada to confirmed LTBI diagnosis was 113 days, which is within the 2-year period of increased risk for TB reactivation. Throughout the process there was patient drop-off in that 5% (24/476) did not return for the TST reading, 12% (11/91) did not complete the IGRA test, 8% (5/60) did not follow up at TB Services and 12% (6/51) did not complete treatment because they were lost to follow-up or non-compliant.

Conclusions and key recommendations: The investigation of the LTBI screening process in Calgary revealed a high rate of LTBI treatment completion in a population that has been historically hard to reach. Addressing the areas of patient drop-off throughout the screening process would improve the rate of detected LTBI and increase opportunity for TB prevention and elimination.

PC-944-05 Risk predictors for developing tuberculosis among adult tuberculosis contacts

P-C Chan,^{1,2,3} Y H Huang,¹ M-J Lu,¹ P-H Lee,¹ C B Hsu,¹ K-F Wang,¹ C-H Chen¹ ¹Centers for Disease Control, Taipei City, ²National Taiwan University, College of Public Health, Taipei City, ³National Taiwan University, College of Medicine, National Taiwan University Hospital, Taipei City, Taiwan. e-mail: pcanita.tw@cdc.gov.tw

Background: Tuberculin skin test (TST) is not routinely recommended for tuberculosis (TB) contacts born before January 1, 1986 in Taiwan due to the concern of bacille Calmette-Guérin (BCG) immunization beyond infancy and isoniazid preventive therapy (IPT) related hepatotoxicity. A pilot program launched during 2010–2012 provided both TST and QuantiFERON®-TB Gold In-Tube (QFT-IT) test to contacts born before January 1, 1986. This study is meant to evaluate the risk predictors for developing TB among these contacts.

Design/Methods: 2203 contacts aged 29 years or older, who received both tests in the pilot program in eleven townships, were enrolled for model derivation. All contacts were cross-linked to the National web-based TB Registry on April 10, 2015 to identify if the contact developed active TB during follow-up. Contagiousness of TB index cases, comorbidities of contacts, results of TST and QFT-IT, exposure periods, and relationships between index cases and contacts were used to generate a Cox proportional hazards model. We used the notification date of an index case related to a contact as the starting point. The endpoint of event-free time could be earlier than the follow-up end date, including: the date on which the contact was notified as an active TB case (event), the date of the commencement of IPT in a contact (censored), or the date of mortality due to any cause (censored).

Results: Of 2203 contacts who completed both TST and QFT-IT, 415 (18.8%) were double-positive (TST $\geq$ 10mm and QFT-IT $\geq$ 0.35 IU/mL) and 194 (47%) of these completed LTBI treatment. Amongst those who received or did not receive IPT, only exposure period was statistically significant ($P = 0.042$, χ^2). The number needed to treat for contacts with double-positive results was 43. At the end of follow-up, 52 contacts died and 8

TB cases developed among contacts: 7 from the contacts with double-positive results and one from the contacts with double-negative results developing culture-confirmed TB at three months after contact investigation (TB risk: 0.032 vs. 0.0006, $P < 0.001$ for Poisson analysis). The table shows a final multivariate Cox regression analysis. The Contacts with double-positive results had a TB risk of 1690/100 000 compared to 60/100 000 for those with single-positive or double-negative results (adjusted hazard ratio [aHR]: 50.9, 95% confidence interval [CI]: 5.9-439.8). Household contacts had a TB risk of 640/100 000 compared to 90/100 000 for non-household contacts (aHR: 9.9, 95%CI: 1.1-93.0).

Conclusion: Among contacts who received BCG immunization beyond infancy, the predictors for developing active TB were double-positivity tested by both TST and QFT-IT and the sharing of a household between index cases and contacts. For adult contacts of contagious TB patients, LTBI screening by using TST and QFT-IT in conjunction with LTBI treatment could be helpful for achieving global TB control goals for 2035.

PC-945-05 Therapeutic education in latent tuberculous infection: analysis of patients' and relatives' needs and proposal of a list of competences to acquire

S Le,¹ A Artebasse-Medjahed,² A Rouault,¹ C Brahmy,² A Bozize,² C Guillet Caruba,³ O Bourdon,¹ F Doucet-Populaire³ ¹Assistance Publique Hôpitaux Paris, Hôpital Robert Debré, Université Paris 13, Paris, France, ²Centre de Lutte Antituberculeuse des Hauts de Seine, Nanterre, ³Assistance Publique Hôpitaux Paris, Hôpital Antoine Béchère, Université Paris Sud, Clamart, France. e-mail: florence.doucet-populaire@abc.aphp.fr

Background: Prevention of Tuberculosis (TB) has major public health implications. We focus on latent tuberculosis infection (LTBI) because its treatment is a key component for controlling and reducing TB disease incidence. For LTBI, starting treatment and following it through is difficult to understand for asymptomatic patients. The patient's acceptance of LTBI treatment is often influenced by the initial approach of the health care provider. French Speaking Pneumology Society recommends therapeutic patient education (TPE) for these patients, however there is no competence guidelines. Our objective was to identify patients' and their relatives' educational needs and to establish a list of competences that patients have to acquire during this TPE program for LTBI.

Design/Methods: Interview guidelines for patients and health care professionals were written following literature analysis. On the basis of these guidelines, semi-structured interviews were conducted until data saturation was reached. Twelve patients (7 males, 5 females, and aged 14 to 49) from a 'fight against TB center' near Paris (Centre de Lutte Anti-Tuberculeuse des Hauts-de-Seine (CLAT)) and 14 health professionals (3 lung specialists, 4 pediatricians, 4 nurses, 1 pharmacist, 1 psychologist and 1 anthropologist) were interviewed.

Results: From these interviews, we identified 32 learning objectives belonging to one of the following topics: knowledge of the disease, medication management and monitoring and psychological aspects. For each learning objective, competences to acquire were defined. The medication management turns out to be the major difficulty, particularly fasting constraint and adherence to the full treatment course.

Conclusion: On the basis of this competences list, the CLAT will be able to create a TPE program for LTBI treatment. Several modules on demand will be offered and taught by a professional trained for TPE, according to the educational diagnostic. They will consist of face to face individual, or for families, collective interviews for about 30-45 minutes. These interviews will take place just after a medical consultation, a blood test or according to the needs expressed by patients. An evaluation session will be planned at the end of the program. The aim of this program is to promote treatment adherence. Moreover, the patients having competences will be a vector for knowledge and competences passing on.

PC-946-05 Correlates of adherence to latent tuberculous infection therapy in children

A Cruz,¹ J R Starke¹ ¹Baylor College of Medicine, Houston, TX, USA. Fax: (+1) 832 825 1182. e-mail:acruz@bcm.edu

Background: Therapy for latent tuberculosis infection (LTBI) is safe and efficacious in children; efficiency is limited by poor adherence. The objective was to determine associations between LTBI completion and demographics and mode of LTBI diagnosis.

Design/Methods: This was a retrospective cohort study of children ≤ 18 -years-old seen for LTBI at a TB clinic in a low-incidence nation. Isoniazid (9-months: 9H), rifampicin (4R), or isoniazid/rifapentine (3HP) were used as directly-observed preventive therapy (DOPT) or administered by the family (self-administered).

Results: 684 children (50% Hispanic, 26% Asian, 14% Black, 10% white) with LTBI had outcomes known; 69% were diagnosed by tuberculin skin test (TST), 17% by interferon gamma release assay (IGRA), and 14% by both TST and IGRA. 36% were identified via contact investigations. 83% completed therapy (82% receiving 9H, 79% receiving 4R, 100% receiving 3HP). On univariate analyses, completion was associated with younger age (7.1 vs. 8.3y, $P = 0.03$), use of DOPT vs. self-administered therapy (94% vs. 67%, odds ratio (OR) 8.1; CI: 5-13), diagnosis by TST vs. IGRA (85% vs. 71%; OR: 2.25, CI: 1.41-3.6), and use of 3HP vs. isoniazid (100% vs. 82%, $P = 0.002$) on univariate analyses. When self-administration regimens were compared, rifampin was more likely to result in completion than isoniazid (80% vs. 56%, OR: 2.6, CI: 1.46-4.64). On multivariate analyses, only the use of DOPT (OR: 9.7; CI: 5.6-16.8), diagnosis by TST (OR 1.6; CI: 1.2-2.3), and use of 3HP (OR 2.2; CI 1.3-3.6) were associated with LTBI completion. Subgroup Overall Completed ($n = 565$) Defaulted ($n = 119$) OR [CI] 9H,

self 149 (22%) 84 (56%) 65 (44%) 1 9H, DOPT 331 (48%) 309 (93%) 22 (7%) 10.9 [6.3-18.7] 4R, DOPT 16 (2%) 16 (100%) 0 $P < 0.001$ 4R, Self 108 (16%) 86 (80%) 22 (20%) 3 [1.7-5.3] 3HP 44 (6%) 44 (100%) 0 $P < 0.001$ Self-administered 260 (38%) 173 (67%) 87 (33%) 1 DOPT 395 (58%) 372 (94%) 23 (6%) 8. [5-13.3].

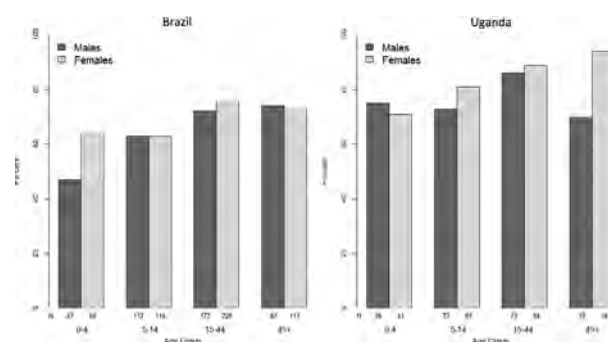
Conclusion: Demographic factors were unassociated with LTBI adherence. Short-course therapy, and therapy via DOPT, were the only variables associated with treatment completion.

PC-947-05 Effect of age and gender on risk of latent tuberculous infection in household contacts: Kampala, Uganda and Vitoria, Brazil

M Gaeddert,¹ E Jones-López,¹ J Ellner,¹ N Hochberg,^{1,2} T Tsacogianis,² L White,² R Dietze,³ I Ayakaka⁴ ¹Boston Medical Center, Boston, MA, ²Boston University, Boston, MA, USA; ³Universidade Federal do Espírito Santo, Vitoria, Espírito Santo, Brazil; ⁴Makerere University, Kampala, Uganda. e-mail: mary.gaeddert@bmc.org

Background: Although there is a male predominance in tuberculosis disease (TB) cases worldwide, there are limited data on whether such differences are seen in latent TB infection (LTBI). We investigated whether there were differences in LTBI by age and sex in two settings.

Design/Methods: We analyzed data from studies in Vitoria, Brazil and Kampala, Uganda that enrolled household contacts (HHC) of pulmonary TB index cases (IC). We collected data on IC and HHC demographics. Tuberculin skin tests (TST) were administered at baseline and 6-8 weeks later if negative at baseline. LTBI was defined as a TST of ≥ 10 mm at either time point. P values were calculated using logistic regression fit with generalized estimating equations.



Results: In Brazil, 423/939 (45.1%) of HHC were male, and the median age was 21.0 years (range 0.3-87.0); in Uganda, 194/442 (43.9%) were male, and the median age was 13.0 years (range 0.1-76.4). In Brazil, 61.9% of males and 69.4% of females had LTBI; in Uganda 77.3% of males and 82.7% of females had LTBI. The LTBI prevalence in Brazil was significantly different between age categories for each gender: 0-4 years (44.9% males, 64% females), 5-14 years (63.4%, 63.2%), 15-44 years (71.5%, 76.4%), and 45+ (47.2%, 72.6%; $P = 0.01$ for males and 0.01 for females). In Uganda, the differences

were not significant for males but were for females: 0-4 years (75.0% males, 70.7% females), 5-14 years (72.6%, 80.7%), 15-44 years (86.3%, 89.4%), and 45+ (70.0%, 99.4%; $P = 0.1$ for males, 0.03 for females). The differences between genders were not significant at either site. In multivariate models that controlled for factors related to IC disease severity (e.g., smear grade) and HHC factors (e.g., sleeping proximity to IC), we found that Brazilian females age 15-44 were 2.8 times (and males 2.0 times) as likely to have LTBI as those of the same gender aged 5-14 years ($P < .0001$ and $P = .004$). In Uganda, males age 15-44 years were 2.4 times as likely to have LTBI as those age 5-14 years ($P = .04$); the difference was not significant in females.

Conclusions: We found notable differences in the age and gender of HHC with LTBI in Brazil and Uganda. The increased odds of infection among adult Brazilian women compared to younger ages (and compared to men) may result from increased biological susceptibility or infection outside the household. Between-site differences in LTBI may reflect differential risk of community infection between Brazil and Uganda.

PC-948-05 Age and gender distribution of latent tuberculous infection cases in a household contact study, India

S Sarkar,¹ P Fernandes,² S Lakshminarayanan,¹ R Kubiak,³ R Horsburgh,³ R Thanjavur,¹ J Ellner,³ N Hochberg³ ¹Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; ²Boston Children's Hospital, Boston, MA, ³Boston Medical Center, Boston, MA, USA. e-mail: priyanka.fernandes@childrens.harvard.edu

Background: Worldwide, there is a clear gender differential in tuberculosis disease with up to seven times more cases occurring among men than women in parts of India. What is unknown is the degree to which men are more likely to also develop latent tuberculosis infection (LTBI) and the age at which gender differences become apparent.

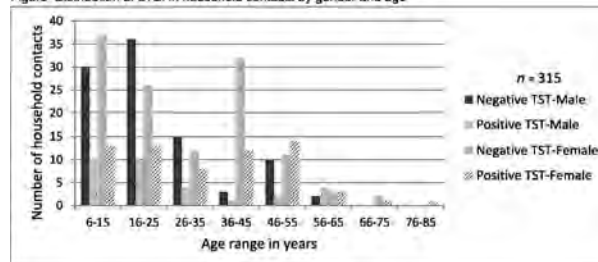
Design/Methods: Data come from the Indo-US Regional Prospective Observational Research for Tuberculosis (RePORT) cohort in Pondicherry and Tamil Nadu in southern India. This prospective cohort follows newly identified culture-confirmed pulmonary TB cases through treatment completion. Household contacts (≥ 6 years of age) are enrolled within 8 weeks of index case enrollment, socio-demographic data are collected and tuberculin skin testing (TST) is performed. We analyzed the age and sex distribution of the LTBI cases, with LTBI defined as TST induration ≥ 10 mm. The χ^2 test was used for statistical comparisons.

Results: Data on 315 household contacts of 94 index cases were analyzed. Among index cases, 72 (76.6%) were male, and the median age was 33 years (interquartile range [IQR] 17-45). The median duration of cough in index cases was 4 weeks (IQR 2-4), and 22 (23%) had a concentrated sputum smear grade of 3+ (12 [13%] were negative, 10 [11%] were scanty, 28 [30%] were 1+, and 22 [23%] were 2+). Of the household

contacts, 127 (40.3%) were male, the median age was 23 years (IQR 15-39), and 63 (20.0%) were spouses of the index case. Of the 96 (30%) household contacts with LTBI, 31 (32.3%) were male, and the median age was 27 years (IQR 16-47). The overall prevalence ratio comparing LTBI in male to female household contacts is 0.73 (0.96 for ages ≤ 15 , 0.68 for ages 16-45, and 0.61 for ages 46-65). Household contacts who were female spouses of index cases were more likely to have LTBI than male spouses of index cases (24 [36.9%] vs. 2 [6.5%]; $P = 0.0017$).

Conclusion: Preliminary analyses of these data show that the male household contacts were less likely to develop LTBI than female household contacts, and that these differences become more apparent with increasing age. Additional analyses are needed to control for potential confounders including infectiousness of index case, sleeping proximity to index case, co-morbidities, and nutritional status. Mechanistic studies are needed to understand why a female predominance is seen among LTBI cases and how this relates to the male predominance seen among TB cases.

Figure Distribution of LTBI in household contacts by gender and age



PC-949-05 Patient perceptions prior to LTBI screening at primary care in Newham, London

S Ikram,¹ H Kunst¹ ¹Barts Health NHS Trust, London, UK. e-mail: sikram26@yahoo.com

Background: The London borough of Newham has the highest rate of tuberculosis (TB) in the UK. In 2013, 335 Newham patients were treated for TB—a rate of 107 per 100 000 people; 87 % of patients diagnosed were born outside of the UK, with the vast majority of cases in patients of Indian sub-continent origin. In Newham, screening for latent TB was started in 2014 with the aim of identifying and treating people with latent TB to prevent development of active disease and spread of TB. The initiative has been incorporated into the 'new patient check' on new patient registration at a general practice surgery. Eligible patients are identified via a series of questions including country of birth; if eligible they are consented and given an information leaflet about TB (in English). Screening is then done in the form of an interferon gamma assay (IGRA) blood test.

Design/Methods: A pilot questionnaire was distributed over a three week period to patients at a large general practice surgery within the borough. All patients applicable for being screened for latent TB were asked

to complete an anonymous questionnaire. The aim was to gain an insight into the demographics, knowledge and understanding of the targeted Newham patient population regarding latent TB infection. The questionnaire was adapted from that used by Goswami et al.

Results: The questionnaire was fully completed by 12 patients. 11 of the 12 patients had been born in the Indian sub-continent. 6 different languages were stated as being the primary language of the patients. None of the patients believed they could have latent TB, and all of them would tell their family if the result of the IGRA was positive. 75% of patients believed that latent TB infection could make them unwell, however all respondents thought TB infection could be cured. 3 patients did not understand the term latent or dormant TB. Only 2 patients were concerned that if the IGRA was positive, others would assume that they had infectious, active TB.

Conclusion: The results show that the screening programme is covering patients from countries of origin known to present with TB in Newham. That patients would inform family members whatever the IGRA result, indicates an openness to discuss TB. However further information including an information leaflet in a number of languages on active and latent TB and their differences, as well as the potential treatment and side effects, is needed at the new patient check stage.

30. Collaborative services for TB and diabetes

PC-950-05 A case-control study of the differences in serum IFN- γ and IL-10 levels in tuberculosis-diabetes comorbidity patients and their controls

L Yuan,¹ X Xiao,¹ C Chen,² Q Shu,³ W L Jiang,¹ B Xu,¹ Q Zhao^{1,2} ¹Fudan University, Shanghai, ²Center for Disease Control and Prevention of Jiangsu Province, Nanjing, ³Center for Disease Control and Prevention of Jiangxi Province, Nanchang, China. Fax: (+86) 215 423 7335. e-mail: zhaoqi@shmu.edu.cn

Background: The burden of diabetes mellitus (DM) and tuberculosis (TB) comorbidity has emerged as a global public health priority, especially in low and middle-income countries. Effects of diabetes on innate and adaptive immunity, which are potentially relevant to tuberculosis defense, have been identified, but have not been verified in the interaction of these two disease states. This study aims to describe serum IFN- γ and IL-10 levels among DM-TB comorbidity patients, pure TB (PTB) patients, pure DM (PDM) patients and healthy controls, and to reflect the influence of coincident diabetes on immune function in tuberculosis patients.

Methods: A case-control study based on the screening of DM in TB patients was carried out in 4 counties in eastern China. All registered active TB patients during April 2013 to March 2014 were screened by fasting blood glucose (FBG) test. Those who had an FBG equal to 126 mg/dl or higher were referred for glycolated

hemoglobin A1C (HbA1C) test for the confirmation of DM. Cases in this study were all diagnosed DM-TB patients, whereas control groups were PTB patients, PDM patients and healthy controls matching with gender and age. Serum levels of IFN- γ and IL-10 were measured by avidin-biotin complex enzyme-linked immunosorbent assay.

Results: In total, 71 DM-TB comorbidity patients, 71 PTB patients, 71 PDM patients and 71 health controls were recruited during the study period. The geometric mean of serum IFN- γ and IL-10 levels of participants were 6.01 and 7.36 pg/ml, respectively; and there were statistical differences among the four groups ($P < 0.001$). The IFN- γ level was higher in PTB patients compared with healthy controls (geometric mean of 8.59 vs. 3.52 pg/ml); whereas it was lower in DM-TB patients compared with PTB patients (geometric mean of 7.88 vs. 8.59 pg/ml). An opposite trend was indicated on levels of IL-10. It increased in turn among healthy controls, PTB patients and DM-TB patients, with geometric mean at 4.85, 9.03 and 14.40 pg/ml, respectively.

Conclusions: DM-TB patients had lower level of IFN- γ and higher level of IL-10 compared with PTB patients. Findings from this study suggested that comorbidity with diabetes may have negative effects on the immune function of TB patients, which might affect the outcome of TB treatment.

PC-951-05 Integrated care for tuberculosis, HIV and diabetes in four public hospitals in two regions of Ethiopia

D J Dare,¹ N Demmelash,¹ T Anteneh,¹ I Jemal Abdulahi,² D Habte,¹ M Aseresa Melese,¹ P G Suarez,³ G Sangiwa³ ¹Management Sciences for Health, HEAL TB Project, Addis Ababa, ²Oromia Regional Health Bureau, Addis Ababa, Ethiopia; ³Management Sciences for Health, Center for Health Services, Arlington, VA, USA. Fax: (+251) 11 372 4473. e-mail: degujerene@gmail.com

Introduction: There is limited experience with integrated management of TB, HIV and diabetes mellitus (DM). Our objective was to develop and test an integrated model of care for TB, HIV and DM in a high TB/ HIV/ DM burden setting with limited resources. We report preliminary results from an ongoing pilot work from four public hospitals in Ethiopia.

Interventions: First, we oriented clinicians working in TB, antiretroviral therapy (ART), and DM clinics on how to identify and manage/refer clients for the three diseases; and provided minor supplies. Clinicians in ART clinics screened patients both for DM and TB; those in TB clinics for HIV and TB; and patients attending DM clinics were screened for TB using symptom-based checklists adapted from the national guidelines. Diagnosis of DM was confirmed if random blood glucose (RBG) was >200 mg/dl or if patient was known diabetic. Where the patient could afford, routine chest x-ray was encouraged. Patients with presumptive TB were further evaluated and sputum microscopy or GeneXpert was done. HIV testing and counseling was done as per the

national standard. We collected and analyzed quantitative and qualitative data acquired during monthly mentoring visits.

Results and lessons learnt: We screened 1156 patients including 268 in TB, 525 in HIV, and 363 in DM clinics. Of 268 TB patients screened, 8 (3%) had DM of which six were known diabetic patients while two were newly detected. Also, 15.1% were co-infected with HIV. Of 525 patients receiving chronic HIV care, 12 (2.3%) had DM of which nine were newly detected. Further, 54 (10.3%) were currently co-infected with TB. Of 363 DM patients screened for TB, eight had previous history of TB and four (1.1%) had active TB at the time of screening (2 currently under treatment and 2 newly diagnosed). Limited experience with symptom-based TB screening and lack of recording and reporting tools were the major challenges encountered in the DM clinics. High patient load was the greatest challenge in the ART clinics while TB clinics did not report any significant challenge. The integrated approach was well received by program managers and clinicians alike.

Conclusion: The yield of TB among DM patients was about three times the prevalence in the general population. Three-fourths of the DM cases among HIV infected patients were newly diagnosed. The screening helped identify a quarter of DM patients detected in TB clinics. The integrated approach should be implemented at wider scale.

PC-952-05 Prevalence of diabetes mellitus among TB patients and impact of diabetes on treatment outcome: a field-based study under the programme setting in India

R Thakur,¹ N Ahmed² ¹World Health Organization Randstad, Shimla, ²O/o CMO Nahan, Sirmour, India. Fax: (+91) 0177 262 7601. e-mail: ravindermph@gmail.com

Background: India is facing a dual burden of merging epidemic of diabetes mellitus (DM) and tuberculosis (TB); there were an estimated 65.1 million people with DM and 2.3 million TB patients living in India in 2013. Routine screening of TB patients for DM under programme setting may be an opportunity for its early diagnosis and improved management and might improve TB treatment outcomes. Current study was conducted to assess the co-existence of DM and TB in persons with established TB and treatment outcome under programme settings.

Design/Methods: Cohorts of notified TB patients in 2013 (3rd and 4th quarters), 2014 (all quarters) and 2015 (1st quarters) in Pounta Sahib TB Unit (Pop: 78 000) in District Sirmour of Himachal Pradesh in India were tested for routine blood sugar using semi-autoanalyser at the time of diagnosis. TB patients with diabetes received anti-diabetic medication from the physicians and ATT under the program. Blood sugar examination was repeated at the end of intensive phase (IP) and end of continuous phase (CP) of ATT. Patient's treatment outcome was compared with level of blood sugar level.

Results: Prevalence of DM among TB patients was reported to be 10%, 5.3% and 7.9% in 2013, 2014 and 2015 respectively. Out of total 48 co-morbid patients, 33 patients had self-reporting history of DM, whereas 15 were newly diagnosed. Most patients were of senior age groups (Mean age; 58 years, range; 40-75 years). 17 (46%) patients under the study were retreatment cases (treatment failure and relapse). Mean random blood sugar level among all cases at the time of diagnosis, end of IP and end of CP was 182 mg/dl, 139 mg/dl and 120mg/dl respectively. Treatment outcome of patients as per the program guidelines was "cured" in 17 (46%) patients and "treatment completed" in 10 (27%) patients. Four (11%) patients defaulted the treatment, while four (11%) other patients had "failure" outcome. Two patients died while on treatment.

Conclusion: The study highlights evidence that DM makes a substantial contribution to TB incidence and increases the morbidity and mortality. Geriatric population is more vulnerable to this co-morbidity. This study emphasizes on the need to raise awareness and policy change on screening for DM in persons with TB and effective anti-diabetic treatment to TB patients with co-morbidity. There is a need to develop a mechanism for coordination between ongoing NCD control program and TB control program in India.

PC-953-05 TB and DM linkage campaigns: how beneficial is screening for people attending camps?

A Madhab,¹ S Chadha,² S Burugina Nagaraja,³ S Satapathy² ¹Jagran Peהל, New Delhi, ²International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ³Employees' State Insurance-Post Graduate Institute of Medical Sciences and Research & Employees' State Insurance Corporation Medical College, Bangalore, India. e-mail: Sachi.Satapathy@theunion.org

Background: In India, tuberculosis (TB) continues to be a major public health problem. The looming epidemic of diabetes mellitus (DM) is presumed to be detrimental to the ongoing TB control efforts in the country. The National TB Control programme has a policy of screening all TB patients for diabetes at districts where non-communicable disease programme is implemented. Jagran Peהל and The Union has launched a project supported by WDF and State Health Society on enhancing awareness about TB and DM linkages in the community at non-NCD implementing districts from the state of Bihar. We conducted a study to determine the usefulness of screening the people for TB and diabetes attending the campaigns.

Design/Methods: The project is being implemented in Bhojpur districts with population of 27.20 lakhs since September 2014; By March 2015 we have been able to complete activities in the districts. The campaign consists two types of activities a) IEC through displaying the posters, pamphlets, wall painting and audio-visuals through mobile vans at villages on prefixed days while the trained personnel at the camps encourage and educate the people to get screened for TB and DM, b)

followed by screening camps for DM-TB the following day. The details of the patients and their results were electronically entered in Epidata data entry format.

Results: A total of 14 434 people were screened for TB and DM during the period. Among them 502 (3.5%) people had suffered from TB and 92 (18.3%) were having diabetes. About 898 (6.2%) of patients were suffering from diabetes and 271 (1.9%) of them were on diabetic treatment; on screening them for TB, 432 (48.2%) patients were found to be sputum smear positive.

Conclusion: Screening of people in TB and DM linkages campaign is found to be beneficial. Nearly one in five TB patients had diabetes and nearly one in two diabetic patients had tuberculosis. The National TB programme should emphasize on TB-DM linkages through extensive Advocacy, communication and social mobilization (ACSM) activities.

PC-954-05 Addressing TB-DM comorbidity in an urban setup: experience from Delhi, India

A Khanna,¹ P Kumar,² S Chandra,³ B Neeti⁴ ¹State TB Officer, Directorate of Health Services, Delhi, New Delhi, ²District TB Officer, Municipal Corporation Delhi, New Delhi, ³Office of the World Health Organization Representative to India, New Delhi, ⁴State TB Office, Directorate of Health Services, Government of National Capital Territory of Delhi (GNCTD), New Delhi, India. e-mail: chandras@rntcp.org

Background and challenges to implementation: The Tuberculosis (TB) and Diabetes Mellitus (DM) dual burden screening framework of World Health Organization endorses that bidirectional screening for both the disease control programs should be delivered within the context of general health systems, with zero cost entailed by the patients. Medical experts have opined that about 10% of TB cases globally are linked to diabetes. Our aim was to assess the TB-DM screening package drafted by Delhi State in context with the above recommendations, along with assessment of its operational feasibility amidst busy working schedule of TB workers in an urban set up.

Intervention or response: Collaborative screening package of TB and DM was rolled out pan Delhi in January 2015. The bidirectional screening framework was in accordance with the Government of India DM screening guidelines. It differed from the Revised National TB Control Program-screening of TB patients for DM framework- as it enrolled registered TB patients more than 30 years age and offered them fasting blood glucose (FBG) test at point of entry into RNTCP (thus omitting DM screening for all registered TB patients and random blood glucose testing protocol).

Results and lessons learnt: From the preliminary reports received for the first reporting quarter of 2015, out of the 2274 registered TB patients who were more than 30 years age, 1715 (75%) were screened for diabetes. In them 225 (13%) were diagnosed as diabetes and were referred to the linked DM treatment centre for their treatment management. Among the 143 (66%) men TB patients with DM, 79% were New TB patients whereas

21% gave prior history of TB disease. The FBG test was available at government peripheral health institutes with the link DM treatment sites in the vicinity of the TB treatment centers. All services were offered free of cost to the patients.

Conclusions and key recommendations: Bidirectional screening especially for DM in registered TB patients with inclusion of age more than 30 years and FBG at point of entry with support from general health system increases the yield of diabetes screening and makes it operationally feasible for patients to undertake the FBG test amidst their busy work schedule in an urban set up.

PC-955-05 High rates of previously known but poorly controlled diabetes among TB patients in Lima, Peru

C Ugarte-Gil,¹ R Van Crevel,² F Pearson,³ D Moore⁴

¹Universidad Peruana Cayetano Heredia, Lima, ²Radboud University Medical Center, Nijmegen, Netherlands, ³St Georges University, London, ⁴London School of Hygiene & Tropical Medicine, London, UK. e-mail: cesar.ugarte@upch.pe

Background: The prevalence of diabetes mellitus (DM) is increasing in low and middle-income countries and is a risk factor for worse tuberculosis (TB) treatment outcomes. Although evidence concerning the TB-DM association is increasing, there are gaps in our knowledge of prevention, treatment and management strategies in patients with these 2 comorbidities. TANDEM (www.tandem-fp7.eu) is a multi-country TB-DM project with field sites in Indonesia, Peru, Romania and South Africa. We present preliminary data on screening TB patients for DM in Lima, Peru.

Design/Methods: Adult patients recently diagnosed with TB were enrolled in 3 DOTS primary health clinics in Lima, and were screened for DM (using HbA1c measured in an accredited laboratory) as a part of the TANDEM project (Jan 2014 – Mar 2015). DM, TB and anthropometric information were recorded. Data captured electronically in a central online database (RED-Cap), and quality assurance programmes created and run regularly to check for missing and out of range data.

Results: 225 TB patients were enrolled, 119 (52.9%) were male and the median age of 34 years (IQR: 23-45). Overall, 21 (9.3%) participants had HbA1c $\geq$ 6.5%, only one was younger than 35 years old (34yo). 20/111 (18.0%) participants older than 35 years old had HbA1c $\geq$ 6.5%. Among the group over 35 years, mean age was 48.4 (SD: 11.6), 53 (47.8%) were male, 32 (28.8%) had a previous history of TB, median BMI was 22.8 (IQR 20.4-25.8) and median waist circumference was 83 (IQR: 75-90). The median HbA1c was 5.4 (IQR 5.1-5.9) with a maximum value of 17.1. 16 (14.4%) had been previously diagnosed with DM before presenting for TB treatment and only 4 (3.6%) didn't know their DM status. Among the 20 participants over 35 years old with HbA1c $\geq$ 6.5%, mean age was 52.5 (SD: 9.4), 8 (40%) were male; median BMI was 22.9 (IQR: 21.6-27.2) and median HbA1c was 10.7 (IQR: 9.8-14.1). Half were diagnosed over 12 months before starting TB

treatment and 11/20 (55%) were taking anti-DM medication (insulin and/or metformin) at the time of enrolment. 4/20 (20%) reported a previous TB episode. **Conclusions:** Among TB patients in Peru, DM is associated with older age, female gender and recurrent TB. The high proportion of previously known, yet poorly controlled DM underlines challenges in chronic care for DM in LMIC, which also impact TB control. More study is needed to develop optimal and sustainable preventive and therapeutic strategies for both diseases.

PC-956-05 Mitochondrial mutations in diabetes and isoniazid treatment of tuberculosis

L Wangh,¹ A Osborne,¹ J A Sanchez,¹ K C Hayes¹

¹Brandeis University, Waltham, MA, USA. e-mail: wangh@brandeis.edu

Background: Diabetics are three times more likely to develop active TB than non-diabetics, and having diabetes adversely affects TB treatment and prognosis. Mitochondrial dysfunction is associated with both diabetes and isoniazid (INH) treatment of TB. It is therefore possible that increased mitochondrial mutagenesis due to drug toxicity may exacerbate development and progression of diabetes and, conversely, that diabetes-dependent mitochondrial mutagenesis may exacerbate the side effects of TB drug treatment. We are examining these complementary hypotheses in cultured human liver cells and in Nile rats (*Arvicanthis niloticus*), a model system that develops diabetes in response to a high carbohydrate diet. We are also attempting to mitigate mitochondrial DNA damage in these systems.

Design/Methods: Non-diabetic and diabetic Nile Rats were scored for disease progression and severity by measurement of random blood glucose and oral glucose tolerance. Disease onset was significantly accelerated by feeding a carbohydrate-rich diet to a diabetes-prone strain of rats. Ingestion of palm fruit juice (PFJ), a water-soluble extract from the kernel of the oil palm (*Elaeis guineensis*), delayed the onset of diabetes. HepG2 cells that activate INH were treated for 30 days, with and without PFJ. Liver cells from age-matched diabetic and healthy rats, and cultured human cells were screened for mutations in multiple regions of the rat and human mitochondrial genome (mtDNA) using LATE-PCR and Lights-On/Lights-Off probes.

Results: Diabetic animals had twice the number of random mtDNA mutations as healthy animals. Mutations accumulated before onset of diabetes symptoms and palm fruit juice reduced the number of mutations in diabetic rats. Mutational load did not correlate with the severity of diabetes. Chronic treatment of HepG2 cells with INH increased mutations in the HV2 and ND3 targets as compared to untreated cells. Preliminary experiments suggest that PFJ co-treatment may reduce these additional mutations.

Conclusion: Mitochondrial mutations due to diabetes and INH therapy raises serious concerns about possible long term consequences for diabetic individuals, particularly those on INH therapeutically or prophylactically

for many months. The potential benefits of PFJ to mitigate mtDNA damage warrant further investigation. Diabetes and drug treatment can be combined in the future using the Nile Rat model system. Supported by a grant from the MPOB.

PC-957-05 Chronic cavitary pulmonary aspergillosis is a common complication of pulmonary tuberculosis: results of a cross-sectional survey

I Page,^{1,2,3} N Onyachi,⁴ C Opira,⁵ J Opwonya,⁶

S Hosmane,¹ S Sawyer,¹ R Sawyer,¹ M Richardson,^{1,2,3}

D Denning^{1,2,3} ¹University Hospital of South Manchester, Manchester, ²University of Manchester, Manchester, ³Manchester Academic Health Science Centre, Manchester, UK; ⁴Gulu Regional Referral Hospital, Gulu, ⁵St. Mary's Hospital, Lacor, Gulu, ⁶Gulu District Health Office, Gulu, Uganda. e-mail: iain.page@manchester.ac.uk

Background: CCPA complicates pulmonary tuberculosis, with a 5-year mortality of up to 85%, but is treatable with itraconazole or surgery. The estimated global prevalence of CCPA secondary to tuberculosis is 0.8 to 1.3 million cases.

Design/Methods: We conducted a cross-sectional survey in Gulu, Uganda. Adults who completed treatment for pulmonary tuberculosis in the last 7 years were recruited. All underwent clinical assessment and chest X-ray. Aspergillus-specific IgG was measured by Siemens Immulite, which has a sensitivity of 96% and specificity of 98% for the diagnosis of CCPA. This assessment was repeated in a resurvey two years later. CT scan was also performed in those with positive serology or chest X-ray changes suggestive of CCPA. GeneXpert TB PCR testing was performed on those with productive cough. CCPA was diagnosed in patients with ALL of the following; 1 – over one month cough or haemoptysis, 2 – raised levels of Aspergillus-specific IgG and 3 – paracavitary fibrosis or aspergilloma or progressive cavitation on imaging. Simple aspergilloma was diagnosed in patients with aspergilloma and positive serology, but no symptoms.

Results: 400 patients were recruited between October 2012 and February 2013. 200 (50%) were HIV positive. Median age was 42 years (range 16-83). 39% of patients were female. Median CD4 count in those with HIV was 415 cells/ μ L (range 0-1400). 284 patients were re-surveyed between October 2014 and February 2015. Frequency of disease is shown in the table. Condition Cases ($n = 284$) CCPA 20 (7%) Simple aspergilloma 4 (1.5%) All chronic pulmonary aspergillosis 24 (8.5%) HIV co-infection had no significant impact on the frequency of CCPA. Three cases of recurrent pulmonary tuberculosis were identified, none of which had CCPA.

Conclusion: CCPA is a frequent complication of pulmonary tuberculosis. This data supports the predicted prevalence of up to 1.3 millions cases worldwide. This represents a significant global public health problem, which is currently neglected. Patients with CCPA will meet the WHO diagnostic criteria for 'smear-negative' tuberculosis. Many cases of recurrent smear-negative tuberculosis are probably CCPA. Accurate diagnosis of

CCPA in this group would avoid unnecessary and potentially harmful TB treatment and also significantly reduce the reported global burden of smear-negative tuberculosis. Further research is now needed to develop appropriate CCPA screening and treatment strategies for use in resource poor settings.

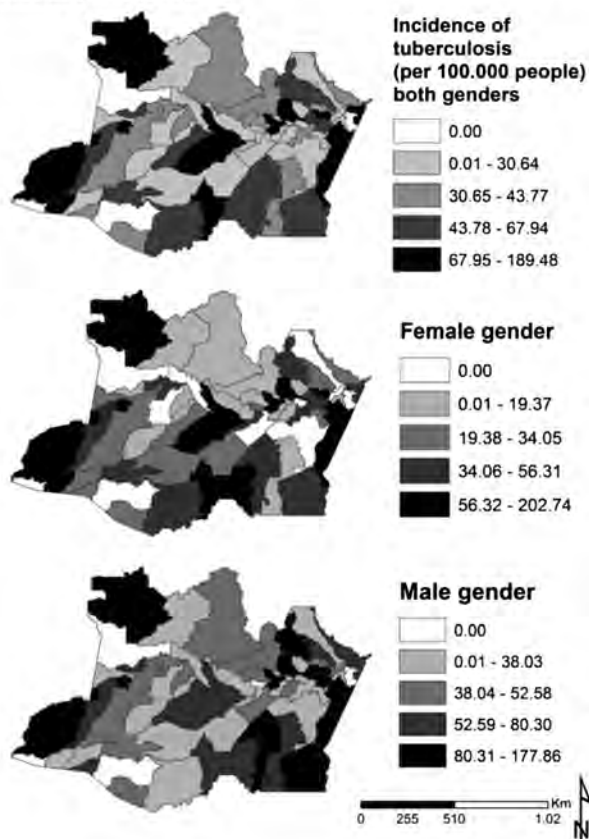
31. Spatial epidemiology of tuberculosis

PC-958-05 A spatial analysis of gender differentials in tuberculosis in the Amazonas State, Brazil, 2013

A Belchior,¹ M Yamamura,¹ M Popolin,¹ M Santos Neto,² M C C Garcia,¹ A Queiroz,¹ A C V Ramos,¹ R Arcencio¹
¹Nursing School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, ²Federal University of Maranhão, Imperatriz, Maranhão, Brazil. e-mail: aylanabelchior14@gmail.com

Background: Considering that gender inequalities may influence the access to health services and delay in tuberculosis (TB) diagnosis, it was necessary to identify TB incidence according to gender in the state of Amazonas, Brazil.

Figure 1: Thematic Map of the spatial distribution of TB new cases in the Amazonas State, Brazil, 2013.



Design/Methods: Descriptive and ecological study that considered data from the Information System of Notifiable Diseases (SINAN) of tuberculosis cases (new extrapulmonary and pulmonary tuberculosis with posi-

tive smear), and also, those recorded in 2013 and reference variables of gender, age, diagnosis month, State of notification, State of residence and municipality of notification. It was possible to estimate female-male incidence per municipality and choropleth maps development through the ArcGIS software, version 10.1.

Results: General TB incidence ranged from 0 to 189.48 cases per 100 000 inhabitants, the female rate ranged from 0 to 202.74 cases per 100 000 female inhabitants and male incidence from 0 to 177.86 cases per 100 000 male inhabitants. The area with the highest incidence rate (Figure) includes 12 municipalities, and five of them: Amaturá, Canutama, IPIXUNA, São Gabriel da Cachoeira and Tabatinga integrate the Arco Norte of the Brazilian international border. A distinctive feature of this region is the presence of indigenous people and their intense mobility in the border region. In addition, three out of six municipalities: Manaus, São Gabriel da Cachoeira and Tabatinga, which are quite necessary for TB control in the Amazon, integrate the group with the highest incidence of TB in women.

Conclusion: Differentiated gender approach was not a priority of the studies conducted in Brazil. However, findings indicate that gender differences can relate to the municipalities' geographic location that may influence women's accessibility to diagnosis and treatment.

PC-959-05 Spatial distribution of tuberculosis cases in São Carlos, São Paulo, Brazil, between 2008 and 2013

S Protti,¹ A Pereira Biffi Fusco,¹
 T Ferraz De Araújo Alecrim,¹ A Alessandra Dos Reis,¹
 R Arcencio,² P F P Pedro Fredemir Palha,² M Yamamura²
¹Federal University of São Carlos, São Carlos, SP, ²University of São Paulo at Ribeirão Preto College of Nursing, Ribeirão Preto, SP, Brazil. Fax: (+55)16 3322 5265. e-mail: tatienf@gmail.com

Background: Tuberculosis is an important public health problem in Brazil, with an estimated incidence of 42 cases per 100 000 inhabitants. Among the various strategies launched to monitor the evolution of the disease in the country, the spatial analysis can highlight the main areas of infection and even identify populations at risk of disease.

Design/Methods: This study analyzed the spatial distribution of tuberculosis in São Carlos (São Paulo state, Brazil). An exploratory study of tuberculosis cases registered in the Information System of the TB-WEB, between the years 2008 and 2013, was performed. The data were geocoded in TerraView software, version 4.2.2, and the interpolation statistical technique used was the Kernel estimative, considering a band of 1000 meters. We used the software Statistica, version 10.1, for bivariate statistical analyzes and the software ArcGIS, version 10.2, for the construction of thematic maps.

Results: We identified 315 cases of tuberculosis, with 290 cases geocoded. Most of the identified cases were male ($n = 224$; 70.89%) with a median age of 40 years. The predominant clinical type was pulmonary ($n = 257$; 81.33%). The spatial distribution of tuberculosis in São

Carlos showed up in a heterogeneous manner, tending to concentrate on specific areas of the city, important in epidemiological terms.

Conclusion: The study highlighted the most problematic areas in relation to tuberculosis, which require further attention, planning and investment by the healthcare management systems. In this sense, respiratory symptoms research programs; early case detection; increased treatment adherence; as well as epidemiological investigation of contacts, should be prioritized in the areas identified as a risk.

PC-960-05 An approach for spatial cluster identification of tuberculosis using surveillance data

D Roth,¹ S Mak,¹ M Otterstatter,¹ J Wong,¹ V Cook,¹ J Johnston¹ ¹British Columbia Centre for Disease Control, Vancouver, BC, Canada. e-mail: david.roth@bccdc.ca

Background: Tuberculosis (TB) incidence is decreasing in many countries, and an increase in the heterogeneity of TB is expected as rates fall. Clustering will not occur equally in all subpopulations, and not all clusters require the same public health response. This necessitates the development of approaches for the timely identification and prioritization of disease clusters using surveillance data. Here we present a simple approach using open source software, and use British Columbia (BC) as a case study for its practical application.

Design/Methods: All cases meeting the national TB case definition from 1990-2013 are geocoded using 3 digit postal code of residence. Clustering in TB incidence is compared: 1) across the province, and then at finer resolution, 2) between Canadian (CB) and foreign-born (FB) cases, and 3) across 3 time periods (1990-1997, 1998-2005, 2006-2013). Gini coefficients are used to quantify and compare the degree of global clustering of cases in the BC population. SaTScan, a spatial scanning window statistic, is used to identify statistically significant disease clusters, with results overlaid on provincial maps of TB rates produced with Geographic Information Systems mapping. Finally, epidemiological reports for key clusters are produced and reviewed to prioritize outreach, control, and education. All analyses are done using freely available software.

Results: The degree of provincial clustering remains stable over 3 8-year periods (Gini coefficient: 1990-97=0.57, 1998-2005=0.54, 2006-13=0.50). However, CB cases show a higher degree of clustering than FB cases, especially in the latter period (Gini coefficient: Can. Born = 0.64, FB=0.33). Incidence mapping and SaTScan analysis reveal a geographically large stable cluster for FB individuals, with smaller and less stable clusters seen in CB populations.

Conclusion: The use of incidence mapping and cluster detection methods together can achieve improved guidance for prioritizing control and resource allocation. While the degree of clustering in BC has remained stable over time, clustering does differ between FB and CB individuals. The usefulness of the cluster analysis may,

therefore, vary among subpopulations depending on the regional epidemiology. This cluster analyses approach can be implemented with open source software.

PC-961-05 Creation of geospatial datasets for the TB control programme and linking it with the patient management information system

A Khanna,¹ D Kundu,² K Rade,² T Bhowmick³

¹Directorate of Health Services, Delhi, ²World Health Organization Country Office for India, Delhi, ³Geospatial Delhi Limited, a Government. of NCT of Delhi Company, Delhi, India. e-mail: debashishkundu@yahoo.com

Background: Geospatial Delhi Limited (GSDL) is the custodian of the affluent database prepared during the Delhi State Spatial Data Infrastructure (DSSDI) project. The project has bestowed Delhi with an extremely rich database with the entire infrastructure and facilities of the city mapped using locality and sub-locality information in Geographic Information System (GIS). To utilise this vast geo-knowledge resource and opportunity within GSDL, it is envisioned to link up the this database with enhanced Nikshay (e-Nikshay), a case-based web application, jointly developed by National Information Centre (NIC) and Revised National Tuberculosis Control Programme (RNTCP) for real time plotting of TB patients location coordinates in GIS platform.

Intervention or response: Mapped locality and sub-locality coordinates of entire Delhi state in the Geo-Web Portal were extracted in excel sheet and transferred electronically to Delhi State TB Control Programme for establishing linkages between 'e-Nikshay' and GSDL database. Each locality and sub-locality area coordinates were filtered from the excel sheet, marked, validated and linked to the respective RNTCP districts and tuberculosis units (TU's) with codes, as unique identifiers, by the RNTCP supervisory staff in the districts. NIC add locality and sub-locality information in Nikshay TB patient registration form for registering a TB case having a valid Delhi residential address in e-Nikshay.

Results and lessons learnt: 3500 Delhi locality and sub-locality coordinates of GSDL Geo-Web Services were segregated and aligned to 25 RNTCP implementing districts and 38 TU's. This was done for the purpose of preparing an interface to plot the point of patient address, registered in e-Nikshay, in GSDL database.

Conclusions and key recommendations: A patient coordinates as a point in locality and sub-locality data of GSDL database is plotted during real time entry of TB cases in e-Nikshay to know the geographic distribution of TB patients. Creation of Geospatial datasets for the TB control program and linking it with the patient management information system in e-Nikshay can assist in identifying unserved geographical areas where TB treatment and diagnosis facilities are insufficient.

PC-962-05 Spatial and temporal TB notification rates among districts in Malawi: how should we interpret this?

B G Belaine^{1,2}, I Dambe¹, K Mbendera¹, F Kassa¹, A A Mwenye¹, J Mpunga¹ ¹National Tuberculosis Programme, Ministry of Health, Lilongwe, ²International Training and Education Center for Health Malawi, Lilongwe, Malawi. e-mail: belaine@gmail.com

Background: According to the 2014 national tuberculosis prevalence survey in Malawi, the prevalence of TB was 451/100 000. With the current trend in TB notification combined with high burden of TB in spite of expansion of DOTs, dwelling on passive approach only will maintain the status quo. Hence it is appropriate to implement active case finding in high burden geographical defined areas and high risk groups. For this, prevalence survey would not help much as it is not designed to provide subnational estimate. Prevalence survey at sub national level requires substantial resources. Hence, use of routine data for decision making seems to be a readily available source. The purpose of this analysis is to show the variation in Tuberculosis notification rate across districts and to review trend and pattern of distribution on notification.

Methods: Districts routinely collect data and compile notification data every quarter. The routine data are aggregated in the data management unit of National Tuberculosis Programme. TB case notification data for 2002, 2008, and 2014 were used. TB case notification rates were calculated for all forms of TB of each respective year and projected mid year population of the districts was used. Epi info 3.5.4 was used to do the mapping using shape files for Malawi. **Result:** The overall notification rate was 104/100 000 in 2014. In 2002 the notification rate was 202 and declined to 181/100 000 by 2008 (–12 %) and in year 2014 rate of decline was 42% from 2008. Districts with relatively high rate of notification were able to maintain their rank among all other districts. Muanza, Blantyre, Nsanje, Chiradzulu and Lilongwe had the highest notification rates consistently. Dowa, Chitipa and Nchisi had lower notification rate consistently (see Figure).



Figure 1 Spatial district of case notification of Tuberculosis in 2002, 2008 and 2014, Malawi

Conclusion: Routinely collected data shows that TB case notification rates are heterogeneous. Although the trend in notification rate declined over the last years, those districts with relatively high rate of TB notification tend to continue with relative high rate when compared others while those with low notification tend to maintain their

low level despite an increased coverage of DOTs service. Hence, the attribution to health system variables is not likely to explain all the difference. The notification data provides reliable information that would help to differentiate districts by disease burden and administer package of intervention that ensure efficiency and effectiveness.

PC-963-05 Early success in community contact investigations within a 50 metre radius of an index tuberculosis case in urban Pakistan: a before and after intervention

R K Fatima¹, E Qadeer¹, A Yaqoob¹, A Kumar², S Majumdar³, H Shewade², M Haq¹ ¹National Tuberculosis Control Programme, Pakistan, Islamabad, Pakistan; ²International Union Against Tuberculosis and Lung Disease South-East Asia Regional Office, New Delhi, India; ³Centre for International Health, Burnet Institute, Vic, Australia. Fax: (+92) 51 843 081. e-mail: drraziafatima@gmail.com

Background: Evidence for effect of active case finding on TB epidemiology is weak as there is dearth of studies with before and after comparison with control group as well as long term follow up. National TB Program of Pakistan adopted a unique and innovative intervention to expand contact investigation beyond household.

Design/Methods: To determine the impact of contact investigation beyond household on TB case detection and case notification rate (CNR) in NTP of Pakistan. Before and after intervention study with control districts were done, in which selected districts were predominantly urban with high concentration of slums as intervention ($n = 4$) and control ($n = 4$) areas which had comparable CNR at baseline. July 2012 – June 2013 and July 2013 – June 2014 was the pre-intervention and intervention period respectively. While passive case finding and household contact investigation was routinely done in all districts, contact investigation beyond household was done in intervention districts: all people staying within a radius of 50 metres (using GIS) from the household of smear positive TB case were screened for tuberculosis and those with presumptive TB were investigated using smear microscopy and as a part of intervention, first time in Pakistan, Xpert MTB/RIF test was applied for smear negatives. All the diagnosed TB cases were linked to TB treatment and care.

Results: In intervention districts, out of total 14 086 infective TB cases notified during intervention period, community contact investigation was done in 5469 (38.8%) cases. Of total bacteriologically confirmed TB notified, 9.5% were detected by the intervention, of which 73% were by contact investigation beyond household. TB CNR per 100 000 populations attributable to contact investigation beyond household (difference in change of TB CNR in intervention and control districts during pre-intervention and intervention period) was 25 and 13 for all forms of TB and bacteriological positive TB respectively.

Conclusion: Community contact investigation beyond household not only detected additional TB cases but also increased TB CNR over a period of one year. However,

further long term assessments of the same are required to ascertain sustainment of increase in CNR.

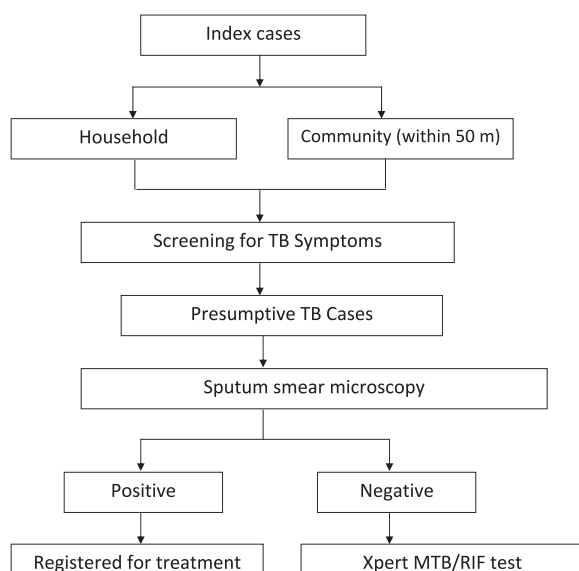


Figure 2: Flow chart to explain the flow of patients in TB Reach project, Pakistan (2013-14)

PC-964-05 Innovative GIS based screening for tuberculosis contacts in household and community contacts in Pakistan: how effective?

R K Fatima,¹ E Qadeer,¹ M Haq,¹ A Yaqoob¹ ¹RESEARCH, National TB Control Programme, Pakistan, Islamabad, Pakistan. Fax: (+92) 51 843 8081. e-mail: drraziafatima@gmail.com

Background: Pakistan ranks fourth globally among the 22 high TB burden countries with 58% of case detection rate and It accounts for 61% of the TB burden in the Eastern Mediterranean Region (WHO). There is a need to enhance TB case finding to meet MDG targets.

Design/Methods: Active case finding through contact screening using GIS software in 3 cities in Punjab Province i.e., Lahore, Faisalabad and Rawalpindi and the Capital Territory utilizing all SS+ notified cases as index cases registered at BMU's. The study aims to determine the effectiveness of community and household contact tracing through outreach using GIS. Project funded through TB Reach wave 3 is focusing on contact screening is being carried out within household and a diameter of 100m around each index case using GIS Technology and therefore strengthen current contact screening strategy adopted by NTP. Household contacts, i.e. those normally resident or sharing the same airspace, are verbally screened initially, following by a widening circle screening of close community contacts. The coordinates of the household are entered into a GIS database via a mobile phone link. There are 50 field officers trained for this project. All the TB presumptive found from the screening are subject to smear microscop-

py; those found positive are registered. However, those found negative are subject to Gene Xpert. Gene Xpert positive cases with or without rifampicin resistance are also registered for treatment at the respective sites. TB presumptive aged less than 15 years identified are referred to child TB managing sites for diagnosis and treatment and are followed up.

Results: Until 7 April 2015, a total of 617 642 individuals were screened, among them 74 329 are household and 543 313 are community based, total TB presumptive found 19 257 (household=4326, community=14 931), in which smear positive cases are 2988 (community=2254, Household=734), gene expert positive cases are 271, MDR cases are 39, child referred are 4875 and total registered cases are 3406.

Conclusion: Contact screening among community is proved to be effective in addition to household screening for early case detection and to limit spread of disease.

PC-965-05 Spatial distribution and cluster analysis of extensively drug-resistant tuberculosis in KwaZulu-Natal, South Africa

T Kapwata,¹ N Morris,¹ T Mthiyane,^{1,2} P Mpangase,^{1,2} P Moodley,² J Brust,³ N Gandhi,⁴ S Shah^{4,5} ¹South Africa Medical Research Council, Durban, ²University of KwaZulu-Natal, Durban, South Africa; ³Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, ⁴Emory University Rollins School of Public Health, Atlanta, Georgia, ⁵U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: saritashah2@gmail.com

Background: KwaZulu-Natal province, South Africa, has among the highest burden of XDR-TB worldwide with 1545 cases diagnosed and a prevalence 3.1/100 000 population in 2012. The majority of cases occur due to transmission. Poor access to health facilities can be a barrier to timely diagnosis and treatment of TB, which can contribute to ongoing transmission. The Transmission of HIV-Associated XDR-TB (TRAX) study recruited adults and children diagnosed with XDR-TB from 2010–2014. Our analysis assessed the geographic distribution of participants around health facilities.

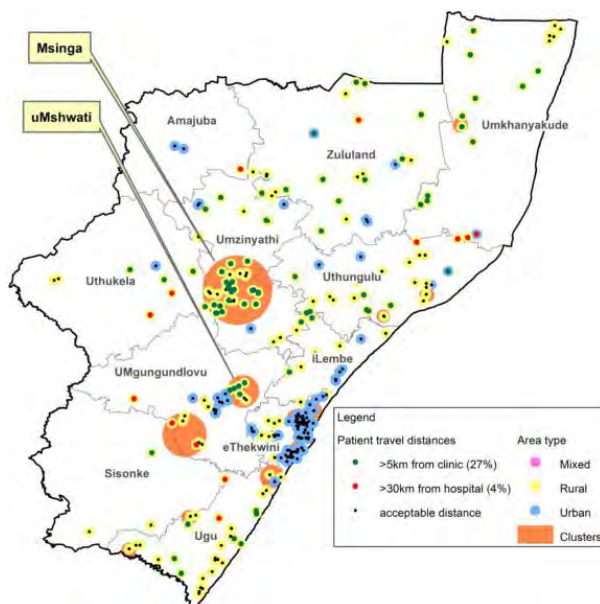
Design/Methods: We calculated distance and time from participants' home to the closest hospital, clinic and community health centre [CHC] using tools within ArcGIS Network analyst. Speed of travel was assigned to the various road classes based on KwaZulu-Natal Department of Transport regulations.

Results were compared to guidelines for the provision of social facilities in South Africa: 5km to a clinic or CHC and 30km to a hospital. Cluster analysis was conducted with SaTScan software using the purely spatial scan statistic and Poisson probability model, with various maximum cluster sizes specified (ranging from 20–50% of the dataset).

Results: We included 321 participants for whom geo-spatial data were available. Cases were distributed throughout all 11 districts in KwaZulu-Natal province. The mean participant distance to the closest hospital, clinic and CHC was 12, 3.5 and 43 kilometres, respectively. Mean travel times were 16, 4 and 109

minutes, respectively. Participants in rural areas were more likely to exceed the recommended distance to a clinic or a hospital (Figure). Preliminary cluster analysis produced several clusters, the most significant of which was located in the rural Msinga area of Umzinyathi District ($P < 0.00001$). The occurrence of these clusters appears related to greater distance from a health facility, mainly clinics (Figure).

Conclusion: Although XDR-TB cases are distributed through the province, geospatial analysis identified possible areas of high transmission. The average travel distance of the participants to hospitals and clinics falls within the CSIR recommended distance; however additional analysis is needed to confirm the correlation between distance from health facilities and clustering. New, rapid molecular tests for drug resistance that are closer to patients may reduce delays in diagnosis and treatment, and reduce transmission.



32. The game of numbers: prevalence and incidence of tuberculosis

PC-966-05 Prevalence and incidence of smear-positive pulmonary tuberculosis in the Hetosa District of Arsi Zone, Oromia Regional State, Central Ethiopia

S Hamusse,^{1,2} M Demissie,³ B Lindtjorn² ¹Oromia Regional Health Bureau, Addis Ababa, Ethiopia; ²Centre for International Health, University of Bergen, Bergen, Norway; ³Addis Continental Institute of Public Health, Addis Ababa, Ethiopia. e-mail: shalohamusse@gmail.com

Background: Understanding the local epidemiology of tuberculosis (TB) is important to design targeted interventions tailored to the specific needs of the districts, as there is huge heterogeneity among districts in terms of TB burden. Community-based survey to estimate the

prevalence and incidence of TB could serve as an alternative option. Our objective was to estimate the prevalence and incidence of TB at a district in Oromia region of Ethiopia.

Methods: We used a population-based cross-sectional survey design at baseline which was followed by prospective cohort study design. We included all individuals aged ≥ 15 years, permanent residents and temporary visitors who arrived 15 days before the study time in as participants. Face to face interviews using standardized TB screening questionnaire were used to identify participants with persistent cough of more than two weeks. Further, spot and morning sputum samples were collected for standard sputum smear microscopy and culture.

Results: We interviewed 33 073 individuals at baseline survey and 32 800 apparently healthy individuals aged ≥ 15 years in the follow up study, and identified 1042 and 468 participants with chronic cough at baseline and during follow up respectively who provided two sputum samples for acid fast bacilli (AFB). Of these, we identified 36 smear and 43 culture positive individuals in the baseline survey, and 70 smear positive individuals during a follow up period of over one year. The prevalence of smear and culture positive TB was 109 and 130 per 105 population respectively, while the incidence was 213/105 person-year. Forty-five PTB+ cases were diagnosed through passive case finding while 36 were identified through active case finding, implying that 44.4% of PTB+ cases were undiagnosed and untreated in the community. Family history of TB contact was independently associated with high risk of TB infection both at baseline (AOR, 3.14, 95%CI: 1.47-6.70) and during follow up (aIRR 9.27, 95%CI: 7.38-11.30).

Conclusion: The burden of bacteriologically confirmed TB was high in the study area, and about 44.4% of the bacteriologically confirmed cases were undiagnosed through the passive approach. Family history of TB contact was an independent risk factor for TB infection. This demonstrates the need to improve TB case findings and intensify contact tracing among household members of TB to detect and treat the undetected PTB+ cases at household level.

PC-967-05 Prevalence of *Mycobacterium africanum* in Ghana over an 8-year period

D Yeboah-Manu,¹ A Asante-Poku,¹ I D Otchere,¹ S Osei-Wusu,¹ E Sarpong,¹ S Gagneux² ¹Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana; ²Swiss Tropical and Public Health Institute, Basel, Switzerland. Fax: (+233) 3021 502 182. e-mail: dyeboah-manu@noguchi.ug.edu.gh

Background: *Mycobacterium tuberculosis* complex (*M. tuberculosis* c) has two species adapted to humans even though there are occasional cross-species infections especially with *M. bovis*. *M. tuberculosis sensu stricto* (*M. tuberculosis* ss) is perceived to have competitive advantage over *M. africanum* (*M. africanum*) and may gradually out-compete *M. africanum*. Our objective was to

analyze the distribution of these species among TB cases over 8-year period.

Design/Methods: Mycobacterial isolates obtained from sputum were confirmed as *M. tuberculosis* c by IS6110 PCR and further characterized by spoligotyping and LSPs (RDs 9, 4, 12,702,711) assays. The distribution of the species isolated was stratified both in space and in time for analyses.

Results: Among 1926 *M. tuberculosis* c isolates obtained from 2007-2014, 1516 (78.7%), 400 (20.8%) and 10 (0.8%) were identified as *M. tuberculosis* ss, *M. africanum* and *M. bovis* respectively. The proportion of *M. africanum* in the same period were 22.2%, 15.4%, 10.7%, 23.1%, 11.5%, 24.6%, 23.0% and 18.5% respectively. *M. bovis* was isolated in 2012 to 2014 as 1.0%, 0.4% and 2.0% respectively when Northern Ghana (NG) was included in the study. Comparing the isolates from 2012 to 2014, we found *M. bovis* to be significantly higher in NG (2.6% of 151) than Southern Ghana (SG; 0.5%) ($P = 0.020$). Among the *M. africanum* isolates, 58.7% and 41.3% of the SG as compared to 48.1% and 51.9% of the NG isolates were lineage 5 and lineage 6 respectively. The most dominant spoligotype of *M. tuberculosis* ss in SG was SIT 61 (42.9%) as compared to SIT 53 (28.7%) in NG. Lineage 6 spoligotype SIT 181 and 326 were the most prevalent in south where as SIT 181 (6.7%) dominate the north.

Conclusion: *M. africanum* contributes significantly to TB in Ghana as its prevalence over the years remains fairly constant.

PC-968-05 Findings from the First Malawi TB Prevalence Survey

R Banda,¹ A Munthali,² J Mpunga¹ ¹Ministry of Health, Lilongwe, ²University of Malawi, Zomba, Malawi. e-mail: rhobanda@gmail.com

Background: Malawi has for a long, time used estimates provided by WHO to determine its TB burden and monitor TB control progress. It was among countries recommended by WHO to carry out a TB prevalence survey by 2015 to better estimate the burden TB. The first Malawi nationwide Tuberculosis prevalence survey was conducted in Malawi (2013- 2014). The overall goal was to determine the prevalence of pulmonary tuberculosis (PTB) among persons aged 15 years and older.

Design/Methods: A multistage cluster-sampled cross-sectional survey was implemented nationwide. All eligible persons aged at least 15 years were screened for TB symptoms the key one of which was a cough of two weeks or more. A chest X-ray (CXR) was then done on all clients in the field. Persons who screened positive for symptoms and/or chest X-ray were asked to submit spot and morning (2) sputum specimens for smear microscopy and culture. These were examined at the National Tuberculosis Reference Laboratory (NTRL). Microscopy was done using fluorescent technique and a Gene xpert performed on all smear positive samples. A bacteriologically-confirmed case was defined as an eligible partic-

ipant with *M. tuberculosis* confirmation by gene-Xpert or culture.

Results: Of the 60 944 individuals enumerated in the census, 39 020 were eligible to participate in the survey from which a sample of 31 579 (80.9%) was drawn. Chest X-ray was performed among 31 561 participants. A total of 3432 (10.9%) participants were eligible for sputum examination. The provisional TB prevalence of bacteriologically-confirmed TB in those 15 years and above is estimated to be 451/100 000 (95%CI 308-594). The provisional adjusted prevalence for all age groups is 286/100 000 which 2 time higher than WHO estimate in 2014. Prevalence increased with age, was higher in men at 543/100 000 (95%CI 327-759) than in women at 374/100 000 (95%CI 245-504). Also, the results indicate that TB prevalence is high among urban residents and in adults aged >55 compared to prevalence in the general adult population (451/100 000).

Conclusion: There is need for the Malawi NTP to strengthen its TB control strategies more specifically towards improving case detection and paying special attention to the selected population groups that indicate a high risk of TB.

PC-969-05 Life-time tuberculosis incidence in Cape Town exceeds that in New York City in the early 20th century and continues to increase

S Hermans,^{1,2} R Wood² ¹Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; ²Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Cape Town, South Africa. e-mail: sabine.hermans@hiv-research.org.za

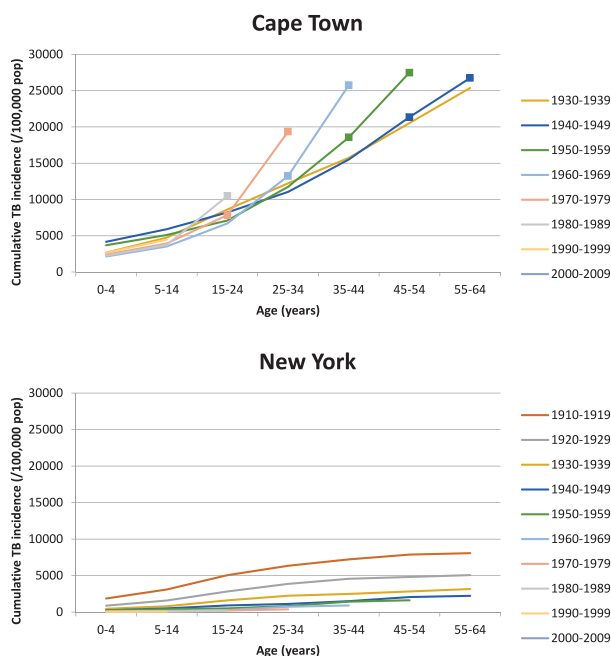
Background: Cape Town reports the second highest TB burden in South Africa, third of the TB high burden countries. At the start of the 20th century, Cape Town and New York City had similar TB notification rates. Despite employing similar TB control strategies, TB rates in Cape Town are currently almost 100-fold those of New York. High quality long term historical data on TB notifications from Cape Town and New York allowed for a comparison between the life-time TB risks of birth cohorts in the two settings, to enable insight into the cumulative impact of TB control strategies and the advent of the HIV epidemic.

Design/Methods: Annual age-stratified TB notifications and mid-year population estimates for 1930-2010 (Cape Town) and 1910-2010 (New York) were used to calculate age-stratified TB incidence rates per 100 000 population. Age cohort analysis techniques were used to calculate cumulative incidence rates by decade.

Results: Over the last century, cumulative life-time TB incidence in Cape Town and New York showed contrasting trajectories: a continuous decline in New York versus a continuous increase in Cape Town (Figure). In 1930 life-time TB risk was 8 fold higher in Cape Town (25.4%) than New York (3.2%). Since then, cumulative TB incidence has been rising steadily in Cape Town with more TB disease occurring at an increasingly younger age. Age-specific cumulative incidence remained

high before the advent of the HIV epidemic, after which it increased by 30-60% from adolescence onward (ages affected by generalized HIV epidemic indicated by marker).

Conclusion: The life-time TB risk in Cape Town prior to HIV remained very high and much greater than in New York City during the same time. The life-time risk of over 25% rather than 10% suggests multiple infections in this setting. The HIV epidemic led to further increases in the cumulative TB incidence which, in addition to faster disease progression among those infected with HIV, could also be due to growing numbers of retreatment disease or to an increasing force of infection. TB control in Cape Town will only be achieved by addressing the drivers underlying the persistent TB epidemic in addition to tackling HIV.



PC-970-05 Prevalence and incidence of tuberculosis among presumptive TB patients in Bagamoyo, Tanzania: a prospective cohort study

F Mhimbira,^{1,2,3} K Ibrahim,^{1,2,3} J Hella,^{1,2,3} F E Haraka,³ E Mfinanga,³ L Jugheli,^{1,2,3} F Lwilla,³ K Reither^{1,2,3} ¹Swiss Tropical and Public Health Institute, Basel, ²University of Basel, Basel, Switzerland; ³Ifakara Health Institute, Bagamoyo, Tanzania. e-mail: fmhimbira@gmail.com

Background: The burden of tuberculosis (TB) has escalated with the emergence of HIV in Sub-Saharan Africa. Identification of presumptive TB patients and subsequent early TB diagnosis and treatment is the hallmark of TB control. The aim of the study was to determine the prevalence and incidence of TB among presumptive TB patients followed for 18 months.

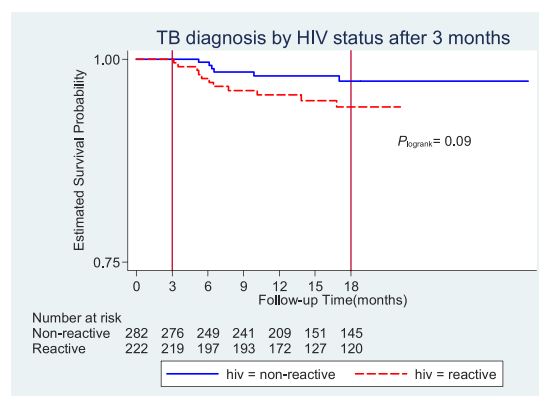
Methods: Presumptive TB patients presenting with cough and other TB related symptoms were enrolled and followed-up at Ifakara Health Institute TB research

from clinic September 2011 to September 2013. The patients were referred from Bagamoyo District Hospital and a diagnostic cohort study. Time of diagnosis refers to the date of microbiological confirmation by either positive smear microscopy or mycobacterium culture or molecular genotyping. Prevalence was defined as TB diagnosed at recruitment or within the following three months. Incidence was defined by any TB diagnosed after three months until 18 months of follow up. Descriptive, logistic regression models, poisson and cox proportional hazards are used.

Results: We analysed 764 presumptive TB patients with median age of 39 years (Interquartile range [IQR]: 31-50), females were 394 (51.6%) and 348 (45.5%) were HIV infected. HIV infection was higher in women than men (216 [54.8%] vs. 132 [35.7%], P value < 0.001). Apart from cough the commonest reported symptoms were fever in 518 (67.8%) patients and un-intentional weight loss 463 (60.6%). Prevalent TB was in 152 (20%) among presumptive TB patients. Prevalent TB was associated with unit increase in age in years [adjusted Odds Ratio [aOR] 0.98, 95% Confidence Interval [95%CI]: 0.97-0.99, P value = 0.015] and Body Mass Index (BMI, kg/m²) (aOR 0.92, 95%CI: 0.87-0.97, P value = 0.003). Excessive night sweat and un-intentional weight significantly predicted TB at recruitment. Additional 19 TB patients were diagnosed between 3 and 18 months of follow-up. The incident rate was 320 per person-month. The incident rate in HIV positives and HIV negative was 338 per person-month and 148 per person-month respectively. The hazard ratio for incident TB for HIV (Hazard Ratio [HR]: 2.60, 0.92-7.40, P value = 0.071).

Conclusion: The TB prevalence among presumptive TB patients was relatively high in the described setting. Furthermore, a substantial number of patients developed TB between three and eighteen months of follow-up, which needs to be considered in follow up strategies for presumptive TB patients.

Figure: Estimate of tuberculosis among presumptive TB patients after three months of follow-up in Bagamoyo, Tanzania



PC-971-05 Prevalent tuberculosis detected by active case finding among adults in the community in Ca Mau, Viet Nam

T A Nguyen,¹ P Nguyen,¹ N V Nhung,² B H Nguyen,² K H Tran,³ J Ho,^{1,4} G J Fox,¹ G Marks^{1,4} ¹Woolcock Institute of Medical Research, Ha Noi, ²National Tuberculosis Programme, Ha Noi, ³Ca Mau Centre for Social Disease Prevention, Ca Mau, Viet Nam, ⁴University of New South Wales, Sydney, NSW, Australia. e-mail: thuanh.nguyen@sydney.edu.au

Background: Interventions that improve detection and treatment of people with tuberculosis (TB) could be an important part of strategies to reduce the prevalence of TB in high-burden settings. We are conducting a cluster randomized trial of community-wide active case finding for TB among adults in the rural province of Ca Mau in Viet Nam. Here, we aimed to determine the prevalence of Xpert positive tuberculosis in the general community, using of active case finding in the intervention clusters during the first year of the study.

Design/Methods: All eligible and consented individuals aged 15 and above in 57 randomly selected sub-communes in Ca Mau province were asked to produce a single spontaneous sputum sample for Xpert MTB/RIF testing, regardless of symptoms. Participants whose sputum was Xpert MTB positive were invited to have a plain chest X-ray and to submit two additional sputum samples for confirmatory liquid culture.

Results: The eligible adult population in the selected sub-communes was 46,694. Of these, 39,403 (84%) agreed to be interviewed (screened) and 21 155 (45% of the eligible population and 54% of those interviewed) produced a sputum specimen that was suitable for Xpert testing. Overall, the sputum of 169 people was positive for Xpert MTB. The crude prevalence was 429/100 000 adults screened (95%CI: 369 - 499). Among those with a positive Xpert MTB test result, 54% had "very low" levels of *M. tuberculosis* detected. Among 140 Xpert MTB positive participants with at least one finalized mycobacterial culture, 83 (59%) were culture positive for *M. tuberculosis*. Cultures for a further 22 (16%) grew non-tuberculous mycobacteria or were contaminated and the remaining 35 (25%) were culture negative. Among the Xpert MTB positive / culture negative participants, 21 (60%) had abnormal chest X-rays.

Conclusion: The prevalence of pulmonary TB detected by screening using Xpert MTB/RIF test in the general population was high. The discrepancy between Xpert and culture results requires further study. Support: NHMRC Project grant (#1045236).

PC-972-05 Gender ratios in tuberculosis prevalence and patient diagnostic rates in low- and middle-income countries: a systematic review and meta-analysis

K Horton,¹ P Macpherson,^{2,3} R Houben,¹ R White,¹ L Corbett^{1,4} ¹London School of Hygiene & Tropical Medicine, London, ²University of Liverpool, Liverpool, ³Liverpool School of Tropical Medicine, Liverpool, UK; ⁴Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi. e-mail: katherine.horton@lshtm.ac.uk

Background: In 2012, the male-to-female (M:F) case notification ratio for smear-positive pulmonary tuberculosis (TB) was 1.9:1. However, a substantial proportion of TB cases remain undiagnosed or unreported, especially in high burden and low resource settings. This study set out to systematically investigate whether observed M:F case notification ratios reflect true population gender differences in disease prevalence and diagnostic rates.

Design/Methods: Studies describing TB prevalence surveys in nationally-representative and sub-national adult populations (age ≥ 15 years) in low- and middle-income countries published between January 1993 and August 2014 were identified through searches of PubMed, Embase, Global Health, the Cochrane Database of Systematic Reviews and the WHO Global TB Report 2014. Gender-specific prevalence of bacteriologically-confirmed (culture- and/or smear-positive) TB was calculated or extracted, and M:F ratios were compared across regions, TB prevalence and HIV prevalence. Patient diagnostic rate (PDR) was calculated as smear-positive TB case notifications per 100 000 divided by bacteriologically-confirmed TB prevalence per 100 000, matching on country and study year(s). Risk of bias was assessed and study quality was ranked using the GRADE system. Heterogeneity was assessed, and random-effects meta-analyses were performed.

Results: Sixty-eight surveys with 2.9 million participants in 30 countries were identified (31 in Africa, 20 in Southeast Asia, 11 in the Western Pacific, three each in the Americas and the Eastern Mediterranean), with 24 nationally representative surveys and 44 at a sub-national level. Among 37 surveys with available data, the overall random-effects weighted M:F prevalence ratio was 2.19 (95%CI: 1.80-2.66; range 0.31 to 11.16). There was consistent male excess in TB prevalence in surveys from all regions except the Americas. The excess of male prevalent cases remained when stratified by TB prevalence and HIV prevalence and in studies with low ($n = 14$) or moderate ($n = 15$) risk of bias. M:F ratios in PDR ranged from 0.39 to 2.92 and were less than one in 23 of 30 surveys with available data.

Conclusions: TB prevalence is significantly higher among men than women in low- and middle-income countries. Gender ratios in PDR indicate that men are disadvantaged in accessing TB care.

33. Molecules, polymorphisms and resistance to TB

PC-973-05 Standardized mycobacterial interspersed repetitive units-variable number of tandem repeat genotyping of *Mycobacterium tuberculosis* in Taiwan

P-C Chuang,¹ R Jou^{1,2} ¹Centers for Disease Control, Taipei, ²National Yang-Ming University, Taipei, Taiwan. Fax: (+886) 2 2653 1387. e-mail: rwj@cdc.gov.tw

Background and aim: The IS6110 restriction fragment length polymorphism (RFLP) was adopted as a standard genotyping method for outbreak investigations of tuberculosis (TB) in Taiwan. It is time-consuming and labor-intensive. Even though 24-loci mycobacterial interspersed repetitive units-variable number of tandem repeat (MIRU-VNTR) typing were recommended for genotyping of *Mycobacterium tuberculosis* complex (*M. tuberculosis* c), the discriminatory power for the prevalent Beijing genotypes in Taiwan is unsatisfactory. In this study, we optimized loci combination and standardized the MIRU-VNTR to improve the turnaround time and genotyping capacity.

Methods: Twenty-nine MIRU-VNTR loci were evaluated using 457 *M. tuberculosis* c isolates collected from January 2013 to June 2014. Of the 457 isolates, 83 (18.2%) were confirmed outbreak isolates belonging to 32 episodes based on results of the IS6110 RFLP fingerprinting. The optimal loci combination of MIRU-VNTR was evaluated and the discriminative power was assessed by parallel comparisons with results of the IS6110 RFLP. Spacer oligonucleotide typing (spoligotyping) was performed with a commercial kit.

Results: The MIRU(10) containing 10 loci, QUB3232, VNTR3820, QUB2163b, QUB18, Mtub21, MIRU26, QUB-26, VNTR4120, Mtub04, and MIRU39, were suggested as an optimal combination. Together with spoligotyping, the MIRU(10) typing revealed results with the highest discriminative power that is compatible with the IS6110 RFLP fingerprinting. However, the RFLP fingerprints of 5 East-African-Indian (EAI) as well as 5 Beijing genotypes were not able to be distinguished even using 29-loci MIRU-VNTR. Our results demonstrated that not only Beijing but also EAI strains had high similarity of MIRU genotypes in Taiwan.

Conclusion: The MIRU(10) typing combined with the spoligotyping was proposed as a new standard genotyping of *M. tuberculosis* in Taiwan. Nevertheless, through epidemiological survey is strongly suggested while the same Beijing and EAI spoligotypes were obtained in outbreak investigations.

PC-974-05 Polymorphisms in the STAT4 gene and tuberculosis susceptibility in Chinese Han people

Q Wu,¹ Y Ji,¹ C Wu,¹ Y Wang,¹ Q He¹ ¹Sichuan University, Chengdu, China. e-mail: 76201313@qq.com

Background: The association between genetic factors and the development of tuberculosis (TB) has obtained much attention. The signal transducer and activator of transcription 4 (STAT4) gene encodes a special transcriptional factor that transmits signals induced by several cytokines which play critical roles in the development of autoimmune and chronic inflammation diseases. It can transduce signals induced by cytokines comprising I interferon (IFN), interleukin-12 (IL-12), and interleukin-23 (IL-23) in monocytes and T cells. IL-12/IFN- γ axis plays a key role for the elimination and control of *M. tuberculosis*. Here, we performed a correlation analysis between STAT4 polymorphisms and TB.

Methods: A total of 636 TB cases and 608 healthy controls were studied to examine the presence of three SNPs (rs7574865, rs4853542, and rs1031509) in the STAT4 locus. The STAT4 SNPs genotyping was performed with the Sequenom MassARRAY SNP genotyping platform (Sequenom, San Diego, CA, USA). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using the multivariable logistic regression analysis. The online software SHEsis program was utilized to analyze genotyping data.

Results: Out of three SNPs tested in the sample, one STAT4 SNP (rs4853542) was related to TB. Compared with the genotype AA, individuals carrying AG had a significantly increased risk of TB ($P = 0.02$, OR=1.15, 95%CI: 1.02-1.30). An allele model revealed that G allele had a 33% increased risk of TB compared with A allele ($P = 0.01$, OR=1.33, 95%CI: 1.06-1.66). We found the haplotype GAT significantly referred to protection against TB (OR=0.562, 95%CI: 0.33-0.96, $P = 0.03$).

Conclusions: In the present study, the rs4853542 polymorphism of STAT4 was suggested to increase risk of TB in Chinese Han people. A study with larger numbers of subjects will be required to confirm our results.

PC-975-05 Genetic polymorphisms of glutathione S-transferase P1 and the incidence of anti-tuberculosis drug-induced hepatitis in a Chinese cohort

J He,¹ Q Wu,¹ Y Wang,¹ C Wu,¹ Y Ji¹ ¹Quan Wu, Chengdu, China. e-mail: 18980602293@qq.com

Background: Anti-tuberculosis drug induced hepatotoxicity (ATDH) is one of the most common adverse effects associated with TB therapy. The GST genes code for a superfamily of enzymes that participate in the phase-II drug metabolism. Several studies in animal models demonstrated the important role of GST in the prevention of chemically induced hepatotoxicity. This study aimed at investigating the relationship between variants

and haplotypes of GSTP1 in TB patients among Chinese population.

Design/Methods: In a prospective study, 247 tuberculosis patients were followed up for three months after initiating anti-tuberculosis therapy. ATDH was defined as an ALT more than twice the upper limit of normal or a combined increase in AST and total bilirubin, and one of them was more than two-times over the upper limit of normal AST or bilirubin value. GSTP1 SNPs were genotyped with the MassARRAY platform. The associations were analyzed by the χ^2 test and also binary logistic regression analysis adjusting for confounding factors, such as age, sex, body mass index (BMI) and drinking history. The online software SHEsis program was utilized to analyze genotyping data.

Results: A total of 247 newly diagnosed TB patients were recruited in this study. Twenty-four cases of ATDH were diagnosed and were considered as experimental group and the rest of subjects (223 cases) were considered as the control group during 3 months follow-up. After correction for potential confounding factors, significant differences were found for rs1695 under an allele model (OR=4.436, 95%CI: 1.159-16.984; $P = 0.03$) and a recessive model (OR=0.24, 95%CI: 0.064-0.898; $P = 0.034$). Week significant differences were also found for rs4147581 under an allele model (OR=2.346, 95%CI: 1.011-5.442; $P = 0.047$). We did not find significant difference in haplotype distribution between the experimental group and the control group in our study.

Conclusion: Our results support the GSTP1 polymorphisms as predictors of ATDH in Chinese Han population treated with anti-tuberculosis drugs.

PC-976-05 Key population for tuberculosis intensified case finding identified through national TB prevalence survey

D B Lolong,¹ O S Simamarta,¹ B Dwihardiani,² M Farid,³ I Pangaribuan,¹ A V Siagian¹ ¹Ministry of Health Republic Indonesia, Jakarta Pusat, ²World Health Organization, Indonesia Country Office, Jakarta Pusat, ³Tuberculosis Operational Research Group, Jakarta Pusat, Indonesia. e-mail: bintari_dwihardiani@yahoo.com

Background: Tuberculosis (TB) is a major public health problem in Indonesia. The gap between the prevalence of bacteriologically confirmed TB found during National TB Prevalence Survey 2013 (NPS) and current case notification is still very large. Only a small proportion of confirmed cases were under treatment. Intensified case finding (ICF) through active screening is one of the proposed strategies to reduce TB incidence and address the detection and notification gaps. Identification of key population groups is needed to improve the effectiveness of ICF.

Design/Methods: Analysis of data obtained from NPS 2013 was conducted. Demographic information, TB history, TB contact history, smoking, were analyzed to find the association with TB cases found from NPS using logistic regression. Prevalence by sex, age group, region, and region and urban/rural stratification was calculated

according to WHO standard method to calculate prevalence

Results: Nationwide survey with 67 946 participants was conducted from April 2013 to June 2014. There were 15 467 (23%) participants with chronic cough or haemoptysis or TB suggested thorax x-ray photo. There were 426 bacteriologically TB confirmed cases detected. Male sex, old age (> 55 years old), previous TB treatment history, existing TB contacts were significantly associated with higher TB confirmed cases. However, estimated prevalent cases are still high among productive age. There is no significant difference of TB prevalence among regions and urban-rural living place. Participants with previous TB treatment history and existed TB contacts had 6.1 (95%CI 4.7-7.8) and 1.8 (95%CI 1.2-2.7) times higher odds to get TB respectively compared to those without the factors.

Conclusion: Concentrating ICF in the group of people with previous TB history, having TB contacts, and in old age and male population may give significant yield for case finding in Indonesia. Further evaluation of their yields, cost effectiveness, and feasibility are needed before incorporating this into policy. As TB burden is still high in productive age population, overall TB control strategies should be improved to treat more cases earlier.

PC-977-05 Trends of fluoroquinolone resistance in *Mycobacterium tuberculosis* mirror resistance trends among community pathogens

S Shakoor,¹ J Farooqi,¹ K Jabeen,¹ F Malik,¹ R Hasan¹

¹Aga Khan University, Karachi, Pakistan. e-mail: sadia.shakoor@aku.edu

Background: Fluoroquinolone (FQ) resistance is widely recognized among *M. tuberculosis* strains from high burden countries and recent literature shows that it impacts development of treatment regimens. Increase in *M. tuberculosis* FQ resistance trends is also documented and is related to the unchecked and inappropriate use of FQs in the population. We hypothesized that the development and spread of resistance in other community acquired (CA) bacteria can be used to predict resistance among *M. tuberculosis* strains in high burden regions. As a first step we have correlated resistance trends among these CA-bacteria with those in *M. tuberculosis* isolated at a clinical laboratory in Karachi, Pakistan.

Design/Methods: Laboratory records were retrieved and duplicate removed for FQ resistance reported among pathogens of interest for the years 2010-2014. These comprised community (and not hospital or long-term facility) culture isolates of *S. pneumoniae*, and *H. influenzae* (HI) among respiratory pathogens and *Salmonella* Typhi and Paratyphi, *Shigella* spp, and *Vibrio cholerae* among diarrheal pathogens, where the use of FQ is common. Data was analysed in MS Excel and bar charts were created. *M. tuberculosis* data was analysed for FQ resistance in the same years and proportion of

resistant *M. tuberculosis* in each year was mapped graphically to visually contrast resistance trends among CA bacteria with *M. tuberculosis*. Coefficient of regression (R^2) values and χ^2 values for trends were calculated in MS Excel.

Results: FQ resistance in HI increased consistently from 9.1% in 2010 to 23.4% in 2014 (linear $R^2=0.9071$). FQ resistance in *Shigella* spp increased from no detectable resistance in 2010 to 20.9% FQ resistance (linear $R^2=0.9066$). *M. tuberculosis* FQ resistance also increased from 27.2% in 2010 to 33.3% in 2014. Linear regression explained only a small proportion of changes in these trends ($R^2=0.26$). However, the increase in resistance is significant ($P < 0.0001$; χ^2 for trend = 95.2423). On visual examination of trends, the trend of resistance development mirrors more closely that in HI, a respiratory pathogen (Figure). HI resistance trends predicted FQ resistance in *M. tuberculosis* (χ^2 for linear trends = 2.7808; $P = 0.09$; non-zero slope).

Conclusion: Variance in *M. tuberculosis* FQ resistance may be affected by changes in testing methods and FQs tested. The evolution of resistance in *M. tuberculosis* is slower than seen in *Shigella* spp, but resembles development of resistance in HI. Similarity between resistance trends in *M. tuberculosis* and HI suggests common driving factors; possibly use of FQ in undiagnosed *M. tuberculosis* patients. Rapid development of resistance in these community pathogens is alarming. Increasing FQ consumption data calls for an urgent public health action to enforce responsible use of FQs in Pakistan.

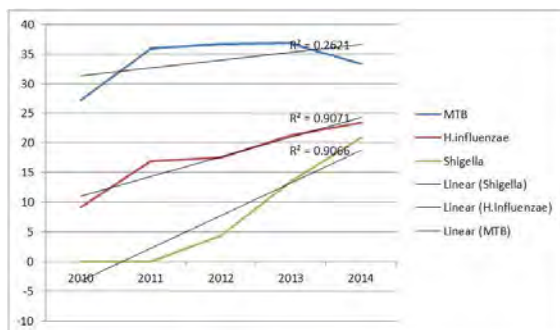


Figure 1: resistance trends (linear) for *M.tuberculosis*, *H.influenzae*, and *Shigella* spp. among community isolates from Pakistan, 2010-2014

PC-978-05 Key genotypes of *M. tuberculosis* responsible for the spread of multi- and extensively drug-resistant disease in the Sakha Republic, Yakutia

M K Vinokurova,¹ N E Evdokimova,¹ G I Alekseeva,¹ A F Kravchenko,¹ E D Savilov,² O B Ogarkov,² S Zhdanova² ¹Research & Practice Center for Tuberculosis of the Sakha Republic (Yakutia), Yakutsk, ²Scientific Center for the Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. e-mail: mkvin61@mail.ru

Background: Sakha Republic (Yakutia) is a northern territory with an unfavorable epidemiological situation for tuberculosis (TB). In view of this, and considering the

growing threat of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, study of the population structure of *M.tuberculosis* (common for Yakutia becomes especially important.

Design/Methods: *M.tuberculosis* isolates from 343 patients with TB were studied by 24-locus MIRU-VNTR genotyping, using MIRU-VNTRplus and SITVIT open databases for strain identification. Drug resistance (DR) was determined using automated BACTEC-960 system based on liquid media, and classical solid culture method.

Results: The following strain families were identified: Beijing (158; 46.1%), Orphan (57; 16.6%), S (39; 11.4%), T/H (27; 7.9%), Ural (22; 6.4%), Haarlem (15; 4.4%), LAM (16; 4.6%), Uganda (9; 2.6%). The 3 families accounting for 74.1% of all the cases were studied in more detail. Beijing genotype was detected in 158 patients, of them 67.1% were male, 54.6% were urban citizens, and the majority (77.8%) were young or middle-aged. Aboriginal residents made 70.7%. DR cases made 68.3%, monoresistance was detected in 1.3%, polyresistance in 1.9%, MDR in 26.6%, and XDR in 1.9% of cases. Next in the incidence was the Orphan genotype. It was detected in 57 patients (57.9% male, 68.2% urban residents, 43.9% young/middle-aged, 52.6% older than 45 years, 2/3 were aboriginal residents). DR was present in 64.9% of cases, with monoresistance in 7.0%, polyresistance in 8.8%, MDR in 12.3%, and XDR in 7.0% of cases. S genotype was determined in 39 patients (69.2% male, 2/3 urban), who were mostly (79.5%) young/middle-aged, and predominantly aboriginal (81.2%). DR was determined only in 7.7% of cases, with polyresistance in 7.7%, high incidence of MDR (74.3%), and XDR in 10.3%.

Conclusion: This was the first study on genotyping *M.tuberculosis* in Yakutia, and it showed the predominance of the Beijing, Orphan, and S families, and these same strains were responsible for the spread of M/XDR in Yakutia. Notably, severe types of DR were observed more often in S family (2.9 and 4.3 times more often, than in Beijing family, respectively). The S family was of particular interest, as in the past, it was found only in singular cases in Russia, and its current global incidence is highly sporadic. In the future, more thorough molecular epidemiological monitoring of the TB causative agent will be needed.

PC-979-05 WGS reveals genetic heterogeneity and suggests the role of selective bottleneck in defining the population structure of *Mycobacterium tuberculosis*

M De Vos,¹ P Black,¹ E Louw,¹ R Van Der Merwe,¹ S Sampson,¹ P Van Helden,¹ R M Warren,¹ P Arnab² ¹Stellenbosch University, Cape Town, South Africa; ²King Abdullah University of Science and Technology, Thuwal, Saudi Arabia. e-mail: margab@sun.ac.za

Background: Whole genome sequencing (WGS) has revolutionised the interrogation of mycobacterial genomes. Recent studies have reported conflicting findings

on the genomic stability of *M. tuberculosis* during the evolution of drug resistance. Some studies have demonstrated genomic stability, while more recent reports have shown genomic instability with the emergence of additional genetic variants independent of those observed in drug target genes conferring resistance. The identification of sub-populations within the context of WGS is dependent on the read frequency cut-off values used in the standard variant filtering approach. This study aimed to define a reliable cut-off for identification of low frequency sequence variants and to subsequently investigate genetic heterogeneity and the evolution of drug resistance in *M. tuberculosis*.

Design/Methods: Single colony forming units were selected from 14 *M. tuberculosis* rifampicin mono-resistant clinical isolates. Two of these patients had follow up isolates which were shown to be multi-drug resistant (MDR) by routine drug susceptibility testing (DST). Genomic DNA was isolated from single colonies for each rifampicin mono-resistant *M. tuberculosis* isolate and the primary cultures of the paired *M. tuberculosis* isolates demonstrating intra-patient evolution of isoniazid resistance. The whole genomes of the *M. tuberculosis* isolates were sequenced using either the Illumina MiSeq or Illumina HiSeq platforms.

Results and discussion: Our data enabled us to define a read frequency cut off of 30% to accurately detect heterogeneous variants. Using this cut-off we demonstrated a high rate of genetic diversity between single colonies isolated from one population, showing that by using the current sequencing technology, single colonies are not a true reflection of the diversity within a whole population and vice versa. In addition, our read frequency filtering approach was used to investigate the evolution of isoniazid resistance in *M. tuberculosis* clinical isolates within two patients. We found that numerous heterogeneous variants emerge and disappear during the evolution of isoniazid resistance within individual patients. Our findings suggest that the isoniazid selective pressure imposed an evolutionary bottleneck, dramatically reducing genetic diversity within the mycobacterial population. This was then followed by the subsequent accumulation of new variants in the mycobacterial population.

PC-980-05 Treatment-based risk factors for tuberculosis drug resistance in Bolivia

A Flynn,¹ J Carlos Mollinedo,² C L Daley,³ A Faino,³ R Flick,¹ E Casso,² M Camacho De Colque² ¹University of Colorado School of Medicine, Aurora, CO, USA; ²National Tuberculosis Reference Laboratory, La Paz, Bolivia; ³National Jewish Health, Denver, CO, USA. e-mail: andrew.flynn@ucdenver.edu

Background: Understanding the epidemiology of drug resistant TB (DRTB) in Bolivia is important for continued progress in TB control. The National TB Laboratory performs drug susceptibility testing (DST) on patients with risk factors identified by the National TB Programme (NTP).

Methods: This is a retrospective analysis of patients diagnosed with DRTB between 2006 and 2013 with risk factors for DRTB. Data collected by the Departmental and National TB Laboratories were evaluated for drug resistance by risk factor: 1) previous treatment—more than thirty days of Category I therapy, 2) lack of clinical response or sputum conversion at two months of Category I therapy, or 3) treatment failure—Category I therapy completion with persistent positive sputum smear. Odds ratios were calculated using SAS version 9.4.

Results: 3791 culture-confirmed patients with risk factors for DRTB received DST from 2006-2013: treatment failures exhibited higher MDR incidence than patients with lack of therapy response at two months (35% vs. 18%, OR=2.3, CI=1.7-3.0) and those with lack of response at two months exhibited higher MDR incidence than patients treated previously (18% vs. 8%, OR=2.7, CI=2.2-3.4). Neither isoniazid nor rifampicin monoresistance were significantly associated with treatment risk factors.

Conclusions: NTP-defined risk factors impart significant risk for MDR in Bolivia, suggesting risk factor criteria appropriately select patients with higher probability of this resistance pattern. Treatment failure was the greatest risk factor for MDR.

34. Thinking broadly to advance the END TB Strategy

PC-981-05 Tuberculosis drug kit implementation eases drug supply management in two regions of Ethiopia

M Weldeselassie,¹ J Degu,¹ H Tesfaye Molamo,² Y Yiegezu Zegioris,³ Y Anteneh Kassie,¹ S Negash,¹ M Aseresa Melese,¹ P G Suarez⁴ ¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, ²Federal Ministry of Health, Addis Ababa, ³Pharmaceuticals Fund & Supply Agency, Addis Ababa, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: mlegesse@msh.org

Background and challenges to implementation: To strengthen TB supplies management, the Ethiopian Ministry of Health (MoH) started TB kit implementation as of July 2012. The USAID-funded HEAL TB Project and MoH supported the implementation of the kits in two regions of Ethiopia. Our objective was to determine the contribution of TB kit implementation to improving drug supply management in selected health facilities (HFs) in the project regions.

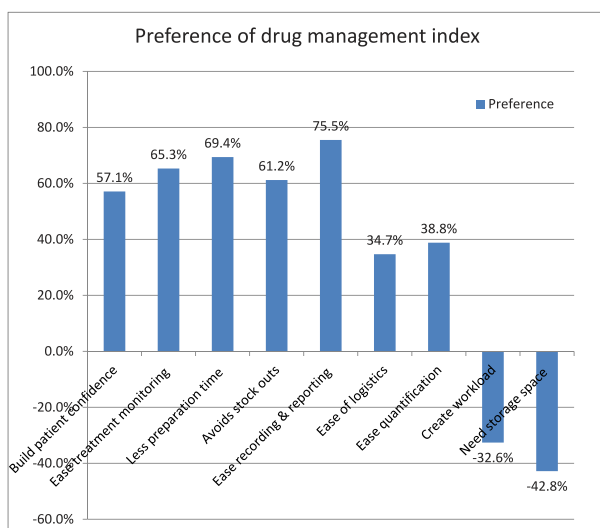
Intervention or response: A cross-sectional study was conducted to estimate the effect of TB kit on easing drug management. We included 98 HFs in the study (49 from each of kit implementing and non-kit implementing sites). Trained data collectors interviewed 98 HF TB focal persons. HF registers were reviewed in the kit implementing and comparison HFs to check for patients'

interruption of anti-TB medications. Qualitative data was analyzed thematically.

Results and lessons learnt: Ninety four percent of the kit implementing HFs ($n = 49$) preferred kit over the loose form of drugs due to its building confidence to patients (57.1%), less preparation time for dose administration (69.4%), ease of recording & reporting (75.5%), treatment monitoring (65.3%), logistics (34.7%), and quantification (38.8%). Moreover, a 7% net increase on the number of patients who do not interrupt their treatment for at least a day was recorded in the TB kits implementation HFs as compared to the comparison group. However, 32.6% HFs cited that they have faced workload due to kit implementation and 42.8% reported shortage of space to store kits. TB kit implementation at health posts (HPs) was only 14% in the kit implementing zones. The reported reasons being TB focal persons not comfortable to give TB drug kits to HPs because of fear of mismanagement and Health Extension Workers would not be always available in the HPs to give the treatment to patients. Additional barriers to kit implementation included absence of sensitization, careful planning and coordination. Regular reporting and requisition, intrinsic nature of kit form to build confidence and ease of drug management were the factors that facilitated kit implementation.

Conclusions and key recommendations: TB patient Kit implementation eases drug supply management. Creating awareness on reconstituting of TB patient kits, providing of shelves for TB clinics, strengthening planning and coordination at each level of the supply chain can further improve the kit implementation process.

Figure Factors favouring or disfavours drug kit implementation as perceived by TB focal persons



PC-982-05 TB lacks space inside the Parliament of India: demands for a call for action to involve more parliamentarians both inside and outside Parliament

S Nayak,¹ S Chadha,¹ R Pathak,² V Ghule,² R Dayal,³ O Bera,¹ P Mishra,³ A Das,¹ P Mishra³ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²World Health Organization Country Office, India, Ranchi, Jharkhand, ³State TB Cell, Ranchi, Jharkhand, India. Fax: (+91) 114 605 4430. e-mail: snayak@theunion.org

Background: India, the highest TB burden country of the globe accounts for 26% TB cases of earth with an estimated incidence of 2.1 million & 2.6 million prevalence per annum. India put ~1.4 million TB patient on treatment in 2013. 1/3rd of cases are still missing from the national notification system. Challenges of M/XDR TB, Pediatric TB, quality of care & private notifications emerge every day/year. Political & admin commitment have been kept in priority in TB Prog., so also in the recent 'End TB strategy'. The objective of this paper is to analyze, how TB as an issue has penetrated into both Upper (Rajya Sabha) & Lower House (Lok Sabha) of Indian Parliament. Design & Method Questions raised in both Rajya Sabha (RS) & Lok Sabha (LS) of Indian Parliament were selected for analysis. Questions (Qs) relating to health & TB in total 15 sessions of the 15th LS (1 Jun 2009 to 21 Feb 2014) represented by 545 elected members & 4 sessions (230 to 233) held in 2014 of RS represented by 250 members were reviewed from sites of both houses. All Qs (starred & unstarred) raised in both houses were studied under 12 categories: 1.TB Epidemiology, 2.National Prog, Diagnosis & Treatment, 3.MDR/XDR/TDR, 4.Global TB Report, 5.Corporate, 6.Drugs/Vaccine, 7.HIV-TB, 8.TB in Women & Children, 9.Policy, 10.Research, 11.External Funding & 12.TB & Nutrition.

Results: 79 401 Qs asked in 5yr term of 15th LS that include 4283(5.4%) Qs on health related issues. Among health questions, TB related was 1.2% (52 Qs) that include 12(3%) starred questions of total 405 starred Qs on health. Similarly, 10 025 Qs raised in RS, include 556 (5.5%) on health. The proportion of TB Qs among health is 3% (17). Out of 795 parliamentarians of both houses, 61(7.6%) raised Qs on TB. Repeat Qs asked by 8(1%) parliamentarians. Review of 69 Qs of both houses reveals, 26% (18) are on National Prog., Diagnosis & Treatment, followed by TB Epidemiology 20% (14), M/XDR 15% (10), Drugs & Vaccine 12% (8). Issues relating to other 8 categories are below 5%. Only 2 Qs raised in RS relating to TB & Nutrition and 2 Qs each on Policy & Research.

Conclusion: TB issues have some space inside the Indian Parliament. However, that is meagre in comparison to other health topics in both inside the Parliament and also among the Parliamentarians. At this hour of enforcing Post 2015 End TB strategy, the component of 'Political Commitment' need to be emphasized & re-emphasized both in and out of the Parliament to substantiate the commitment of India.

PC-983-05 The need to establish regulatory framework for TB notification

K Chopra,¹ D Kundu,² A Khanna,³ N Sharma,⁴ S Saini,⁵ TJ Padmini³ ¹New Delhi Tuberculosis Centre, Delhi, ²World Health Organization Country Office for India, Delhi, ³Directorate of Health Services, Delhi, ⁴South Delhi Municipal Corporation, Delhi, ⁵Jag Pravesh Chandra Hospital, Delhi, India. e-mail: debashishkundu@yahoo.com

Background: An important component of the WHO End TB Strategy is to have regulatory frameworks for case notification. Government of India had declared TB as a 'notifiable' disease. There are many regulatory acts in the country wherein reporting a 'notifiable' and 'dangerous disease' is compulsory. For instance, in the Delhi Municipal Corporation (DMC) Act, TB is defined as a 'dangerous disease' and the DMC act also mandates reporting under section 371 to the Municipal Health Officer. Also, not reporting a notifiable disease is a violation of Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002 under regulation 7.14. However, there is no standard regulatory framework for TB notification resulting in weak notification from the private sector.

Intervention or response: Delhi State TB Control Programme had taken initiatives for improving notification of TB cases from the private sector in 2014. Key steps taken were to constitute a state level TB notification committee to oversee the progress of TB Notification efforts in the state and direct 'one to one' sensitization of PP's (in single PP's clinic, corporate hospitals and laboratories) by the state notification teams with the help of available tools for sensitising the private practitioners (PP) on TB notification - TB Notification Government Order, Guidance Tool for TB Notification and Standards of TB Care in India. State TB notification committee convened 10 focussed action oriented meetings with all stakeholders for strengthening TB notification in the state.

Results and lessons learnt: TB notification cases from the private sector rose from 200 (2013) to 4000 (2014). 6% (100/1800) of registered private health facilities in Nikshay notified TB cases in 2014, with a marginally rise from 4% in 2013. More than 90% of private health facilities in Delhi are still not notifying to the public health authorities.

Conclusions and key recommendations: Active state level initiatives have led to increase in TB case notification, but not much improvement is seen in number of PP's notifying the cases. Lack of regulatory measures at policy level and lack of awareness among private health care providers are major challenges in TB notification implementation. Public health efforts thus need to be aligned through a framework of complementary measures, both regulatory and enabling, that promote an adequate level of vigilance. The notification of TB should be made compulsory at all levels.

PC-984-05 The role of medical colleges in tuberculosis notification

S Chandra,¹ N Sharma,² K Chopra,^{3,4} A Khanna,³ TJ Padmini³ ¹World Health Organization, Country Office for India, New Delhi, ²Maulana Azad Medical College, New Delhi, ³Directorate of Health Services, State TB Office, New Delhi, ⁴New Delhi Tuberculosis Centre, New Delhi, India. e-mail: chandras@rntcp.org

Background and challenges to implementation: Medical Colleges are the hub for referral and tertiary care services and cater to a large medical outdoor which is not bound by State boundary. Notification of TB through college window is of paramount importance as majority of TB patients get referred for treatment outside the State, which seldom gets reflected as disease burden in program records. In order to effectively plan any public health intervention, it is vital to have a complete burden estimate by notifying all the TB cases. It is imperative then that the referred patients do not get missed and get notified under the program umbrella.

Intervention or response: In 2014, Delhi State took the initiative to notify TB patients not only from private sector but also from the bustling outdoors of all its eight government Medical Colleges. Under the Revised National Tuberculosis Control Program, NIKSHAY online web based system is used for TB notification. As there was no separate portal for Medical College notification under NIKSHAY, each department of Medical College was registered as an independent referring health facility with their own web space for TB notification. This helped track patient referrals from each department and made the departments accountable for the patient referrals and feedback. Those patients were omitted from the notification portal whose feedback of treatment initiation had been received by the Medical College. This measure was adopted to avoid record duplication.

Results and lessons learnt: Out of the 11 906 TB cases diagnosed in 2014 by the eight Medical Colleges in Delhi, 11 158 were referred for treatment outside the State and feedback was received for 8433 (76%) patients. 1195 (48%) of the remaining 2725 TB patients whose feedback was not received, were notified in the NIKSHAY under the designated referring health facility portal created for each Medical College department. The entries for later half of 2014 are ongoing. Without this domain in the notification portal, these patients would have been lost for treatment follow up and missed in the community.

Conclusions and key recommendations: Medical Colleges play a pivotal role in TB notification as each year considerable load of TB patients get referred from Medical College across the country. Separate notification domain for individual departments of Medical College ensures that the referred patient gets notified under the program umbrella and does not get missed in the community.

PC-985-05 Targets vs. impacts: understanding the impact of the Global Fund's performance based funding modality in the Nepalese health care sector

K Dahal,^{1,2} R Khatri,¹ S Khanal,¹ S C Baral,¹ I Harper^{1,3}

¹Health Research and Social Development Forum, Kathmandu, ²Tribhuvan University, Kathmandu, Nepal; ³University of Edinburgh, Edinburgh, UK. Fax: (+977) 1 410 2016. e-mail: kapildahal@gmail.com

Background: The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) is distinct among funding agencies because of its lack of country presence and performance based financial disbursement mechanism. It operates through distributing funds to the Primary Recipients (PRs), which can be either government entities or organizations from the non-governmental sector. These then disperse resources to their implementing partners, the Sub-Recipients (SRs) who implement programmes. Outputs, calculated against proposed targets, are measured through specific recording and reporting, monitoring and evaluation systems.

Design/Methods: The data for this study was collected between 2013 and 2015. Extensive in-depth interviews were carried out with those responsible for implementing the TB and HIV components of GFATM work in government departments, with PRs, SRs and people living with HIV and AIDS (PLHAs) and their networks, from the central to peripheral levels in Nepal. Participant observation of different meetings, workshops and interactions were also another crucial means of data collection.

Results: Despite its claim of being a simple funding disbursement mechanism, GFATM has contributed to increasing bureaucratization in the health sector. There is a disjuncture between the government budget release through the "Red Book", which records all government planned activities and the GFATM form of disbursement. In addition, reporting against outputs has become more focused on targets at the expense of evaluating programmatic impact. This has, ultimately, made the stakeholders involved in the GFATM process focus on measuring activities, in order to reach targets so that further funds can be released. In such a situation, the problem is further compounded by delayed disbursement in an unstable political context and the highly politicized health service delivery environment.

Conclusion: Greater awareness of the unintended difficulties of managing GFATM projects is required to appreciate the entanglement of GFATM projects with Government and NGOs. Appreciation of this can be achieved through qualitative research performed with those involved in running the programmes.

PC-986-05 Pakistan's National TB Control Program's response to the 'End TB' Strategy

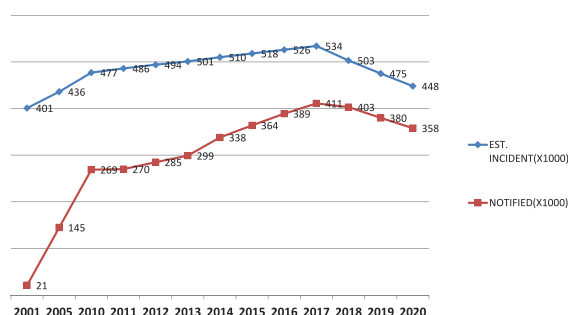
E Qadeer,¹ B Khan,¹ N Safdar,² S-E Ottmani,³ M Ahmad¹

¹National TB Control Program, Islamabad, ²Social & Health Inequalities Network, Islamabad, Pakistan; ³Independent Consultant, Geneva, Switzerland. Fax: (+92) 843 8081. e-mail: drbasharatjaved01@gmail.com

Background: A vibrant National TB Control Program in Pakistan since 2001 has provided free of cost standardized TB diagnosis and treatment to about 2.5 million sensitive and six thousand resistant cases in the country. A nationwide population-based TB prevalence survey (2010-11) and drug resistance survey (2012-13) reported an estimated TB prevalence of 342/100 000 populations and drug resistance of 3.7% among new and 18.1% among previous treated TB case. The NTP Pakistan, being responsive to End TB Strategy, imminent Sustainable Development Goals and growing TB burden has given its strategic vision and securing resources to reduce TB incidence.

Intervention: The NTP Pakistan in 2014 developed a costed National Strategic Plan (NSP) 'Vision 2020' envisaging The End TB Strategy with full expression of demand worth US\$ 876M. The NSP included innovative interventions to find missed cases through systematic screening, maximizing public sector investments and accountability, universal access to susceptible and drug resistance TB, addressing TB-HIV and other co-morbidities and prioritizing research. In addition, NTP Pakistan developed concept note for New Funding Model of Global Fund for a period 2015/17, mainly to address missed TB cases and managing DR-TB cases.

IMPACT OF TB CASE NOTIFICATION ON INCIDENT TB CASES (NSP TARGETS)



If NSP targets are followed, the incidence would start declining by 2018 onwards @ 5% annually.

Results: The milestones of End TB Strategy were adapted as goal of NSP Vision 2020 i.e., to reduce 50% the prevalence of TB by 2025 in comparison to 2012 in Pakistan and reduce new TB cases at 5% annually from 2018. This implies that in 2018 the NTP Pakistan will be notifying 420,000 cases (71%) from current 316,544 (62%) at an incremental effect of about 2.5% annual increase in case notification (Figure). It is expected that social determinants will also impact the TB incidence by 2018 as Gross Domestic Product (GDP) shows a positive correlation since the inception of TB program (2001-GDP 72.3, 2013-GDP 237). The investment through

NSP will also help reducing by at least 5% per year by 2020 the prevalence of DR-TB among TB patients who have never received any TB treatment and to strengthen programmatic and operational management capacity of the TB Control Program while enhancing public sector support by 2020.

Conclusion: The NTP Pakistan based on the NSP Vision 2020 has secured a grant of US\$ 125M from Global Fund up to 2017. The TB control program is also developing plans to secure public sector support to address the funding gaps to achieve its targets in pursuance of The End TB strategy.

PC-987-05 Social drivers of TB in the context of an increasing burden of non-communicable diseases: evidence from South Africa

P Naidoo¹ ¹University of the Western Cape, Cape Town, South Africa. e-mail: pnaidoo@hsrc.ac.za

Background and challenges to implementation: Deaths due to non-communicable diseases (NCDs) are expected to increase by 17% over the next 10 years with the largest increase of 24% expected to be in Africa. In South Africa (SA) this rise in the NCDs cluster which includes mental disorders, such as depression and anxiety, is exacerbated by the existing burden of HIV and TB and is the second leading cause of death after HIV. In 2009, 9% of individuals 30 years and older were estimated to have Type2-diabetes mellitus, representing approximately 2 million people.

Intervention or response: There is also evidence to show that in a country such as SA there are numerous social drivers and risk factors that are common to both the NCDs cluster and communicable diseases, such as TB. Despite South Africa being categorized as a middle-income country by the World Bank, there are glaring levels of social and economic inequalities, which are associated with poor health outcomes and ill-health. On closer examination the South African disease burden profile resembles that of many low-income countries.

Results and lessons learnt: At population level there was a 9.6% prevalence of diabetes reported in the 1st South African National Health and Nutrition Examination Survey [SANHANES I]. Adding to this burden of disease is the fact that the country has 28% of the world's HIV positive adult TB cases and the world's highest TB incidence. Diabetes predisposes patients to developing TB with indications that diabetes is associated with a 3-fold incident risk of TB. Moreover, the mediating effect of common mental disorders (CMDs), especially depression and anxiety, on the health outcome of individuals with diabetes, HIV and TB is poorly characterized given the fact that there is an 11% life-time prevalence of depression in low and middle income countries, including SA. Data from the SANHANES I, indicated that at least 28.4% of the South African population 15 years and older have symptoms of anxiety and depression.

Conclusions and key recommendations: Given the epidemiological pattern of the NCDs cluster, HIV-TB diseases in SA it is evident that the country is facing a

multiple burden of disease. To address the disease burden it is also important to understand the social epidemiological profile of the country. Public Health Policy adjustments need to be made for both NCDs and HIV-TB given their increasing co-existence.

PC-988-05 Use of regulatory action in tuberculosis control in New York City, 2011-2013

J Burzynski,¹ R Oken,¹ D Nilsen,¹ M Robinson,¹ R Acevedo,¹ J Martinez,¹ M Macarai¹ ¹New York City Department of Health and Mental Hygiene, Queens, NY, USA. e-mail: mmacarai@health.nyc.gov

Background: The tuberculosis (TB) resurgence in New York City (NYC) in the early 1980s to 1990s led to a series of enhanced TB control measures, including revising the NYC Health Code to allow for regulatory action against non-adherent infectious TB patients. Regulatory action is only permissible if the patient is a threat to public health and attempts to achieve voluntary adherence have failed or were considered and ruled out. After over two decades of decline in TB incidence, the use and impact of regulatory actions in NYC's TB control program were examined.

Design/Methods: All *Mycobacterium tuberculosis* culture-positive pulmonary patients reported to the NYC Department of Health and Mental Hygiene between January 1, 2011 and December 31, 2013 were obtained from the TB registry. Patients referred for regulatory action were identified using referral log sheets. Demographic, clinical, and social characteristics of patients were examined. The proportion of patients with an order for TB examination, treatment, and detention was calculated. Characteristics and treatment outcomes of patients issued an order were compared to those who were not. Pearson's χ^2 was used to compare proportions and the Wilcoxon rank-sum test to compare medians.

Results: During this period, there were 1542 culture positive pulmonary TB patients reported in NYC, of whom 146 (9%) were referred for possible regulatory action. Sixty-four (44%) referrals were resolved without regulatory action. Of the 82 patients who received an order, 52 (64%) were issued an order to attend outpatient examination or complete treatment, primarily under directly observed therapy; 10 (12%) an order to be detained until no longer infectious; and 20 (24%) an order to be detained until completion of treatment. Compared to patients who were not issued an order, those with an order were more likely to have TB with drug resistance, including multidrug-resistant TB (27% vs. 11%, $P = 0.02$), and report homelessness (26% vs. 11%, $P = 0.03$) and drug use (35% vs. 14%, $P < 0.01$). Treatment completion did not differ significantly between the two groups (82% vs. 85%, $P = 0.65$).

Conclusion: Regulatory action in NYC is used sparingly and only after efforts have been made to achieve voluntary compliance or where voluntary compliance is not feasible. Orders were more likely issued to patients at high risk for non-adherence. Regulatory measures

continue to play an important role in NYC's TB control efforts.

PC-989-05 Generating sub-national estimates of the effectiveness of tuberculosis policy interventions to meet the post-2015 global TB targets

Z McLaren,¹ K Schnippel² ¹University of Michigan, Ann Arbor, MI, USA; ²Right to Care, Johannesburg, South Africa. e-mail: zmclaren@umich.edu

Background: The WHO Global TB Programme strategy sets ambitious targets for the reduction in TB cases and TB deaths post-2015. Modeling has been conducted at the national level to inform the choice of interventions, scale and resource allocation to support country program planning. This study leverages the wealth of data available at the sub-national level in South Africa to guide region-specific policy that is targeted to areas where it meets local needs of populations and is likely to be most effective and cost-effective. Tuberculosis has been the leading cause of death in South Africa for the past decade and there is an urgent need for effective sub-national policy to address the epidemic. There are important implications from this study for program implementation by WHO GTB, STOP TB Partnership, Global Fund, UNAIDS and other key global stakeholders.

Design/Methods: We use data from the National Health Laboratory Service database on TB diagnostic tests performed on patients in public health facilities and Census data from 2011 to calculate the burden of TB cases per capita by 226 local municipalities. We examine factors related to (1) early diagnosis of tuberculosis including universal drug-susceptibility testing and (2) treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support. Using regression analysis, we evaluate the relationship between the TB burden and measures of the poverty rate, access to primary health care, and clinician compliance with current diagnosis guidelines.

Results: Local municipalities with a greater fraction of urban residents and higher rates of household access to a cell phone have higher tuberculosis rates per capita. Counter-intuitively local municipalities with lower unemployment rates have higher TB rates per capita, which may be driven by urban residency and better access to health facilities.

Conclusion: This analysis focuses on population characteristics and service-delivery factors that influence the cost-effectiveness of WHO interventions. It highlights factors that are most associated with high TB burdens, and would therefore need to play a large role in any effective targeting strategy. Allocating additional resources for sub-national analysis will conserve resources with improved program cost-effectiveness over time.

35. Financial impact of TB

PC-990-05 BRICS: cooperation and innovation towards tuberculosis elimination

C Oliveira Dantas,¹ P Bartholomay Oliveira,¹ A Torrens,¹ D Pelissari,¹ F Moherdau,¹ D Barreira¹ ¹Ministry of Health, Brasília, Distrito Federal, Brazil. e-mail: cintia.dantas@saude.gov.br

Background and challenges to implementation: The BRICS countries label refers to a select group of 5 large, developing countries (Brazil, Russia, India, China and South Africa). These countries are promising emerging markets, leading the world in public policies. In terms of health, tuberculosis (TB) is a common threat. The World Health Organization (WHO) estimates that Brazil, Russia, India, China and South Africa account for almost 50% of all world's reported cases, adding up to 2 830 807 TB cases in 2013 and a high amount of patients in these countries did not have access to free of charge and quality-assured treatment.

Intervention or response: Considering that TB is a poverty related disease and aligned with the Tuberculosis prevention, care and control after 2015, BRICS came together on an innovative proposal involving universal access to First Line TB Drugs (FLD) to BRICS countries and, gradually to 83 low and middle income countries selected based on data from the World Bank and the WHO tuberculosis report.

Results and lessons learnt: Data assessment was conducted to understand the real number of cases not covered by the public sector, as well the costs dimensions to provide universal access to FLD within the BRICS, and later, to low and middle income countries. In 2013, BRICS notified 46.4% of the world's TB cases. Currently the gap among cases not covered by public sector is almost 880,000 patients, representing almost 30% of all TB cases notified by BRICS. Brazil estimative treatment expenditure for FLD was approximately US\$ 24.00 per patient in 2013. To cover the treatment for those cases within the BRICS, it is estimated that US\$ 18 702 027. is needed. In addition, for that same year, low and middle income countries reported 41.2% (2 511 734). Considering BRICS TB cases, in total, 88% (5 342 541) of all world's tuberculosis cases will be covered by the proposal. In terms of budget, it is estimated that US\$ 128 220 984. is needed, considering all TB notified cases in BRICS and other selected countries. The sharing of this amount will respect BRICS consensus.

Conclusion and recommendations: BRICS are currently negotiating the next steps of the Tuberculosis Cooperation Plan. In addition, a Commitment Term must be put in place, in which recipient countries will grant their former TB budget addressed to drugs to be applied on another TB need – lab strengthening, second line drugs, early diagnosis investments, R&D, and so forth.

PC-991-05 Multi-channel fundraising mechanism demonstrated to reduce the economic burden of tuberculosis patients in China

I Wang¹ ¹Chinese Center for Disease Control and Prevention, Beijing, China. e-mail: quyan@chinatb.org

Background and challenges to implementation: As part of massive scale-up of Nation TB control Program in 2004 in China, policy of free TB screening examinations and free anti-TB drugs and follow-up examinations for all confirmed TB cases was implemented nationwide. In spite of this progress, however, the epidemic remains a serious public health issue and is compounded by the emergence of drug resistance. Based on the ongoing strengthening TB control strategy in China, innovative financing models should be established for diagnosis, treatment and case management of TB patients. Chinese National Health and Family Planning Commission (NHFPC) and Bill & Melinda Gates Foundation cooperated to explore the feasibility of the multi-channel fundraising mechanism for TB and MDR-TB control since 2009.

Intervention or response: Local governments in Zhenjiang city of Jiangsu province, Yichang city of Hubei province, and Hanzhong city of Shannxi province as well as 26 counties and districts affiliated to the 3 cities, representing different geographical and economic situation in the east, middle and west regions of China TB control were advocated to demonstrate financing and reimbursement policy for the costs of essential services through local urban residents' medical insurance, new rural cooperative medical insurance, civil affairs aid and related charitable institutions, expected the rifampicin susceptible TB patients paid no more than 30% of the total cost out-of-pocket cost in the service package and rifampicin resistant TB patients no more than 10%.

Results and lessons learnt: In the project cities, the new financing and reimbursement policy developed and demonstrated since 2013. As results, all Rifampin Sensitive TB patients just paid 20% costs of the services received in Zhenjiang and Yichang and 30% in Hanzhong respectively, while the remaining cost were covered by medical insurances. For the Rifampin Resistant TB patients, the service costs were 100% in Zhenjiang and Hanzhong and 90% in Yichang covered by medical insurances (urban/rural), local civil affairs aid and charitable organizations.

Conclusions and key recommendations: The multi-channel fundraising mechanism demonstrated in project cities dramatically reduced the economic burden of both Rifampin Sensitive/Resistant TB patients, which proved the feasibility of fundraising mechanism for TB treatment in different regions of China.

PC-992-05 Out-of-pocket expenditure on private health care providers among TB patients in Salem district, Kerala, India

M Arulanantham,¹ C Joltin,¹ V Sameer,¹ P Bhat,¹ T Thomas¹ ¹The Catholic Health Association of India, Secunderabad, India. e-mail: sameer-valsangkar@chai-india.org

Background: The initial point of contact for seeking health care is a private service provider among more than 80% of the population in India and TB is no exception to this norm. This is despite the free DOTS treatment provided through the public health system. The current study was conducted to assess out of pocket expenditure on private healthcare providers among TB patients in Salem district, Kerala, India.

Design/Methods: The study was conducted in Salem District of Tamil Nadu, South India. A convenient sample of 50 patients who were attending a Government Treatment center and receiving Category-I (new cases) treatment were selected and interviewed with a structured questionnaire. Expenditure patterns among patients who had initially contacted a private service provider were assessed. Consent was taken from District TB officer and the patients.

Results: Only 10% of the sample respondents were aware of free treatment and directly went to government health service. 20% of the TB patients had spent nearly Rs.100 000 in private treatment. 20% of the TB patient had spent Rs.10 000 to Rs. 25 000. 45% of the TB patients had spent Rs.2000 to Rs.5000. The remaining 5% had spent less than Rs.1000 in private health facilities. 90% of the patients belonged to low socio-economic status. 92% of the patients were satisfied with the treatment and government health facilities.

Conclusion: The main reason for seeking private facilities is lack of knowledge on TB and free DOTS treatment. Dissemination of key messages on TB and free treatment is the only way to reach the poor people to stop their economic downfall and expenditure on private providers for tuberculosis despite free treatment being available.

PC-993-05 Rural India paying more towards direct and indirect costs for pre-treatment evaluation of TB: expenditure analysis in rural and urban Pune

O Bera,¹ M Chandge,² S Kamble,³ B Pawar³ ¹The Union South-East Asia Office, New Delhi, ²District TB Office, Mumbai, ³State TB Office, Pune, India. e-mail: oprakash@theunion.org

Background: Patients cost are, in part a function of the structure of health system, with pre diagnostic costs reflecting accessibility of diagnosis. The present study was undertaken to estimate overall (direct and indirect) cost incurred by patients in rural and urban areas for pre-treatment evaluation of TB.

Intervention: Cross sectional questionnaire based study was conducted among new adult smear positive pulmonary TB patients during the period Jan – Dec 2014 in

Pune. New sputum smear positive TB patients having HIV negative status having completed intensive phase of treatment were included. Pune urban has 6 tuberculosis units (TU) having population of 1.2 million and rural part has 12 TUs with population of 4.7 million. Out of the shortlisted TB patients from the TB register 120 TB patients each from rural and urban area were randomly selected, including 20% non-response rate. Information regarding direct cost (medical and non-medical) and indirect cost was estimated for two periods (1) Before treatment (two months prior to start of TB treatment) (2) During Intensive phase (two month treatment period) (3) During Continuation phase. All calculations are in terms of Indian Rupees (Rs). Result: Of the 240 TB patients, 205 were interviewed. 15 were excluded as outliers based on interview. Analysis was done for 190 patients [93 and 97 from urban and rural respectively]. 79% patients belonged to age group of 15- 54 years. Study group included 59.4% males and 40.6% females. About 51% in urban had per capita income of less than Rs 2250 and 56% in rural had per capita income of less than Rs 1100. During pre-treatment phase, it was observed that 91.8 % and 98% of rural patients are paying towards direct medical and non-medical cost in comparison to 83.9% and 92.5% urban patients in the same head respectively. Also rural patients are paying more towards indirect cost; 89.7% rural in comparison to 54.8% urban patients. During treatment phase, rural patients (32%) are paying more towards indirect cost as compared to urban patients (24.7%).

Conclusion: Low awareness among patients about disease, free TB diagnosis and treatment have forced them to go on a spiral shopping trend for treatment resulting in increased pre-treatment cost in rural areas . Although there have been multiple commitments from national and state governments, still large scale public health programmes are not reachable to common man.

Table Pre-treatment costs to Urban and Rural TB patients

Table 1: Pre-treatment costs to Urban and Rural TB patients				
		Cost Incurred		
	Nil cost	≤ Rs	> Rs	Total
	<i>n</i> (%)	1000	1000	<i>n</i> (%)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Pre-treatment cost to Rural TB patients (<i>n</i> = 97)				
Direct Medical Cost	8(8.2)	44 (45.4)	45 (46.4)	89 (91.8)
Direct non-medical cost	2(2)	33 (34)	62 (64)	95 (98)
Indirect cost	10(10.3)	36 (37.1)	51 (52.6)	87 (89.7)
Pre-treatment cost to Urban TB patients (<i>n</i> = 93)				
Direct Medical Cost	15(16.1)	41(44.1)	37(39.8)	78 (83.9)
Direct non-medical cost	7 (7.5)	56 (60.2)	30 (32.3)	86 (92.5)
Indirect cost	42 (45.2)	36 (38.7)	15 (16.1)	51 (54.8)

PC-994-05 The role of the Public-Private Mix team is key to the success of PPM implementation in East Jakarta: from theory to practice

Y N Sumarli,¹ I Kurniaty,² Y Tahir,³ I Ibnu,⁴ D Setyawati,⁵ Y I Hiola,⁶ M R Christian⁷ ¹Cipinang Detention Center, Jakarta ²East Jakarta District Health Office, Jakarta, ³KNCV Tuberculosis, Jakarta, ⁴Cipto Mangunkusumo Hospital, Jakarta, ⁵Family Health International 360, Jakarta, ⁶District Office Ministry Law and Human Rights, Jakarta, ⁷World Health Organization Country Office Jakarta, Indonesia. Fax: (+62) 218 591 1415. e-mail: dr.yulius.st@gmail.com

Background and challenges to implementation: National health survey in 2010 showed that 63.9 % tuberculosis patients seek treatment to hospitals. The data from MoH in 2009 only 17% of the hospitals implement DOTS optimally of which only 28% hospital follow the treatment guideline, and only 40% hospital do reporting and recording timely. East Jakarta city has 571 health care facilities, 88 primary HCF, 22 hospitals, 4 prisons, 20 private clinics, and hundreds of private practitioners. Therefore engaging hospital and private sectors sector is of utmost priority for Tuberculosis (TB) Control Program in East Jakarta

Intervention or response: To response the problem, Public Private Mix team in east Jakarta was established in August 2013 The team consists of representative from doctor association, hospitals, prisons, district health office, provincial office of MoLHR, and NGOs. The aims of the establishment PPM team was to find and treat TB patient, provide access to quality TB services through ISTC implementation, thus reducing TB morbidity and mortality in east Jakarta and prevent MDR. The expected roles are to act as a counterpart from DoH to evaluate and monitor the process of PPM implementation, to raise the team's awareness and belonging to the program, to have a uniform system and understanding of reporting recording, diagnosis, treatment, and case management, and to create linkage among the health care facilities in east Jakarta

Results and lessons learnt: By the end of 2014 all Prisons in East Jakarta, 7 private practitioners, and 4 clinics have implemented DOTS and submit report in timely manners and contribute 46 % of TB case finding in East Jakarta. The team had also facilitated the establishment of East Jakarta local TB movement (GERDUDA), and MoU signing among stakeholders to fight against Tuberculosis in East Jakarta. Series of advocacy to the east Jakarta Mayor have been conducted to achieve the mayor commitment. A circulating letter to all HCF in East Jakarta emphasizing the importance of TB prevention and control has been issued by the local government.

Conclusions and key recommendations: The establishment of PPM team plays an important role in engaging more sectors in PPM. The team can build the linkage and enhance the partnership. It can also help to advocate and strengthen DOTS implementation. Therefore it needs to be promoted and strengthened continuously.

PC-995-05 Engagement of pharmacists to ensure TB commodity security for public sector TB patients in Kenya

H Kalili,¹ R Muthoka,² B Mungai,¹ E Masini² ¹Centre for Health Solutions Kenya, Nairobi, ²Ministry of Health, Nairobi, Kenya. e-mail: hellenben@hotmail.com

Background and challenges to implementation: TB is the 4th leading cause of death in Kenya, with 89 170 cases notified in 2013. An uninterrupted supply of TB drugs is imperative for a successful TB national program. Although pharmacists play a crucial role in TB treatment, their involvement in the national TB control program (NTP) has been sub-optimal. Since 2006, management of TB drugs in NTP was performed by an epidemiologist. The program experienced delayed deliveries, stock-outs, expiries and inaccurate forecasting. In response, the Ministry of Health (MOH) in 2008 recruited a pharmacist to NTP, which resulted in improved planning for future procurements, resource mobilization and central distribution of drugs. The distribution system beyond the county level however remained weak with poor commodity management practices. County TB officers in their role as commodity managers had limited capacity in pharmaceutical management.

Intervention or response: In 2010, NTP recruited 2 pharmacists and established a national commodity security committee. NTP shifted roles and responsibilities of county TB commodity managers from TB officers to pharmacists. Between 2010 and 2011, 400 pharmacists received training on commodity management and pharmacovigilance. In 2014, 2 workshops for 47 county pharmacists were conducted on forecasting and quantification including use of QuanTB tool. County pharmacists now participate in quarterly and annual performance review meetings, where they present data on current stock. They also attend national quantification workshops.

Results and lessons learnt: 47 county budgets were developed to justify allocation of funds. As a result, 8 county governments allocated 850 000 USD for drug procurement. The increased involvement of pharmacists in management of TB drugs at all levels of health care has improved efficiency throughout the system. At county level, sharing of supply chain information has enabled the identification of gaps, and informed reverse logistics. 256 TB drug distribution points were established in counties.

Conclusions and key recommendations: Active engagement of pharmacists at national and county levels, contributes to the success and sustainability of effective TB pharmaceutical management. There is need for regular dialogue and capacity enhancement for increased support and commitment. The impact achieved in Kenya suggests that this model could be applicable in high TB burden countries.

PC-996-05 Previous tuberculosis experience and its impact on household income: a historical analysis, South Korea, 1980–2012

C Hongjo,¹ H Chung² ¹Korean Institute of Tuberculosis, Osong, ²Korea University, Seoul, Republic of Korea. e-mail: hongjochoi@gmail.com

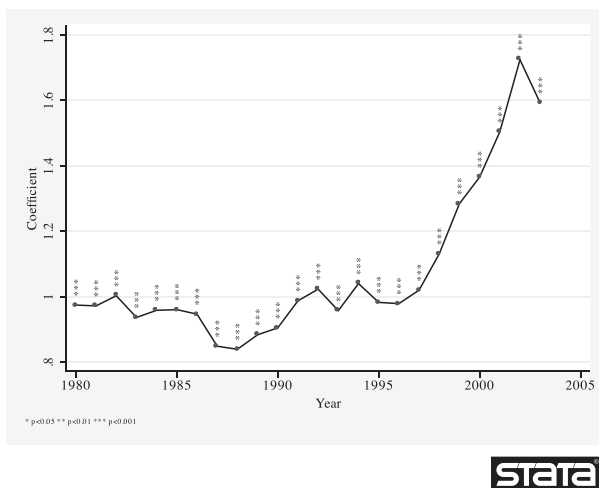
Background: A myriad of studies has focused on the pathway from social factors to tuberculosis (TB), but no studies have investigated the reverse mechanism from TB to social outcomes. The study aims to investigate relationship between social outcomes measured by household income and the previous TB experience stratified by paternal education attainment in South Korea. We focused on finding the historical trends of TB and a shift or a break time point of its trends.

Design/Methods: We used the Korean National Health and Nutrition Examination Survey from 2007 to 2012. Four exposure groups were constructed with lifetime TB experience ("TB" or "non-TB") and the level of paternal education ("High-Edu" or "Low-Edu"): TB with Low-Edu, TB with High-Edu, non-TB with Low-Edu and non-TB with High-Edu. Outcome measure was a quartile of current household income (1 to 4, 4: the highest income group). A multinomial logistic regression model, adjusting for age, gender, occupation and education, was used. In addition, we applied 'recursive regression model' suggested by Isaac & Griffin (1989). In the first analysis, TB cases being diagnosed from 1980 to 2012 and all non-TB cases were included. We dropped the first year in the second analysis and subsequently dropped the previous year in the next analysis. The last analysis included TB cases being diagnosed from 2003 to 2012 and all non-TB cases. Consequently, different point estimates were calculated at each time period from 1980-2012 to 2003-2012.

Results: In the first analysis (1980-2012), the "TB with Low-Edu" group was likely to be presented as the lowest current household income compared to the "non-TB with High-Edu" group (coefficient: 0.966, 95%CI: 0.63–1.30, *P* value: < 0.001). In the last analysis (2003-2012), the magnitude of trend was strengthened (coefficient: 1.512, 95%CI: 0.73–2.31, *P* value: <0.001). The trend was not considerably changed during a study period from 1980-2012 to 1997–2012 (coefficient: 0.993), but its magnitude started to become stronger after dropping the year of 1997.

Conclusion: The study revealed that previous TB experience in lower paternal education group is associated with current lower household income. The magnitude of trend has become stronger since the year of 1998 that was hit by economic crisis in South Korea. Thus, the year of 1998 would be considered as a shift or break point that helps better understanding of social outcomes generated by previous TB experience. TB requires at least more than 6 months to be treated and it may cause financial difficulties. This study suggests three plausible pathways to explain these disparities among the "TB with Low-Edu" group since 1998. Firstly, social resilience to overcome financial difficulties derived from the diseases may be weakened after the Korean economic

crisis in 1998. Secondly, individuals with low-income were diagnosed TB more than those with high-income since 1998, so the result may reflect the reverse mechanism from low income to more TB experiences. Lastly, interactions between social outcomes and TB may simultaneously occurred right after the Korean economic crisis. Therefore, the recursive regression model would be a useful way to investigate the relationship between health and social outcomes and to study social impacts on specific diseases.



PC-997-05 The use of incentives to accelerate tuberculosis case notification: current available knowledge reviewed

L Blok,¹ M Tijm,¹ O Ramis,² M Bakker¹ ¹Royal Tropical Institute, Amsterdam, Netherlands; ²Mott MacDonald, London, UK. Fax: (+31) 20 568 8444. e-mail: l.blok@kit.nl

Background: Incentives are frequently used in public health interventions to influence behavior of patients or providers. Also in tuberculosis control we observe increased interest in incentives as a supportive strategy to enhance tuberculosis control. While there are studies on the effectiveness of incentives to support treatment completion and improve treatment outcomes, little is known regarding its effectiveness in increasing case notification. Our aim is to review current knowledge on use of incentives for patients or providers in increasing detection of active TB.

Design/Methods: We performed a systematic review of studies published between 1995 and Nov 2014 using Pubmed, EMBASE and Cochrane, supplemented with studies found through snowballing and relevant website searches. Search terms included a combination of a term related to tuberculosis AND a term related to motivation/incentives/enabler AND a term related to diagnosis/case-detection. Abstracts and shortlisted full articles were reviewed by two reviewers independently and data were extracted using a standard template.

Results: The search identified 1095 articles, 178 of which were identified as possibly relevant for our study questions and their full text was read. We found only

four studies of robust design aiming at measuring effect of incentives on case detection or on return rates for skin test reading showing varying levels of effectiveness. A good number of additional studies described the use of incentives but only as a supportive strategy in a wider intervention. A preliminary analysis shows great variety in types of incentives used (from flat rate to results based payments) and in their operationalization. While some authors strongly believed that incentives were crucial in achieving the program goals others expressed concerns on costs implications and sustainability. Only few described assumptions underpinning design and context necessary to fully appreciate operational challenges.

Conclusion: While incentives for patients and providers are frequently used in programs aiming at increasing TB case detection, little is known on their effectiveness and on specific conditions for successful implementation. There is an urgent need to supplement anecdotal information currently used by proponents and opponents with robust evidence, a more contextualized description of lessons learned and better research on the dynamics of organizations including human motivation.

PC-998-05 Impact of providing financial incentive to tuberculosis patients on treatment outcomes in a low-resource setting: implications for the End TB strategy

K Ukwaja,¹ I Alobu,² M Gidado,³ J Onazi³ ¹Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, ²National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, ³KNCV Tuberculosis Foundation/TB CARE I Project, Abuja, Nigeria. e-mail: ukwajakingsley@yahoo.co.uk

Background: Poverty undermines adherence to tuberculosis treatment and patients' cost of care is one of the major barriers against tuberculosis care. Previous studies have shown that these costs are catastrophic to households and may discourage tuberculosis patients from initiating or continuing care. The aim of this study was to evaluate the feasibility and effectiveness of delivering economic support to patients with tuberculosis in a high-burden setting with significant resource limitations.

Design/Methods: A before-and-after implementation design was employed. The study was carried-out in a large rural health facility in Ebonyi State, Nigeria. We prospectively enrolled all registered tuberculosis patients in the facility during April to June 2014 into the intervention arm. Then, all registered tuberculosis patients during January to March 2014 were used as the control arm. Patients in the intervention arm were offered a monthly financial incentive of N2500 (US\$15) until the completion of their treatment. Patients in the control arm received the usual care. Logistic regression analysis was used to identify the determinants of treatment success.

Results: A total of 294 tuberculosis patients were registered; (173 and 121 in the control and intervention arms respectively). The patients did not differ according to their demographic or clinical characteristics ($P > 0.05$). Treatment success rate was 104/121 (86.0%) in

the intervention, and 123/173 (71.1%) in the control period ($p=0.003$). The proportion of patients who were lost-to-follow-up significantly decreased during the intervention period (20.2% vs. 5.0%; $P < 0.001$). There were no differences in death rates (6.6% vs. 5.8%; $p=0.8$) or treatment failure rates (1.7% vs. 2.9%; $P=0.5$) between patients in the intervention and control arms respectively. Also, among smear-positive tuberculosis patients, there was no difference in the rate of sputum-smear conversion after the intensive phase of treatment in the intervention and control arms respectively (88.1% vs. 91.5%; $P=0.5$). Independent determinants of treatment success were; female gender (adjusted odds ratio [aOR] 1.9), HIV-negative status (aOR 2.5), and receiving financial incentives (aOR 2.3).

Conclusion: Financial incentives proved to be effective in improving treatment success and reducing loss-to-follow-up among tuberculosis patients in Nigeria. The findings suggest that providing financial incentives can be utilized to enhance case management of tuberculosis in under-resourced populations. These observations should inform policy on the End-TB strategies.

PC-999-05 Impact of economic crisis on the incidence of tuberculosis in the city of Barcelona

A Prats-Urbe,^{1,2} J P Millet,^{2,3} A Orcau Palau,^{2,3} J A Caylà^{2,3} ¹Unitat Docent de Medicina Preventiva i Salut Pública PSMar-UPF-ASPB, Barcelona, ²Epidemiology Service. Public Health Agency of Barcelona, Barcelona, ³Ciber De Epidemiología y Salud Pública, Barcelona, Spain. e-mail: albert.pratsu@gmail.com

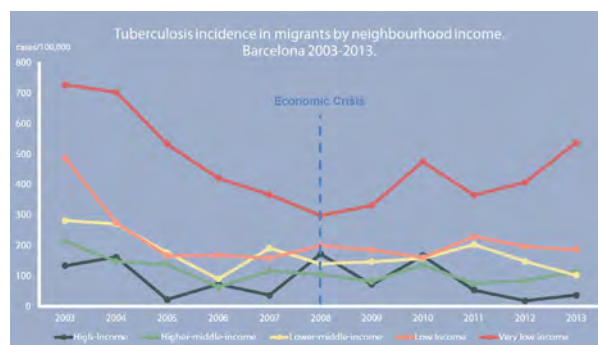
Background: There is plenty of evidence of economic crises affecting health in several aspects, including communicable diseases. The actual economic crisis has affected the city of Barcelona incrementing inequalities and may have influenced the tendency of tuberculosis (TB) incidence, especially for the more disadvantaged groups.

Design/Methods: Population-based incidence study. All TB cases living in Barcelona who started treatment between 2003 and 2013 were studied. A descriptive and analytical study of socio-demographic, epidemiological and clinical features of the cases was conducted, comparing pre and post-crisis periods (2003-08 vs. 2009-13). The annual incidence was calculated for each neighbourhood globally and by migrant status. A panel negative binomial regression model was adjusted to examine differences in the trends of these incidences before and after the crisis, and by the neighbourhood family income.

Results: There is a global trend towards reduction of the TB incidence citywide, with no overall effect of the crisis on it. Differences in the incidence of TB were found in relation with family income level, where lower income neighbourhoods had 80% more TB incidence than the less deprived. The separate analysis of migrants and native population shows a clear difference in the behaviour of trends: The previous downward trend of TB incidence in migrant population has been stopped

and slightly inverted: from a 12% annual decrease in the pre-crisis period to a 0.5% increase in the post-crisis period. Also, in this population the inequality by income is much stronger, as migrants living in lowest income neighbourhoods have an incidence 3 times greater than that of the richest neighbourhoods. In indigenous population, the economic crisis has not affected the downward trend in incidence, but they are also affected by the effect of income inequality: a low-income neighbourhood has a 34% higher incidence than a high income neighbourhood.

Conclusion: The downward trend in the incidence of TB has suffered a clear slowdown in the migrant population since the beginning of the crisis and the cuts in social protection policies. In addition, the highly unequal distribution of TB by income level leads to differences between neighbourhoods comparable to those occurring between Western countries and low income countries. Measures to protect the migrant community are essential to reduce inequalities and the incidence of TB in Barcelona.



PC-1000-05 In Peruvian shantytowns, the financial impact of TB-related and catastrophic costs has not changed over the past decade, despite changes in TB rates

T Wingfield,^{1,2,3} M Tovar,^{1,4} D Huff,^{1,5} D Boccia,^{1,6} R Montoya,¹ E Ramos,⁴ J Lewis,^{1,6} C Evans^{1,2,4} ¹Innovación Por la Salud Y Desarrollo (IPSUD), Lima, Peru; ²Imperial College London, London, ³North Manchester General Hospital, Manchester, UK; ⁴Universidad Peruana Cayetano Heredia, Lima, Peru; ⁵Tulane University, Tulane, LA, USA; ⁶London School of Hygiene & Tropical Medicine, London, UK. e-mail: tom.wingfield@ifhad.org

Background: Catastrophic costs incurred during TB illness are associated with adverse treatment outcome and thus may negatively effect TB control. The World Health Organisation (WHO) has mandated that no TB-affected family should incur catastrophic costs. In order to inform the design and implementation of a complex social protection intervention to control TB, we measured catastrophic costs of "free" TB treatment and compared the results to costs data from the same study site in 2004.

Design/Methods: Between February and August 2014, consecutive TB patients diagnosed by the Peruvian

National TB Program in 32 contiguous shantytown communities of north Lima, Peru, were invited to participate in the study. Healthy controls were randomly-selected and recruited concurrently. Patient households' direct out-of-pocket expenses, lost income, and total costs were recorded throughout treatment. Catastrophic costs were defined as total costs of $\geq 20\%$ of the annual income of the same household, as previously defined in the study setting and endorsed by the WHO. In addition, a composite poverty score in arbitrary units was derived by principal component analysis from 13 stable socioeconomic variables.

Results: 312 TB patients were invited to participate, of whom 282 were recruited and had costs and data available for analysis. TB patient households were poorer than healthy control households (40% [95%CI=34-45] versus 27% [95%CI=22-32] in the lowest poverty tercile, $P < 0.002$). Comparing 2014 and 2004 costs data, it was found that: pretreatment total costs as a proportion of mean household monthly incomes were lower in 2014 (0.51 [95%CI=0.4-0.6] versus 1.1 [95%CI=1.0-1.2], $P < 0.0001$) despite symptom duration prior to diagnosis being the same (median 30 days); the proportion of patient households incurring catastrophic costs (44% [95%CI=38-50] versus 39% [95%CI=36-43], $P = 0.1$, Figure) and total costs as a proportion of mean household monthly incomes during the entire illness (2.2 [95%CI=1.9-2.4] vs. 2.3 [95%CI=2.2-2.4], $P = 0.1$) were similar (Figure).

Conclusion: The proportional decrease in pretreatment total costs between 2004 and 2014 require further exploration and may relate to increased costs of TB-related travel and food, better coverage of national health insurance, or improved healthcare access. However, this decrease was offset by a proportional increase in total costs during treatment. Thus, in these Peruvian shantytowns, the financial impact of having TB disease has not diminished over the last 10 years despite a decrease in TB case notification rates. This may hamper further TB control, especially amongst high-risk patients such as those from the poorest households or with MDR-TB.

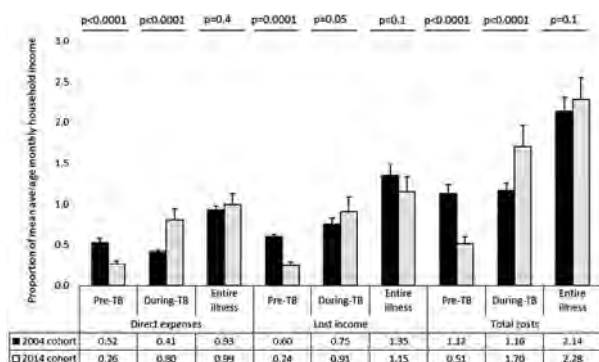


Figure: Household direct expenses, lost income, and total costs as a proportion of mean monthly income pretreatment, during treatment, and throughout the entire illness. Data is compared between the original study of a patient cohort in 2004 [Wingfield *et al.* PLOS Medicine 2014, n=276] and the current CRESIPT study of a patient cohort in the same study setting in 2014 (n=282).

36. Molecular diagnostics: pitfalls and improvements

PC-1001-05 Xpert® MTB/RIF for the diagnosis of smear-negative pulmonary TB in Ethiopia: can bleach concentration increase detection of *M. tuberculosis*?

M T Jano,¹ D Beyene,¹ G A Ayana¹ ¹Jimma University, Jimma, Ethiopia. e-mail: mulualemt.tadesse@gmail.com

Background: Recently the number of smear-negative cases is more than the smear positive pulmonary TB cases. This is a peculiar picture seen in Ethiopia for over a decade. The national TB Prevalence survey in 2010/11 showed that smear negative cases accounted for 57% of culture positive cases. This indicates the need for more sensitive and specific diagnostics for improving the diagnosis of smear negative TB cases. The GeneXpert MTB/RIF assay has been endorsed by the WHO as a replacement for sputum smear microscopy. However, there is no report regarding the performance of bleach concentrated sputum for the diagnosis of smear negative TB by Xpert.

Design/Methods: Two sputum specimens (spot and morning specimen) were collected from each of patients with suspected smear negative TB. The spot sputum was analysed for culture (Löwenstein Jensen & Mycobacteria Growth Indicator Tube 960) and direct Xpert test. The morning sputum was processed for direct and bleach concentrated Xpert tests. The sensitivity and specificity of the Xpert with 95%CI was calculated by using culture as reference method.

Results: Out of 185 patients with suspected smear negative TB, *M. tuberculosis* was confirmed in 16 (8.6%) cases by the composite reference standard (L-J and/or MGIT 960). The detection rate of direct Xpert was 5.4 % (10/185) on spot and 6.5% (12/185) on morning specimen while the detection rate increased to 11.4% (21/185) by bleach concentrated Xpert test. More than half of Xpert positive cases on bleach treated sputum specimen were culture negative. Direct Xpert had sensitivity of 50.0% and specificity of 97.6%. The sensitivity and specificity was 56.2% and 93% respectively by bleach concentrated Xpert test. The sensitivity of direct Xpert test on spot and morning sputum was similar (50.0%). Xpert on bleach treated sputum had 4.9% incremental yield than the direct one. All Xpert positive cases were sensitive for rifampicin.

Conclusion: A significant proportion of patients with suspected smear negative TB missed on conventional Ziehl-Neelsen method were detected on direct and bleach concentrated Xpert test. Bleach concentration method for Xpert had relatively higher sensitivity than the direct one and can potentially improve the diagnosis of smear negative TB. The use of only one sputum sample could be sufficient for TB diagnosis with Xpert test.

PC-1002-05 Xpert® MTB/RIF (CBNAAT): an initial analysis of errors, indeterminates and invalid results

P Desikan,¹ S Dhawan,² A Pauranik,¹ S Mirza,¹ S Mannan,³ A Sangwan,⁴ N Kulshreshta,⁵ M Pandey¹

¹National Reference Laboratory, Bhopal Memorial Hospital & Research Centre, Bhopal, ²International Union Against Tuberculosis and Lung Disease / Central TB Division, New Delhi, ³World Health Organization Country Office for India, New Delhi, ⁴CHAI/Central TB Division, New Delhi, ⁵Central TB Division, New Delhi, India. e-mail: prabhadesikan@yahoo.com

Background: India's NTP has deployed 119 Xpert MTB/RIF machines. Xpert MTB/RIF is a sophisticated instrument & test failures can occur. Identifying causes for test failures can help institute corrective measures. We assess the performance of Xpert MTB/RIF at NRL, Bhopal Memorial Hospital & Research Centre (BMHRC), India.

Design/Methods: Retrospective analysis of report failures generated from Xpert M MTB/RIF software & causes for test failures (indeterminate, no results, invalids and errors) from April 2014-March 2015 at NRL, BMHRC.

Results: Of 1052 samples tested on Xpert, 735 were pulmonary and 317 non-pulmonary. There were 392 valid results from pulmonary & 263 from non-pulmonary samples. Initial test failures in pulmonary samples included 3.13% (23/735) indeterminates, 2.17% (16/735) no results, 2.17% (16/735) invalids & 11.7% (86/735) errors. Initial failures from non pulmonary samples included 2.52% (8/317) indeterminates, 1.57% (5/317) no results, 0.31% (1/317) invalids & 12.6% (40/317) errors. Reasons for test failures included inadequate sample processing in 91/126-(72.2%) samples, {73.2% (63/86) pulmonary & 70% (28/40) non-pulmonary}. Equipment malfunction led to 4.6% (4/86) failures in pulmonary samples only. 52.3% (11/21) tests failed due to power failure {(62.5% (10/16) pulmonary, 20%(1/5) non-pulmonary)}; Xpert-computer communication error led to 13.5% (17/126) failures {9.3%(08/86) pulmonary & 22.5% (9/40)non-pulmonary}; & temperature related errors caused 2.38%(3/126) tests to fail{2.32% (2/86) pulmonary & 2.5 % (1/40) non-pulmonary}. To resolve failures, the available 119 pulmonary samples were retested. Initial retesting resolved 78 & next retesting resolved 11. 39 non pulmonary samples were retested. Initial retesting resolved 33 & next retesting resolved none.

Conclusion: Overall test failures were low {18.53% (195/1052) initial, 0.66% (7/1052) final}. Commonest reason was inadequate sample processing. Appropriate sample viscosity & homogeneity can avoid this. The NTP can highlight importance of sample preparation in the guidance document. Regular maintenance can prevent equipment malfunction & Xpert-computer communication errors. Invalids can be reduced by avoiding PCR inhibitors in samples. Since many test failures were resolved & additional TB cases identified by retesting the 2nd sample, the NTP should retain the policy of

collecting 2 samples for diagnosis by Xpert to ensure that an additional sample is readily available for retesting.

PC-1003-05 Rapid TB diagnosis using GeneXpert®: promising yet fragile?

N Rachmayanti,¹ R Chandra,¹ B Sonata,¹ C Widaningrum,² D A Riana,³ A Rukmana⁴ ¹KNCV Tuberculosis Foundation, Jakarta, ²National Tuberculosis Control Program, Jakarta, ³Directorate of Medical Services Support, Jakarta, ⁴National TB Reference Laboratory Microbiology UI, Jakarta, Indonesia. Fax: (+62) 218 379 3353. e-mail: novia.rachmayanti@kncvtbc.org

Background and challenges to implementation: To increase MDR TB case detection, since 2012 Indonesia has been implementing GeneXpert as a rapid TB diagnostic tool. WHO recommendation in 2013, has encouraged the country to expand the diagnostic services. Under support from USAID and Global Fund, 41 GeneXpert 4 modules has operated and has conducted 13,858 tests by the end of 2014. Besides the benefits, the expansion of service also bring challenges to the country to be dealt with. One of them is the increase of error result which has been notified since the second year of implementation, particularly sites with high work load.

Intervention or response: A total 41 sites at 28 out of 34 provinces has been fully operating in 2014. Each site has been trained centrally and locally for basic knowledge about processing sample and maintenance, and supervised 3-6 months after installation. National TB Program, BPPM, National Reference Lab, and TB CARE I/ KNCV analyzed the data of GeneXpert reports (41 sites, 2 0 1 2 - 2 0 1 4) , s u b m i t t e d t o genexpert.indonesia@gmail.com, and conducted supervisions on selected sites for a closer look to the error cause.

Results and lessons learnt: Data 2014 showed the error rate reached 5.3% (740/13 858), higher than tolerated level <5%. Since there is no real time reporting system in the country, only 487 out of 740 errors are notified with error code. Data suggested the errors were more likely because of cartridge related issues (error code 5006 (38%), 5007 (22%), 5011 (21%)) rather than sample processing errors (error code 2008 (8%)) or hardware failures (6%). Machines have been operating for two years tend to have higher module failure rate. Despite of all machines are under warranty, 9 out of 164 modules have been replaced due to failure. By comparing the same sites that were installed in 2012, the calibration failure rate increased from 0% (0/24) in 2013 to 41.6% (10/24) in 2014. Cartridge related issues increased significantly on Jul (7%) and Aug (10%) 2014. The cartridges were the same batch procured in one shipment on Nov 2013 (8 months storage). Error rates decrease on Sept (6%), Oct (4%), Nov (2%), and Dec (4%) 2014. The cartridges were a new batch came to the country in separate shipments with 4 months interval. The storage had met the standard, but errors happened on Jul-Aug 2014 slightly indicate was caused by a long storage.

Conclusions and key recommendations: Expansion of GeneXpert service should be in line with a good monitoring system, including test results monitoring, error results, and logistics management. Procurement with at least 3 years warranty package is recommended to cope up with the problems.

PC-1004-05 The outcomes of Xpert® MTB/RIF test scale-up in Kenya: machine utilization rates since installation

J Ogoro,¹ E Masini,¹ M Kamene,¹ T Miura² ¹National TB Program Kenya, Nairobi, ²Japan International Cooperation, Nairobi, Kenya. Fax: (+254) 271 3198. e-mail: jeergo@yahoo.com

Background: The Ministry of Health Kenyan through the National Tuberculosis Leprosy and Lung Disease Program has been rolling out the Xpert MTB/RIF assay since 2011. The NTP through various support has a total of 70 machines whose implementation has been in a phased manner. Each of the consignment had one year worth of cartridges, calibration kits and one year warrant. In 2014, Antiretroviral Therapy guidelines and the GeneXpert algorithm were revised in which Xpert MTB/RIF test was recommended as the first test for diagnosis of tuberculosis among Persons Living with Human Immunodeficiency virus and children <15 years. The rollout was to improve timely detection of TB and identify rifampicin (RIF) resistance so that they may initiate appropriate treatment as soon as possible. We describe herein the utilization outcomes of the 70 machines two years since arrival and installation.

Design/Methods: Before the procurement was initiated, facilities were assessed for their preparedness to meet set criteria. The sites were then identified based on available previous years data of HIV and TB caseloads. Prior to machine delivery and installation, priority health Care workers were trained on testing procedures and clinical algorithm for Xpert MTB/RIF test. At installation, each machine was given a target of processing at least 8 specimens per day. The facilities were monitored every month to track utilization electronically and through submission of reports from facilities based on installation dates, expected tests and actual tests done.

Results: Of the 70 machines, 63 (90%) had data uploaded into the TB program reporting system. As of April 2015, there were 45 246 specimens processed within the 70 facilities with tuberculosis identification rate of 23% as seen in table below: Of the 63 facilities, only 15 (23.8%) machines were able to process on average 4 to 10 specimens per day. The usage of (31%) of the machines was between 25% and 45%, the remaining 67% had utilization below 25%.

Conclusion: Overall, the machines were under-utilized although the general trend shows the longer the live period, the better the utilization results except. The error rates were below 5% implying good laboratory training and practices.

PC-1005-05 Effect of sputum quality on microscopy and Xpert® MTB/RIF results in the detection of *Mycobacterium tuberculosis*

F Orina,¹ M Mwangi,² W Githui¹ ¹Center for Respiratory Disease Research, Kenya Medical Research Institute, Nairobi, ²Center for Public Health Research, Kenya Medical Research Institute, Nairobi, Kenya. e-mail: orinafred@gmail.com

Background: The common problem in management of TB is misdiagnosis of cases. Determining the sputum quality in relationship to bacillary yield is important in enhancing prompt detection of cases and preventing wasting of laboratory resources. In this study we compared the effect of sputum quality in diagnosis of TB using microscopy and Xpert® MTB/RIF (GeneXpert).

Design/Methods: Spot and morning sputum specimens were collected from persons presumed to have pulmonary TB enrolled in nine East Africa Public Health Laboratory Networking (EAPHLN) Project study sites in Kenya. The specimens were appropriately packaged and transported to KEMRI Mycobacteriology research laboratory where they were macroscopically characterized into muco-purulent; mucoid, salivary or blood stained. Each specimen was processed for microscopy (Ziehl Neelsen and fluorescent), GeneXpert testing and culture.

Results: A total of 839 sputum specimens with microscopy, GeneXpert and culture results were used to determine the diagnostic performance of Ziehl Neelsen, fluorescent and GeneXpert. The highest sensitivity was obtained with muco-purulent sputum (92.9%, 92.9%, and 87.5% respectively) compared to salivary sputum (44.2%, 53.5% and 76.7% respectfully). Diagnostic performance of ZN, FM on salivary specimens indicated higher sensitivity in HIV negative (52.4(95%CI:31.0-73.8)% and 66.7(95%CI: 46.5-86.9)% respectively) though not significant than HIV positive (42.9(95%CI:17.0-68.8)% and 42.9(95%CI:17.0-68.8)% respectively). Using salivary sputum, GeneXpert sensitivity was higher in HIV positive (85.7%; 95%CI, 67.4-100 %) than HIV negative (71.4%; 95%CI, 52.1-90.7) and significantly different compared to ZN microscopy.

Conclusion: The significance difference in the sensitivity of salivary specimens between ZN microscopy and GeneXpert in HIV positives emphasizes the importance of advocating for use of good quality sputum specimens for detection of *M. tuberculosis* especially when using microscopy compared to GeneXpert.

PC-1006-05 Usefulness of the Xpert® MTB/RIF assay in gastric aspirates for the diagnosis of tuberculosis in adult patients

S Tahseen,¹ C Schmotzer,² F M Khanzada,¹ A Hussain,¹ E Qadeer,³ W Aslam¹ ¹National TB Reference Laboratory, Islamabad, ²Rawalpindi Leprosy Hospital, Islamabad, ³National Tuberculosis Control Programme, Islamabad, Pakistan. e-mail: sabira.tahseen@gmail.com

Background: Pakistan is 4th high burden country for Tuberculosis and MDR-TB. In Pakistan Xpert MTB/RIF assay is recommended for diagnosis of drug resistant TB

in patient at risk and for diagnosis of TB in vulnerable groups or those having difficulty in diagnosis. Diagnosis of tuberculosis is challenging in adults patient who are unable to expectorate sputum or good quality sputum. Usefulness of Xpert MTB/RIF assay was evaluated in gastric aspirates for diagnosis of Tuberculosis in adults. **Design/Methods:** Retrospective cross sectional study. Adult patient who had gastric aspiration (GA) performed for diagnosis of PTB based on X-rays finding suggestive of tuberculosis but sputum smear was either negative or not performed because of difficulty in expectoration were included. Children under 15yrs and adults patient reported AFB smears positive on sputum prior to gastric aspiration were excluded. AFB microscopy and Xpert MTB/RIF assay was performed on sediment of gastric aspirate in National TB Reference laboratory

Presumptive TB case	AFB smear results	Xpert /MTB Rif assay			
		#Tested	Error, NO result	MTB+	Rif Resistant
NO Known risk of MDR	AFB Sm Pos	17	0	17(100%)	2(11.8%)
	AFB Sm Neg	73	4	8(11.0%)	0(0.0%)
	Sub -Total	90	4	25(27.8%)	2(8.0%)
At risk of MDR (Previous TB treatment /MDR contact)	AFB Sm Pos	98	2	88(89.0%)	20(22.7%)
	AFB Sm Neg	301	12	39(13.0%)	6(15.4%)
	Sub -Total	399	14	127(31.8%)	26(20.5%)
All Combined	AFB Sm Pos	115	2	105(91.3%)	22(21.0%)
	AFB Sm Neg	374	16	47(12.6%)	6(12.8%)
	Total	489	18	152(31.1%)	28(18.4%)

Table: Diagnostic yield of Xpert MTB/Rif assay versus AFB microscopy in gastric aspirate

Results: GA (GA) from 489 adult patients received in 2013-14 were evaluated, 68 (13.9%) of these patient were reported AFB smear negative on sputum and others had difficulty in expectorating good quality sputum. 92.6% (453) of these samples were received from single TB care facility in city. Of all included 254 were females and 235 male and mean age was 38.7 yrs. 399 patients (81.6%) were at risk of MDR because of history of previous TB treatment (389) or contact with MDR patient and 18.4 % (90) had no known risk of MDR. GA of 115 (23.5%) patients were positive on AFB microscopy whereas *M. tuberculosis* was detected on Xpert MTB/RIF assay in 152(31.3%) cases. Use of Xpert provided bacteriological diagnosis in 47 cases reported negative on AFB microscopy and in 8/115 cases reported AFB positive, *M. tuberculosis* was not detected on Xpert. Error or no result was reported in 3.7 % (18) of total tested. GA of 18.9% of new and 24.6% of previously treated were positive on AFB microscopy compared to 27.8% and 31.8% on Xpert MTB/RIF assay. RIF resistance was detected in 8.0% of new cases and 20.5% of patient with history of previous treatment ($P = 0.141$). There was no significant difference in RIF resistance ($P = 0.229$) in smear positive (21.0%) and smear negative cases (12.8%)

Conclusion: Use of Xpert MTB/RIF assay in Gastric aspirate is recommended for diagnosis of tuberculosis in adult patients at risk of MDR who encounter difficulty in expectorating good quality sputum.

PC-1007-05 Comparison of the Xpert® MTB/RIF assay in bronchoalveolar lavage and gastric lavage samples

A Kumar,¹ Ravi Mahat¹ ¹Jinnah Posgraduate Medical Centre, Karachi, Pakistan. e-mail: ashokpanjwani2002@hotmail.com

Background: About 50% suspected cases of pulmonary tuberculosis do not present sputum. For diagnosis of these cases either bronchoscopy with BAL, Induced sputum or Gastric lavage is used. Bronchoscopy with BAL requires special facilities, trained staffs and is not accessible in many regions because of the limited resources. Additionally, due to its invasive nature many patients may not prefer and tolerate this. Although yield of induced sputum has favorable results but its use requires isolation rooms with negative pressure which may not be available in many health care facilities. The GL method is preferred in diagnosis of TB in children who swallow their sputum and cannot expectorate. Many studies has shown good result of GL for AFB smear and culture. In the centers where who has provided GeneXpert machine, it can be very helpful to make bacteriological diagnosis within 2 hours.

Objective: To compare the yield from gastric lavage (GL) and Broncho alveolar lavage (BAL) samples in adult patient suspected case of TB but not producing sputum

Design/Methods: Total 80 consecutive adults with suspected case of tuberculosis who were not producing sputum were recruited. 72 patients prospectively subjected to one gastric lavage and followed by Broncho-alveolar lavage on the same morning. The collected samples were subjected to GeneXpert MTB/RIF Assay.

Results: Sample of 72 patients were collected. Mean age was 38.6 ± 18.3 . 41(56.9%) were male and 31(43.1%) were female. History of TB contact was present in 34.8%. Total 37 (51.4%) patients had GeneXpert MTB/RIF positive on BAL and/or GL samples. The GeneXpert MTB/RIF of BAL fluid was positive on 35(48.6%), which was not significantly greater than that for specimens from GL i.e. 28 (38.9%) ($P > 0.05$). In 26 (36.1%) cases GeneXpert MTB/RIF was positive both in both BAL and GA samples.

Conclusion: This study showed that the yield of GeneXpert MTB/RIF in GL was equally effective to BAL to detect *Mycobacterium tuberculosis* complex. Patients who can't produce sputum, GL can be a good alternative to BAL to detect *Mycobacterium tuberculosis* complex in resource poor areas and patient who doesn't tolerate Bronchoscopy.

PC-1008-05 The use of national Xpert® MTB/RIF's cycle threshold as an audit indicator for program and laboratory performance

L Scott,¹ K Schnippel,² S Molapo,³ R Berhanu,² L Berrie,³ A Van Rie,⁴ W Stevens^{1,3} ¹University of the Witwatersrand, Johannesburg, ²Right to Care, Johannesburg, ³National Health Laboratory Service, Johannesburg, South Africa; ⁴University of Antwerp, Antwerp, Belgium. e-mail: lesley.scott@nhls.ac.za

Background: The South African National Priority Program has performed >5.6million Xpert MTB/RIF tests since 2011 in 207 smear microscopy centres. All GeneXpert instruments are connected by a laboratory information system (LIS) and all test results collected in a central data warehouse. This data not only contains the qualitative result [positive or negative for *Mycobacterium tuberculosis* complex (*M. tuberculosis* c) and rifampicin (RIF) status (sensitive, resistant or indeterminate)] and pathology review, but also the quantitative molecular characteristics of each test in the form of the cycle threshold (Ct) value for each molecular beacon hybridized (probe A-E) to rpoB region and the internal control. We investigated the utility of these Ct values.

Design/Methods: Ct values from 24 months (January 2013 – December 2014) across all nine provinces from Xpert MTB/RIF version G4 were analysed in Stata v13.

Results: A total of 4 034 831 Xpert tests were successfully reported, with 11.3% detecting *M. tuberculosis* c and 452 368 (99.3%) generating Ct values in the LIS. Rifampicin resistance was detected in 6.6% ($n=29\,876$), with a frequency of the molecular probes (dropout or delayed hybridization) reporting Rif resistance as: E:531bp (55.7%), D:526bp (18.6%), B:516bp (18.2%), A (6.0%), C(1.5%). This frequency pattern varied across provinces: in the Eastern Cape E:(48.8%) and B:(31.1%) while in the Western Cape E:(68.6%) and B:(9.72%). Amongst RIF resistant tests, the ratio of delayed probe ($\Delta Ct > 4$) to drop-out probes was 1:4.76 (IQR 4.19, 5.35), with increased variability in delayed probes. This ratio is lower than the 1:9 relationship previously reported. Probe B accounted for 32.9% of delayed hybridizations results. There was also variability in the Rif indeterminate rate ($n=11\,265$, 2.4% [IQR 1.7%-2.9%]) by week over the two years. The average national Ct (mycobacterial burden) for probe C was 22.6 (95% CI: 22.56, 22.64), with a significantly lower disease burden in Gauteng Ct=23.0 (22.9, 27.38) and significantly higher burden in the Western Cape Ct=21.8 (21.68, 21.89).

Conclusion: The molecular characteristics of Xpert MTB/RIF showed geographic variability of *M. tuberculosis* c, mycobacterial burden (Ct value) and assay performance. Using the LIS, these audit indicators can be observed in near real time down to sub-district level and assay lot number which may assist in improving laboratory algorithms, program monitoring and national surveillance.

37. Rapid diagnosis the world over

PC-1009-05 Evaluation of the use of Xpert® MTB/RIF to diagnose and treat MDR-TB under routine program conditions in Botswana

R Boyd,^{1,2,3} L Kuate,^{4,5} T Kuebrich,¹ C Modongo,⁶ T Lere,⁴ B Kgwaadira,⁴ H Cox,² A Finlay^{1,3} ¹Centers for Disease Control Botswana, Gaborone, Botswana; ²University of Cape Town, Cape Town, South Africa; ³Division of Tuberculosis Elimination, Atlanta, GA, USA; ⁴Ministry of Health, National Tuberculosis Program, Gaborone, ⁵University of Botswana, Gaborone, ⁶Botswana University of Pennsylvania Partnership, Gaborone, Botswana. e-mail: icg7@cdc.gov

Background: The Botswana MoH revised tuberculosis (TB) guidelines in 2011, incorporating Xpert® MTB/RIF (Xpert) for diagnosis of TB among people living with HIV and those at risk of multidrug-resistant (MDR) TB; 34 Xpert devices were installed from 10/2012 to 12/2014 in 26/28 districts. WHO recommends that people with rifampicin resistance (RR) detected by Xpert initiate category IV MDR-TB treatment while waiting for confirmatory drug-susceptibility testing (DST). An assessment was conducted to determine the rate of RR-TB and how patients with positive or indeterminate RR Xpert test results were managed.

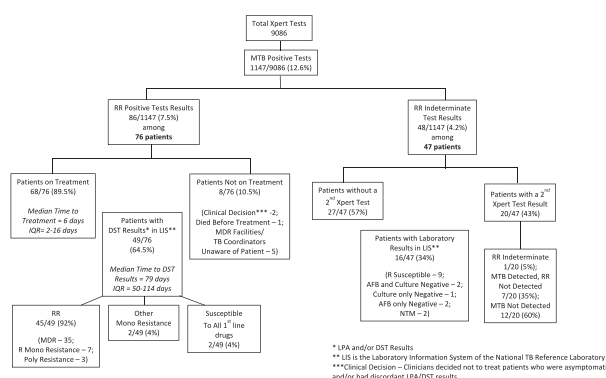
Methods: Xpert test results were extracted from archived files covering the period from 10/2012 – 12/2014. Patients with a positive RR test result were identified and patient lab and clinical data was collected from the National TB Reference Laboratory and MDR TB treatment facilities to evaluate patient management.

Results: Data were obtained from 31 of 34 Xpert sites; three sites were unable to archive data and were excluded. A total of 9086 Xpert tests were conducted; 1147 (12.6%) detected *Mycobacterium tuberculosis* (*M. tuberculosis*), 86 (7.5%) detected RR from 76 patients and 48 (4.2%) had an indeterminate RR result from 47 patients (see Figure). Overall, 68/76 (89.5%) patients with an RR test result initiated Category IV treatment and 49/76 (64.5%) patients had confirmatory DST; 4/49 had discordant genotypic and phenotypic results. The median time from the Xpert RR test result to treatment initiation was 6 days (IQR: 2-16 days); 78.5% were initiated within 20 days. Median time to phenotypic DST was 79 days (IQR; 50-114 days). Five (6.6%) patients with an RR result were not registered with the MDR-TB program. Of the 47 people with RR indeterminate results, 20 (43%) had a second Xpert test in which no RR was detected.

Conclusions: Improvements are needed to follow-up patients with RR indeterminate results and confirm diagnosis. Most patients with RR detected by Xpert rapidly started Category IV treatment in Botswana; however confirmatory DST was not always conducted and is important for patient management. The national TB diagnostic algorithm should be updated to guide clinicians on interpretation and management of patients with discordant genotypic and phenotypic results. This analysis enabled the program to identify previously unknown patients with an RR test result; the program

is now working to locate and enroll these patients into care.

Figure 1 – Rifampicin Resistance Detected and Rifampicin Resistance Indeterminate Results by Xpert, Botswana 2012-2014



PC-1010-05 Cost-effectiveness of the Xpert® MTB/RIF assay for tuberculosis diagnosis in Brazil

M F T Pinto,¹ R Steffen,² F Cobelens,³ S Van Den Hof,³ A Entringer,¹ A Trajman^{2,4} ¹Oswaldo Cruz Foundation, Rio De Janeiro, ²Rio de Janeiro Federal University, Rio de Janeiro, Brazil; ³KNCV Tuberculosis Foundation, The Hague, Netherlands; ⁴McGill University, Montréal, QC, Canada. e-mail: ricardo.steffen@gmail.com

Background: The Xpert MTB/RIF assay is being implemented as a substitute for sputum smear microscopy (SSM) in many low- and high-tuberculosis burden countries, including Brazil, a country with low multidrug resistance and moderate HIV co-infection rates.

Design/Methods: We conducted a cost-effectiveness analysis considering a hypothetical cohort of 100 000 individuals, stratified by HIV status, suspected of having TB and going through all the TB diagnostic procedures recommended by the Brazilian National Guidelines. We estimated the incremental cost-effectiveness ratio (ICER) of one Xpert MTB/RIF as a substitute for two SSM for diagnosing susceptible tuberculosis from the Brazilian National TB Program (NTP) perspective. The main endpoint was the number of bacteriologically confirmed TB cases detected. The secondary endpoint was the number of false-positive TB diagnoses avoided. Because of the low MDR-TB prevalence in Brazil, we focused this analysis on first-line drug treatment only. Costs for confirming each additional case and for avoiding empirical treatment from false-positive diagnoses were estimated. The model was parameterized using data on bacteriological confirmation and clinical diagnosis among presumptive TB patients derived from the pragmatic trial of Xpert MTB/RIF in Brazil, and using TB treatment outcomes from the National TB Information System.

Results: The ICER was US\$ 437 for each additional TB bacteriological confirmation and US\$ 23 489 for each false tuberculosis diagnosis averted assuming an 80% specificity of clinical diagnosis using both strategies. The

model was highly sensitive to changes in the specificity of clinical diagnosis following laboratory testing, when increasing the specificity of clinical diagnosis after an Xpert MTB/RIF by 1 percent-point steps, the newer technology became dominant at a specificity of 83%. The two-way sensitivity analysis showed that Xpert MTB/RIF would remain dominant for avoiding false diagnoses if the specificity of clinical diagnosis after a negative Xpert MTB/RIF was $\geq 3\%$ higher than that after two negative SSM.

Conclusion: Although the NTP has no threshold for cost-effectiveness, our model can support decision-makers in Brazil and other countries with low resistance rates. A potential economical benefit was shown in case physicians rely more on a negative Xpert MTB/RIF result.

PC-1011-05 Modeling demonstrates that targeted use of Xpert® MTB/RIF is a cost-effective and affordable option for tuberculosis diagnosis in Addis Ababa, Ethiopia

A Bika,¹ D F Adhana,² D Assefa Lemma,² E Klinkenberg,² S Blanco,³ I Langley⁴ ¹Addis Ababa City Admin Health Bureau, Addis Ababa, ²KNCV Tuberculosis Foundation, Addis Ababa, ³Addis Ababa University, Addis Ababa, Ethiopia; ⁴Liverpool school of Tropical Medicine, Liverpool, UK. e-mail: atabrish@gmail.com

Background: To reduce the global tuberculosis (TB) burden, active disease must be diagnosed quickly and accurately. In Ethiopia, however, TB diagnosis mainly relies on spot-morning-spot sputum smear analysis using Ziehl-Neelsen (ZN) staining techniques, which fails to identify some people who have TB. So the objective of our study was to project the effects of alternative diagnostic algorithms on patient, health system and costs, and identify the most applicable algorithm.

Design/Methods: An observational quantitative modeling framework was applied using the Virtual Implementation approach. The model was designed to represent the operational and epidemiological context of Addis Ababa. We compared the base diagnostic algorithm with eight different alternative algorithms of light emitting diode (LED) fluorescence microscopy and Xpert MTB/RIF.

Results: If society were willing to pay up to the average per-capita GDP (US\$630 for Ethiopia) for each averted disability-adjusted life-year (DALY), our results suggest that three of the modeled algorithms are cost-effective, and would have important patient, health system and population level effects in the context of Addis Ababa: Full rollout of Xpert MTB/RIF would avert 91170 DALYs (95% credible interval [CrI] 54 888.3 – 127 447.5) with an additional health system cost of US\$ 11.6 million over the next 10 years. The incremental cost-effectiveness ratio (ICER) is \$370.1 per DALY averted. Same day LED combined with Xpert MTB/RIF targeted to HIV positive and High multi drug resistance (MDR) risk groups would avert 73600 DALYs (95% CrI 48372.8 - 99213.6) with an additional cost of US\$5.1

million over the next 10 years. The ICER is \$168.8 per DALY averted. The third alternative is same-day LED fluorescence microscopy at ICER of \$12.6 per DALY averted. The other options would produce DALY gains at a higher incremental cost and are dominated by other options in the context of Addis Ababa.

Conclusion: Full rollout of Xpert MTB/RIF is predicted as the best alternative to substantially reduce the TB burden of Addis Ababa and is cost effective. However, the additional financial burden would be substantial and beyond the budget of the TB control program. So targeted use of Xpert MTB/RIF for HIV positive and High MDR risk groups with same-day LED fluorescence microscopy for other presumptive TB cases would be a good affordable alternative in area where financial resources are limited.

PC-1012-05 Comparative performance and reproducibility of Xpert® in the diagnosis of TB in different geographical settings in Kenya

W Githui,¹ M Mwangi,² F Orina¹ ¹Center for Respiratory Disease Research, Kenya Medical Research Institute, Nairobi, ²Center for Public Health Research, Kenya Medical Research Institute, Nairobi, Kenya. Fax: (+254) 202 729 308. e-mail: wgithui@yahoo.com

Background: Overall performance of GeneXpert for diagnosis of pulmonary tuberculosis has recently been documented in Kenya and is comparable with previous findings from a few studies in African. To our knowledge, no study has compared performance and reproducibility of GeneXpert results in different geographical settings within the same country. Our study set to undertake to determine these aspects.

Design/Methods: A cross-sectional study was conducted between February 2013 and December 2014 in four selected public health facilities namely Busia, Kitale, Machakos and Malindi. People with presumptive TB aged 18 years and above were consecutively recruitment at each site. Spot and morning sputum were collected. At the study site, a proportion of each specimen was processed for GeneXpert. The remainder of the specimen was shipped to the TB research laboratory at the Kenya Medical Research Institute (KEMRI), Nairobi, where specimens were processed for GeneXpert and culture in accordance with standard procedures. Löwenstein Jensen (LJ) culture was used as a goldstandard.

Results: A total of 1576 specimens with culture results for *M. tuberculosis* were included in the analysis. Performance of GeneXpert across different geographical location in Kenya was comparable. At KEMRI, sensitivity of GeneXpert ranged from 84.8(95%CI: 72.6-97.1%) for Busia to 91.1(95% CI: 84.8-97.4%) for Kitale. At the sites, sensitivity of GeneXpert was 82.4(95%CI: 69.1-94.9%) for Busia and 91.3(95% CI: 85.9-96.7%) for Kitale. Using homogeneous sample done at the sites and KEMRI, a high level of reproducibility of GeneXpert was observed at KEMRI. However, sensitivity of GeneXpert varied, insignificantly between sites ranging from 66.7(95% CI: 13.4-100%) in Busia to 100(95% CI: N/

A%) in Machakos, all were reproduced at KEMRI. Specificity was also comparable and reproducible in all the sites including KEMRI.

Conclusion: Overall performance of GeneXpert in the four sites remained constant and comparable with recent findings from Kenya. Comparable variations in sensitivity observed in different sites were also reproduced at KEMRI, indicating that if GeneXpert is performed meticulously, results are reproducible regardless of geographical locations. Further studies involving more sites are required to ascertain these findings.

PC-1013-05 Countrywide roll-out of Xpert® MTB/RIF in Swaziland: the first three years of implementation

W Sikhondze,¹ D Khumalo,^{1,2} T Dlamini,¹ G Maphalala,³ H Albert,⁴ J Wambugu,⁴ S S Ade,⁵ A D Harries⁵ ¹National Tuberculosis Control Programme, Manzini, ²National TB Reference Laboratory, Mbabane, ³Swaziland Health Laboratory Services, Mbabane, Swaziland; ⁴Foundation for Innovative New Diagnostics, Geneva, Switzerland; ⁵International Union Against Tuberculosis and Lung Disease, Paris, France. e-mail: welile.sikhondze@gmail.com

Setting: All 18 public health laboratories in Swaziland that had Xpert MTB/RIF machines installed as part of countrywide roll-out between June 2011 and June 2014. **Objective:** To evaluate the utilization and functionality of Xpert MTB/RIF from 2011 to mid-2014

Design: Descriptive study of Xpert MTB/RIF implementation using routinely collected data.

Results: There were 48 829 Xpert tests conducted. Of these, 93% were successful of which 14% detected *Mycobacterium tuberculosis* with 12% showing rifampicin resistance. The commonest cause of unsuccessful tests was an 'Error' result (62%). Similar findings were obtained in government-supported and partner-supported laboratories. Annual utilization of Xpert MTB/RIF improved from 51% of maximum capacity in 2011 and 2012 to 74% in 2013 and 2014. A monitoring and supervision exercise of all Xpert testing sites in 2014 showed a generally good performance with over 50% of laboratories achieving a score $\geq 80\%$ on most components. However, poor scores were obtained with equipment use and maintenance (6% achieving a score of $\geq 80\%$), internal audit (19% achieving a score of $\geq 80\%$) and process control (25% achieving a score of $\geq 80\%$).

Conclusion: Countrywide roll-out of Xpert MTB/RIF in Swaziland has been successful although some operational issues have been identified and need to be resolved.

PC-1014-05 Use of Xpert® MTB/RIF to diagnose TB in reference-level mycobacteriology laboratory in Port-au-Prince, Haiti

A Duncan,¹ M Mabou,² P Christos,¹ D Fitzgerald,¹ W Morose,³ P Joseph,² J W Pape,^{1,2} O Ocheretina^{1,2} ¹Weill Cornell Medical College, New York, NY, USA; ²Les Centres GHESKIO, Port-au-Prince, ³National Tuberculosis Program, Port-au-Prince, Haiti. e-mail: ayd2001@med.cornell.edu

Background/Objectives: The traditional diagnostic algorithm for tuberculosis in Haiti relies on smear microscopy of three sputum samples. This study aims to assess the performance and feasibility of a diagnostic algorithm including the Xpert MTB/RIF assay compared to smear microscopy for patients with clinically suspected TB in Haiti. **Design:** This is a retrospective analysis of data collected by GHESKIO laboratory in Port-au-Prince, Haiti. Three sputum samples were collected using a "spot-morning-spot" protocol. Between June 2011 and July 2012 all three samples from 4043 patients were analyzed by smear microscopy. Between September 2012 and February 2013, microscopy for the morning sample from 1650 patients was substituted with the Xpert MTB/RIF assay.

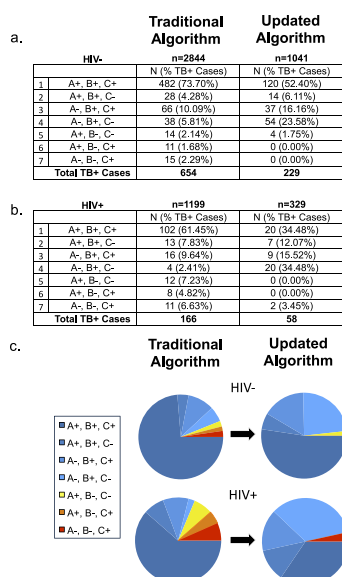


Figure 1. Summary data tables for a) HIV-negative and b) HIV-positive patients diagnosed with TB using the Traditional Algorithm (left) and the Updated Algorithm (right). A, B, and C designate sputum samples collected by the "spot-morning-spot" method. All A and C sputa were analyzed with AFB smear. All B samples in the Traditional Algorithm were analyzed with AFB smear, and all B samples in the Updated Algorithm were analyzed by the Xpert MTB/RIF assay. "+" and "-" indicate positive and negative test results, respectively. c) Contribution of AFB smears for samples A and C to diagnosed TB cases. TB patients with a positive test result for sample B are presented in shades of blue. TB patients with a negative test result for sample B are shown in orange (both samples A and C AFB-positive), yellow (only sample A AFB-positive) and red (only sample C AFB-positive).

Results: 1) The morning sample has a higher diagnostic value than spot samples (91.4% positivity rate compared to 81.8% and 86.8% for first and second spot samples, respectively), 2) a single Xpert MTB/RIF test detected more TB cases in HIV-positive patients than smear microscopy of three samples (17.2% vs. 13.9%, $P = 0.06$), and detected as many TB cases in HIV-negative

patients as smear microscopy of three samples (22.1% vs. 23.0%), 3) after implementation of Xpert MTB/RIF, the diagnostic yield of smear microscopy for a third sputum sample was reduced from 2.29% to 0% in the HIV-negative group and from 6.59% to 3.45% in the HIV-positive one, and 4) reduction in the laboratory workload compensated for the higher cost of the GeneXpert reagents.

Conclusions: A TB diagnostic algorithm with one Xpert MTB/RIF test and one AFB smear on two collected sputum samples results in a higher diagnostic yield in HIV-positive patients compared to the traditional three sputum smear diagnostic algorithm. Routine use of the Xpert MTB/RIF assay to diagnose TB is feasible in a resource-limited setting like Haiti.

PC-1015-05 GeneXpert® shortens time to treatment initiation for Latvian MDR-TB cases

H Stagg,¹ P White,^{2,3} V Riekstina,⁴ A Cirule,⁴ J Brown,^{1,5,8} G Dravniece,^{6,7} E Adam,⁷ C Jackson¹ ¹University College London, London, ²Imperial College School of Public Health, London, ³Public Health England, London, UK; ⁴Centre of TB and Lung Diseases, Riga East University Hospital, Riga, Latvia; ⁵Royal Free London NHS Foundation Trust, London, UK; ⁶KNCV Tuberculosis Foundation, The Hague, Netherlands; ⁷Otsuka SA, Geneva, Switzerland; ⁸Centre for Respiratory Medicine, Royal Free London NHS Foundation Trust, London, UK. e-mail: h.stagg@ucl.ac.uk

Background: Rapid diagnosis of multidrug resistant tuberculosis (MDR-TB) is vital for the prompt initiation of appropriate treatment. In 2010 GeneXpert MTB/RIF was recommended by the World Health Organization and adopted by Latvia for individuals considered at high MDR-TB risk. We sought to establish the impact of GeneXpert on time to treatment initiation in Latvia.

Methods: The 2009-2012 Latvian MDR-TB treatment cohort was evaluated, excluding cases with solely extrapulmonary TB and prison cases. Use of GeneXpert was categorised as either a binary (not used (baseline); used) or ternary variable (not used (baseline); cases not rifampicin resistant (RIF-R) TB by GeneXpert; cases RIF-R TB by GeneXpert). Time (in days) between presentation to hospital and MDR-TB treatment initiation was calculated. Descriptive analyses were undertaken, followed by univariate Poisson regression. Multivariable Poisson models adjusting for confounding and effect modification were built.

Results: 398 cases were available for analysis; 10 were excluded due to missing dates and 6 more due to being solely extrapulmonary. 259 did not have GeneXpert (100%, 84%, 46%, 40% of cases from 2009-12, respectively), 15 were not identified as MDR-TB by GeneXpert (11 TB not detected, 3 RIF sensitive, 1 sensitivity undetermined), 108 were RIF-R TB by GeneXpert. The median time to treatment initiation was 27 days (95% confidence interval 22-30) for cases where GeneXpert was not used and 5 days (3-7) for cases with GeneXpert. The univariate rate ratio (RR) for the association between the use of GeneXpert and time to treatment initiation was 3.05 (2.40-3.87), P value <0

.001 and the multivariable RR (controlling for gender, age, region, site and HIV) 3.40 (2.52-4.60), <0.001.

Results: controlling for year (excluding 112 cases from 2009 when GeneXpert was not used in Latvia) were similar. The median time to treatment initiation was 58 days (7-99) when GeneXpert did not detect RIF-R TB and 4 days (2-6) when it did. Univariate RRs using no GeneXpert as the baseline were 0.63 (0.37-1.07) and 6.52 (5.09-8.36), respectively (*P* value 0.01). A multivariable model gave similar results (0.55 (0.32-0.94), 6.26 (4.96-7.89); <0.001).

Conclusions: The use of GeneXpert in Latvia shortened the time to treatment initiation for MDR-TB cases. Cases not diagnosed as RIF-R TB by GeneXpert had similar times to treatment initiation as those for whom GeneXpert was not used. This project was supported through a grant by Otsuka SA.

PC-1016-05 Use of GeneXpert® to support fully ambulatory treatment of TB in Kyrgyzstan

M Joncevska,^{1,2} G Kurbaniyazova,³ S Kalon,³ G Kalmambetova,⁴ T Mohr¹ ¹Project HOPE, Almaty, Kazakhstan; ²Project HOPE, Skopje, Macedonia, Yugoslav Rep; ³Project HOPE, Bishkek, ⁴National TB Institute, Bishkek, Kyrgyz Republic. Fax: (+389) 2270 0601. e-mail: joncevs.kam@yahoo.com

Background and challenges to implementation: Kyrgyzstan is a high TB and MDR-TB prevalence country in Central Asia, with TB case notification rate of 128 per 100 000 population, reporting one of the highest MDR-TB rates globally. According to the data presented from the National Drug Resistance Survey, 26.4% of newly diagnosed TB cases and 51.6 % of previously treated patients have MDR-TB. The current approach in TB treatment includes hospitalization of all TB patients during the intensive phase of treatment and full hospital treatment for MDR-TB.

Intervention or response: In order to support the ongoing Health Sector Reform and rationalization of health care services, the NTP of Kyrgyzstan developed a plan for reducing the number of beds in inpatient TB facilities, by introducing full ambulatory treatment of TB. Xpert *M. tuberculosis* Rif testing was introduced to support the new policy for ambulatory treatment, integrated in the Primary Health Care level laboratory services to make the rapid diagnosis and timely start of treatment available for TB patients close to their place of living. The new policy was introduced through a pilot project, implemented within the USAID Quality Health Care Project, during the period 2012–2014. Issyk Atta district, located in the Southeast of Chui Province, was selected as a pilot implementation site. GeneXpert platform was placed in the district polyclinic, providing access to *M. tuberculosis* Rif testing for 3 districts and one city covering a population of 270 000 people.

Results and lessons learnt: During the period 2012-2014, a total of 1819 *M. tuberculosis* Rif tests were done and 461 TB cases were confirmed as *M. tuberculosis* +. 140 cases among them were Rif resistant. Following the NTP diagnostic algorithm, it was possible to immediately start

the treatment for TB and MDR-TB. Ambulatory treatment was started for 148 TB patients, including 32 resistant cases. Based on the results from Issyk Atta, the ambulatory model was rolled-out to other districts in Chui Oblast.

Conclusions and key recommendations: 1. Initial results from the pilot project support the NTP plan for ambulatory treatment of TB, followed by the nationwide scale-up of Xpert MTB/RIF testing. 2. Further downsizing of existing inpatient TB facilities is a process, which requires step wise approach, leading to full outpatient treatment for a larger number of TB patients. 3. A critical issue for countrywide implementation of Xpert MTB/RIF would be development or reliable sputum transportation mechanisms

38. Phenotypes and genotypes: deciphering resistance development

PC-1017-05 Molecular and phenotypic detection of fluoroquinolone resistance

A Aubry¹ ¹National Reference Center for Mycobacteria, Paris, France. Fax: (+33) 1 45 82 75 77. e-mail: alexandra.aubry@upmc.fr

As a consequence of the use of fluoroquinolones (FQ), resistance to FQ has emerged, leading to nearly untreatable, extensively drug-resistant tuberculosis. *M. tuberculosis* conventional phenotypic susceptibility testing is cumbersome and takes several weeks. The recommended critical concentration, for FQ susceptibility testing, defined by WHO as the ability of the bacilli to grow on medium containing 2 or 4 mg/l ofloxacin is to a large extent based on consensus rather than scientific evidence. Moreover, from a medical point of view, using a single breakpoint does not allow delineating the different levels of resistance, thus impeding therapeutic decision about whether maintaining or not FQ depending on the resistance level. Therefore, molecular assays allowing rapid detection of resistance to antituberculous agents are of major interest in routine practice. For FQ, these assays, detecting mutations within the DNA gyrase Quinolone Resistance Determining Regions, may be able to predict FQ level of resistance if properly used. We will review the advantages and drawbacks of the available phenotypic and genotypic methods for FQ resistance in *M. tuberculosis*, in regard with the laboratory capacities.

PC-1018-05 Slow recovery of *Mycobacterium africanum*-infected patients post-treatment in associated with high content of persistor-like bacilli in sputum

L Tientcheu,¹ A Bell,² N J Garton,² J Sutherland,¹ H Dockrell,³ B Kampmann,¹ M R Barer² ¹Medical Research Council Unit The Gambia, Banjul, Gambia; ²University of Leicester, Leicester, ³London School of Hygiene & Tropical Medicine, London, UK. Fax: (+220) 449 5442. e-mail: ltientcheu@mrc.gm

Background: *Mycobacterium africanum* (*M. africanum*) causes 40% of all tuberculosis (TB) cases in The Gambia. It grows more slowly in culture, has similar transmission capacity but slower progression to active disease compared with *Mycobacterium tuberculosis* (*M. tuberculosis*). Our previous work comparing *M. africanum* versus *M. tuberculosis*-infected patients before and following anti-TB treatment showed a similar profile of clinical and immunological parameters pre-treatment, but significant differences in body mass index, chest X-ray scores and antigen-specific immune responses between *M. tuberculosis* and *M. africanum*-infected patients post-treatment. We hypothesise that these differences could either be due to significant differences between the strains in relation to drug resistance or the percentage of persistor-like lipid bodies positive bacilli.

Design/Methods: To explore these hypotheses, drug susceptibility testing of pre-treatment sputum isolates was carried out using the BACTEC MGIT 960 method, and the content of acid-fast bacilli (AFB) and lipid body-positive bacilli in sputum were analysed using Auramine and LipidTOX Red neutral lipid staining respectively.

Results: Low levels of drug resistance were observed in both groups. Two MDR (resistant at least to rifampicin and isoniazid) and three isoniazid mono-resistant cases were seen among *M. tuberculosis*-infected patients, while there were three streptomycin mono-resistant Maf-infected patients. Although AFB-positive bacilli percentages were similar between the groups ($P = 0.821$), lipid body-positive bacilli percentages were significantly higher in *M. africanum* ($n = 24$) compared to *M. tuberculosis* ($n = 36$)-sputum ($P = 0.0059$). In addition, bacillary length was significantly higher in *M. africanum* than *M. tuberculosis*-sputum ($P = 0.0007$).

Conclusion: The slow recovery of *M. africanum* relative to *M. tuberculosis*-infected patients post-treatment might be at least partially associated with the persistence of drug tolerant "fat and lazy" bacilli.

PC-1019-05 Clinico-immunological diagnostic criteria for the progression of multidrug-resistant tuberculosis

A Alenova,¹ E Berikova,¹ B Toksanbaeva,¹ D Sabazova¹ ¹National Center for Tuberculosis Problems, Almaty, Kazakhstan. e-mail: arike.alenova@mail.ru

Background: Despite a decrease of incidence of tuberculosis and its mortality rate in Kazakhstan, there is a growth of the progressive forms of the multidrug-resistant tuberculosis (MDR-TB). The objective of this

study is to make a comparative analysis of immunity of the lung tuberculosis patients with the preserved sensitivity to the anti-TB drugs (group A) and with the progressive MDR-TB (group B).

Design/Methods: CD3, CD4, CD8, CD16, CD95; IL-1, IL-2, IL-4 IL-8, IFN-g and antituberculous antibody levels have been studied in ELISA on the peripheral blood of 62 A-group patients and 50 B-group patients.

Results: It has been observed that the patients of group B had the following difference with the patients of group A: 1) Group B had a reasonably more frequent reduction of CD4 as compared to group A ($24.4 \pm 2.3\%$ versus $42.4 \pm 3.1\%$ in group A) and of CD16 ($5.1 \pm 0.3\%$ vs. $10.8 \pm 0.5\%$ in group A). 2) Group B had a reasonably more frequent increase of CD95 lymphocytes ($49.9 \pm 3.2\%$ vs. $28.1 \pm 2.2\%$ in group A) and of antituberculous antibodies (0.75 ± 0.09 absorbance units [au] vs. 0.29 ± 0.05 au). It was defined that the deficiency of IL-2 of less than 165.0 pcg/ml and of IFN-g of less than 15.1 pcg/ml causes the phagocytosis and macrophage depression and leads to a severe specific process in the lungs.

Conclusion: It is found that one of the tuberculosis progression reasons is a serious disorder of the immune system, namely the balance change of CD4, CD16 and CD95 lymphocytes and the lymphocyte-derived IL-2 and IFN-g cytokines.

PC-1020-05 To ascertain the proportion of drug-resistant tuberculosis among people living with HIV in Abia State

O Okorie,¹ M Gidado,² C Osakwe,³ E Ubochioma,² V Ibeziako,² G Akang,² R Eneogu² ¹Tuberculosis Control Program, Abia, ²Tuberculosis Unit, Abuja, ³Tuberculosis Unit, Enugu, Nigeria. e-mail: onphil200@yahoo.co.uk

Background and challenges to implementation: The emergence of drug resistance Tuberculosis (TB) is a major public health challenge and threatens progress made in global TB control. The 2012 National Tuberculosis drug resistant prevalence survey conducted in Nigeria showed a prevalence of 2.9% among new TB cases and 14.3% for retreatment TB cases. Drug resistance TB arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB. This is as a result of, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Diagnosis of TB among PLWHIV is difficult and problematic especially those with low CD4 count. Consequently there is under diagnosis and over diagnosis of HIV associated Tuberculosis. With the advent of Xpert MTB/RIF, diagnosis of HIV associated TB and Rifampicin resistant TB is more expedient and within reach. It is against this backdrop that the State control program proposed a study to ascertain the proportion of TB among PLWHIV with Xpert MTB/RIF assay.

Intervention or response: All the presumptive drug resistant TB cases and symptomatic PLWHIV were examined with GeneXpert and recorded in DR-TB register.

Results and lessons learnt: A total of 1392 Drug resistant presumptive cases screened with gene xpert machine in 2014, 17 % (240) were *M. tuberculosis* positive and 2 % (31) were rifampicin resistant. More so out of 416 TB symptomatic HIV patients screened, 4% were rifampicin resistant

Conclusions and key recommendations: The result depicts that PLWHIV has 50% risk of developing resistant tuberculosis when compared to the general population

PC-1021-05 Morphological characteristics of *Mycobacterium tuberculosis* strains failing to grow on 7H10 agar proportion drug susceptibility testing

J Farooqi,¹ K Jabeen,¹ S Shafiq,¹ S Ali,¹ R Hasan¹ ¹Aga Khan University, Karachi, Pakistan. e-mail: joveria.farooqi@aku.edu

Background: Drug susceptibility testing (DST) of *M. tuberculosis* in the Aga Khan University (AKU) Clinical Laboratory is performed by agar proportion method on Middlebrook 7H10 agar after preparing a 1:10 dilution of the organism suspension as recommended by CLSI. In our experience certain strains of *M. tuberculosis* fail to grow on DST when tested with 1:10 dilution of the inoculum, delaying the DST report. In this study we aim to describe the strains which do not grow on DST with 1:10 dilution but grow well without diluting the inoculum, so that they may be identified before DST is set up, preventing delayed reports.

Design/Methods: DST was performed on *M. tuberculosis* strains obtained from culture on LJ, and MGIT subculture on 7H10 agar as recommended by CLSI (M24-A2 2011). Briefly, a 0.5 McFarland (McF) organism suspension was made and diluted 1:10 times before inoculating 0.1 ml onto 7H10 agar 4 quadrant plates with a drug free quadrant for growth control. Strains which failed to grow in the growth control were chosen to be re-tested in parallel with a 1 McF suspension, with and without 1:10 dilution and the results recorded. Treatment history and description of morphology on LJ and 7H10 agar for these strains were also noted.

Results: Out of 149 strains tested in January and February 2015, 14 *M. tuberculosis* strains failed to grow on routine DST and were tested in parallel with and without dilution of 1 McF organism suspension. All 14 strains grew on undiluted DST, while 10 strains did not grow on 1:10 dilution. Details of treatment and colony morphology are given in table below: DST result (14 cases) Treated (history available in 7 cases) 7H10 (morphology recorded in 7 cases) LJ (morphology recorded in 14 cases) Dry and rough Wrinkled and raised Dry Hard/ wrinkled Growth on dilution 2 1 0 1 3 No growth on dilution 5 3 3 3 7

Conclusion: *M. tuberculosis* strains that fail to grow on DST by dilution were more likely to have hard, wrinkled colonies and isolated from patients on ATT. With an adequate sample size, the results of this study may

confirm our hypothesis that recognizable strain characteristics can predict which strains will not grow using routine DST recommendations.

PC-1022-05 Resistance pattern, prevalence and predictors of fluoroquinolone resistance among multidrug-resistant tuberculosis patients

N Ahmad,¹ A H Khan,¹ S A S Sulaiman,¹ A Javid²

¹Universiti Sains Malaysia, Pulau Pinang, Malaysia;

²Postgraduate Medical Institute, Peshawar, Pakistan. e-mail: nafeesuob@gmail.com

Background: Fluoroquinolones form the backbone of MDR-TB treatment regimen. Despite MDR-TB high burden country, little is known about drug resistance pattern, and prevalence and predictors of fluoroquinolones resistance in MDR-TB patients from Pakistan.

Design/Methods: This was a cross-sectional study conducted at programmatic management unit of drug resistant TB (PMDT), Lady Reading Hospital Peshawar, Pakistan. Two hundred and forty three newly diagnosed MDR-TB patients consecutively enrolled for treatment at study site from January 1, 2012 to July 28, 2013 were included in the study. A standardized data collection form was used to collect patients' socio-demographic, microbiological and clinical data. SPSS 16 was used for data analysis.

Results: Majority patients were females (55.6%), Pakistanis (91.8%), aged 21-40 years (46.1%), baseline weight >40kg (62.1%), rural residents (77%), previously treated for TB (91.4%), non-smokers (87.2%), previously treated for TB at a public facility (54.7%) and had no history of SLD use (95.1%). Only 39.5% patients had cavities on baseline chest X-ray and concurrent co-morbidity (14.4%). High degree of drug resistance (median 5 drugs, range 2-8) was observed. High proportion of patients was resistant to all five first-line anti-TB drugs (62.6%) and second line drugs (55.1%). Among three first-line anti TB drugs, the rate of resistance was highest for pyrazinamide (97.5%) followed by ethambutol (81.1%) and streptomycin (70%). Resistance to ofloxacin was observed in 52.7% patients. Upon multivariate analysis, previous TB treatment at private (OR =1.953, *P* = 0.034) and public private mix (PPM) sectors (OR= 2.824, *P* = 0.046) were predictors of fluoroquinolones resistance.

Conclusion: The high degree of drug resistance observed particularly to fluoroquinolones is alarming. Irrational prescriptions, frequent use of fluoroquinolones for respiratory tract infections other than TB and non-prescription sale of antibiotics are the probable reasons for high fluoroquinolones resistant *Mycobacterium tuberculosis*. Adoption of more restrictive policies to discourage the use of fluoroquinolones, and training doctors in both private and PPM sectors to diagnose and manage TB in line with national guidelines is necessary for halting further increase in fluoroquinolones resistance.

PC-1023-05 Profil de résistance aux antituberculeux de souches provenant de patients présentant une tuberculose pulmonaire ou extra-pulmonaire en 2012

A Ba Diallo,¹ A Thiam,¹ M Y Fall Niang,¹ A Ndiaye Diawara,¹ S Lo,² A Gaye Diallo¹ ¹Laboratoire de Bactériologie Virologie, Unité de Mycobactéries du CHU Aristide Le Dantec, Dakar, ²UFR Sciences de la Santé, Université Gaston Berger, Saint Louis, Senegal. Fax: (+221) 338 213 825. e-mail: choux_ba@yahoo.fr

Introduction: L'étude de la sensibilité aux antituberculeux est importante dans le cadre de l'éradication de la tuberculose surtout pour les pays qui ne disposent que du niveau central pour faire ce test. Le diagnostic de la tuberculose dans les pays en voie de développement est basé sur la microscopie et très souvent le patient est mis sous traitement sans que la nature de la souche ne soit connue. Ce travail avait pour but de déterminer les profils de résistance parmi des patients nouvellement infectés ou en retraitement reçus pour diagnostic au laboratoire hospitalier du CHU A. Le Dantec.

Méthodologie: Les échantillons étaient décontaminés par la méthode NALC puis mis en culture sur milieu Lohenstein Jensen et Bactec MGIT 960. Les tests de sensibilité étaient effectués sur milieu liquide MGIT960 avec les molécules de première et seconde ligne

Résultats: Les patients comportaient 149 nouveaux cas et 6 cas de retraitements. Ils étaient âgés de 14 à 82 ans avec une médiane de 33,5. Les hommes représentaient 62% versus 37% pour les femmes et le statut HIV était de 10,3%. La proportion de ceux qui présentaient une tuberculose pulmonaire était de 87,09% contre 12,6% de tuberculose extra pulmonaire. Les souches étaient isolées de prélèvement extra pulmonaires comprenant des Pus, Liquide pleural, LCR, Liquide articulaire, Urines et de prélèvements d'origine pulmonaire. La résistance aux antituberculeux parmi les nouveaux cas était respectivement pour la Streptomycine de 13,4%, (20,8%) pour l'Isoniazide, (12,08%) pour la Rifampicine et l'Ethambutol (8,7 %). Tandis que les patients en retraitement avaient 83,3% de résistance à la Streptomycine et isoniazide et 50% de résistance à la Rifampicine et Ethambutol. La mono résistance était respectivement chez les nouveaux patients de 6,04%, 7,3%, 0,6% et 1,3% respectivement pour S, I, R, E. Les cas de multirésistante parmi les nouveaux cas étaient de 7% pour HR, 1,34% pour HRE et HRS et 2,68% pour HRES. Aucun cas de souches ultrarésistantes n'avait été détecté parmi celles testées.

Conclusion: La problématique des patients nouvellement infectés qui sont mis sous traitement sans le profil de sensibilité de la souche causale doit être mis en exergue puisque cela pourrait encore accroître les risques d'apparition de souches multirésistantes aux antituberculeux disponibles.

PC-1024-05 Feasibility of molecular testing for drug resistance as part of a TB clinical trial screening protocol

P Shete,^{1,2} H Nguyen,³ N Hung,⁴ T L Luu,⁵ N Hung,⁴ M Tran,² H Phan,⁶ N Phuong,⁴ A Cattamanchi,^{1,2} P Nahid^{1,2} ¹San Francisco General Hospital, San Francisco, CA, ²University of California, San Francisco, San Francisco, CA, USA; ³Hanoi Lung Hospital, Hanoi, ⁴National Lung Hospital, Hanoi, ⁵Hanoi Department of Health, Hanoi, Viet Nam. Fax: (+1) 415 206 1551. e-mail: pbshte@gmail.com

Background: Late exclusion of TB clinical trial participants due to drug resistance is a costly and resource-consuming process. Sample size calculations for clinical trials need to be inflated in anticipation of late exclusions. Molecular testing of drug resistance directly on sputum has the potential to address these challenges. As part of a CDC-TB Trials Consortium (TBTC) study in Hanoi, Viet Nam, participants were screened for enrollment using standard interview, sputum smears and culture, and Hain Genotype® MTB-DRplus (Hain Lifescience, Nehren Germany), a molecular test that detects the presence of *M. tuberculosis* (TB) as well as isoniazid (INH) and rifampin (RMP) resistance. We sought to assess the feasibility and performance of using MTB-DRplus directly on sputum as a screening tool for clinical trial enrollment.

Design/Methods: This cross sectional study was conducted during consecutive screening of 64 patients for enrollment into TBTC Study S29X between February and October 2012. MTB-DRplus was performed directly on smear positive sputum specimens within 24 hours of collection in addition to standard enrollment procedures. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MTB-DRplus using results of drug susceptibility testing (DST) on Lowenstein-Jensen (LJ) media as the reference standard.

Results: Results were missing for eight patients (six for M MTB-DRplus and two for LJ DST), two patients had indeterminate MTB-DRplus results and one patient tested negative for *M. tuberculosis*. Among the remaining 51 patients, MTB-DRplus identified 9 of 12 with INH-resistant TB by LJ DST (sensitivity 75%, 95%CI 43-94%), all of whom had mutations in *katG*. MTB-DRplus was negative for INH-resistance in all 39 patients with INH susceptible TB by LJ DST (specificity 100%, 95%CI 91-100%). MTB-DRplus results were available within 36 hours, enabling all 9 patients with positive molecular results for INH resistance to be excluded from the clinical trial prior to randomization and instead be referred for treatment by the Viet Nam National TB Programme.

Conclusion: Use of MTB-DRplus directly on sputum is a feasible component of the screening process for TB clinical trials. Diagnostic performance characteristics are similar to that reported in non-trials settings. Further studies are needed to quantify the time and cost savings of routine use of MTB-DRplus during eligibility screening for clinical trials focused on drug-susceptible TB.

Table Performance characteristics of MTBDR_{plus} in S29X as compared to LJ- DST

	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Rifampin	3/3, 100% (31-100)	48/48, 100% (93-100)	100% (31-100)	100% (31-100)
Isoniazid	9/12 75% (43-94)	39/39 100% (91-100)	100% (66-100)	93% (80-98)
MDR	2/2 100% (19-100)	49/49 100% (93-100)	100% (19-100)	100% (93-100)

39. Tuberculosis drug resistance and susceptibility testing in a nutshell

PC-1025-05 Determinants of pulmonary tuberculosis among women in Afghanistan

S D Mahmoodi,¹ M Seddiq,¹ M R Aloudal,² M Mashal,¹ S S Mohammad,¹ G Qader³ ¹Ministry of Public Health, Kabul, ²World Health Organization Country Office, Kabul, ³Challenge TB, Management Sciences for Health, Kabul, Afghanistan. e-mail: ntp.mahmoodi@gmail.com

Background: Afghanistan is one of the 22 TB high-burden countries and TB is a major public health problem in the country. WHO estimates that approximately 61,000 all types of TB cases occur every year with incidence rate of 189/100 000 population per year. More female cases (particularly, aged 15 to 45 years old) compared to males are seen for any form of TB infection (female to male ratio 2:1). Causes of this predominance are not known and this important information gap has been repeatedly highlighted. This study aims at filling this void by examining the likely risk factors including socio-cultural, nutrition, economic, environmental, and health seeking behavioral factors that may be underlying this high burden of TB among women.

Methodology: A case-control study was conducted whereby a sample of new smear positive pulmonary TB cases among adult females was enrolled from a randomly selected sample of health facilities. An equal number of adult males diagnosed with smear positive pulmonary TB living in the same community was selected as first controls and an equal number of adult males diagnosed with smear positive pulmonary TB from a different community were selected as the second control.

Results: Women who were younger than 18 years at the time of their first marriage (early marriage) had 25 times higher risk of getting TB compared to those married at 31 years or older. Severely malnourished women were 2.72 times more at risk of getting TB compared to well-nourished people. Women living in families where five or more people sleep in the same room during the night reported higher risk of getting tuberculosis compared to those where less than five people slept under the same roof. The study indicated that women who use private health service providers have higher proportion of tuberculosis compared to those who used public health services.

Conclusion: The results of the present study suggest that early marriage, women's malnutrition, lack of financial autonomy and living in crowded families has independent significant positive association with prevalence of TB among women in Afghanistan. Efforts should be centered on the enforcement of legislation to discourage early marriage, removing the barriers for women's financial autonomy and increasing the quality of living conditions in order to combat the spread of tuberculosis in Afghanistan.

Table 1: Association (adjusted) between socio-economic, environmental and health seeking behavior and Tuberculosis among women in Afghanistan

Socio-cultural factors		Case			p-value
		OR	CI		
Age at first marriage (Ref= 31 years and more)	10-17 years	25.2	8.4	75.0	0.0
	18-30 years	3.3	1.2	9.3	0.0
Number of rooms (Ref= 5 or more rooms)	1-2 rooms	1.3	0.8	2.1	0.3
	3-4 rooms	1.9	1.1	3.1	0.0
Nutrition/Status of Women (Ref = Normal)					
Mild		1.0	0.6	1.5	0.9
Moderate		1.5	0.9	2.3	0.1
Sever		2.7	1.9	3.9	0.0
Socio-economic factors					
Spending money without family permission (Ref is yes)	No	3.0	2.0	4.5	0.0
	Yes	1.0	0.6	1.6	0.9
Environmental Factors					
Number of persons per room in night (Ref=1-4 persons per room)	5 or more persons per room	1.5	1.0	2.2	0.0
Health Seeking behavior factors					
Cautious at early stage for health problems (Ref=Don't know)	Yes	0.9	0.3	2.9	0.9
	No	0.5	0.1	1.9	0.3
Preference for type of Health facility (Ref =Both)	Public	0.8	0.5	1.2	0.3
	Private	2.0	1.2	3.4	0.0
Tuberculosis related factors					
Having contact with TB confirm case (Ref= Don't know)	Yes	1.5	0.9	2.4	0.1
	No	1.2	0.7	1.8	0.5

PC-1026-05 Evaluation of the BACTEC MGIT 960 system for bedaquiline susceptibility testing of *Mycobacterium tuberculosis*

G Torrea,¹ N Coeck,¹ C Desmaretz,¹ T Van De Parre,¹ T Van Poucke,¹ N Lounis,² B C De Jong,¹ L Rigouts¹

¹Prince Leopold Institute of Tropical Medicine, Antwerp,

²Janssen Infectious Diseases, Beerse, Belgium. Fax: (+32) 3 247 63 33. e-mail: gtorrea@itg.be

Background: After the approval of Bedaquiline (BDQ) by the U.S. Food and Drug Administration (FDA) the compassionate use of the drug and expanded access programs have been established in many countries, creating the need to monitor the susceptibility pattern of strains isolated from patients receiving BDQ. The lack of bacteriological data lead us to evaluate the feasibility and accuracy of Minimal Inhibitory Concentration (MIC) determination of BDQ in BACTEC MGIT 960 versus the Middlebrook 7H11 (M7H11) method.

Design/Methods: In a first phase the wild-type MIC distribution was determined to establish the Epidemiological cut-off (ECOFF) or breakpoint to declare a strain as resistant to BDQ, using 47 strains from BDQ-treatment-naïve patients both in MGIT960 and on M7H11 agar. In the second phase the accuracy of MGIT960 was evaluated versus M7H11 using 74

‘probable susceptible’ and 18 ‘probable resistant’ strains. Repeatability and reproducibility of MGIT960 were assessed using 5 strains showing different BDQ resistance levels.

Results: The wild-type MIC distribution ranged from ≤ 0.03 mg/L to 1.00 mg/L in MGIT960 and from ≤ 0.008 mg/L to 0.25 mg/L on M7H11 with suggested ECOFFs of 1.00 mg/L and 0.25 mg/L respectively. Applying these ECOFFs, the probable susceptible and resistant strains were distinguishable by both methods. However, only a twofold increased MIC was observed for one of the resistant strains compared to the ECOFF both in MGIT960 and on M7H11. Inter-method agreement to classify the isolates was excellent (100%). All replicates in the repeatability and reproducibility experiments fell within the normal range.

Conclusion: MGIT960 proved to be highly accurate and reproducible relative to M7H11 to determine BDQ MIC. The small margin between the suggested ECOFF and the lowest MIC of the mutant strains risks making both methods prone to discordant results. Further validation in clinical settings linking with treatment outcome data is needed.

PC-1027-05 The potential impact of up-front drug susceptibility testing on India's MDR-TB epidemic

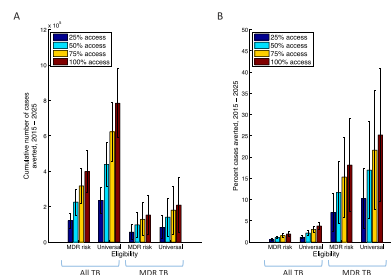
K S Sachdeva,¹ N Raizada,² A Sreenivas,³ C Denkinger,² C Paramasivan,² S Kulsange,² C Boehme,² N Arinaminpathy⁴ ¹Central TB Division, New Delhi, India; ²Foundation for Innovative New Diagnostics, Geneva, Switzerland; ³World Health Organization Country Office, New Delhi, India; ⁴Imperial College, London, UK. e-mail: drneerajraizada@gmail.com

Background: In India, as elsewhere, multi-drug resistance (MDR) poses a serious challenge in the control of tuberculosis (TB). The End TB strategy, recently approved by the world health assembly, aims to reduce TB deaths by 95% and new cases by 90% between 2015 and 2035. A key pillar of this approach is early diagnosis of tuberculosis, including universal drug susceptibility testing (DST), and systematic screening of high-risk groups. Despite limitations of current laboratory assays, universal access to rapid DST could become more feasible with the advent of new and emerging technologies. Here we use a mathematical model of TB transmission, calibrated to the TB epidemic in India, to explore the potential impact of a major national scale-up of rapid DST. Towards this we take GeneXpert technology as an example that could enable scale-up of rapid DST, drawing from findings of recent multi-centric Xpert MTB/RIF demonstration study conducted in India to construct such a model.

Results and Conclusion: We find that widespread, public-sector DST, with Xpert MTB/RIF appropriately linked with treatment, could substantially impact MDR-TB in India: 75% access amongst all cases being diagnosed for TB could avert over 180 000 cases of MDR-TB (95% CI 44187 – 317077 cases) between 2015 and 2025. Sufficiently wide deployment of Xpert could,

moreover, turn an increasing MDR epidemic into a diminishing one. While improved second-line treatment and private sector engagement remain important factors in the control of TB in India, our results illustrate the potential impact of new and emerging technologies that enable widespread, timely DST.

Figure: Impact of Xpert deployment in the public sector, at different levels of access. Simulations assume a linear scale-up of Xpert deployment, over a three-year period, to the levels shown here. On the horizontal axis, 'MDR risk' denotes those with treatment history and/or HIV co-infection, while 'Universal' denotes all TB suspects. Panel A shows the cumulative numbers of cases averted from 2015 to 2025, while panel B expresses this impact as a proportion of the cases that may have occurred under the baseline scenario.



PC-1028-05 Linezolid susceptibility of XDR-TB strains from Pakistan tested on the MGIT 960 system

J Farooqi,¹ K Jabeen,¹ S Shafiq,¹ R Hasan¹ ¹Aga Khan University, Karachi, Pakistan. e-mail: joveria.farooqi@aku.edu

Background: According to WHO 2014 data, Pakistan has the highest MDR-TB burden in the Eastern Mediterranean Region and increasing frequency of XDR-TB amongst MDR strains is a major concern. In 2012 W.H.O. Global TB program released updated critical concentration for linezolid amongst Group-5 anti-tuberculous agents (ATT) and recommended MGIT960 as the testing method. In this study we report the results of linezolid drug susceptibility testing (DST) on MGIT960 in XDR-TB strains isolated in our laboratory.

Design/Methods: Nineteen XDR-*M. tuberculosis* strains isolated from specimens received at Aga Khan Clinical Laboratories from July 2014 to January 2015 were tested against linezolid 1 mcg/ml on Bactec MGIT960 system. DST results for other first and second-line ATT were also recorded. Frequencies of resistance were calculated for each drug amongst the linezolid susceptible strains.

Results: Eighteen out of 19 XDR-TB isolates were found to be susceptible to linezolid. The linezolid resistant strain was susceptible only to ethionamide 5 mcg/ml and resistant to all first-line (streptomycin, ethambutol and pyrazinamide) and second-line (amikacin, kanamycin, capreomycin and ofloxacin) drugs tested. Resistance rates of first- and second-line amongst linezolid sensitive strains were: 89% (16) streptomycin, 77% (14) ethambutol, 94% (17) pyrazinamide, 61% (11) amikacin, 67% (12) kanamycin, 100% (18) capreomycin and 39% (7) ethionamide.

Conclusion: The resistance against linezolid amongst 19 XDR-*M. tuberculosis* strains from Pakistan was found low (5%) while resistance against ethionamide was 39%. This suggests that linezolid and ethionamide may be used

for treatment of XDR-TB in addition to other Group-5 ATT while awaiting susceptibility results.

PC-1029-05 Comparison of the MDR/XDR-TB Colour Test, Xpert® MTB/RIF, and MODS assays to diagnose rifampicin-resistant TB

M Tovar,^{1,2} E Ramos,¹ T Valencia,¹ S Datta,^{1,2} R Montoya,² R Montoya,² T Wingfield,^{1,2} A Valencia,³ R Patrocinio,¹ C Evans^{1,2,4} ¹IFHAD Innovation for Health and Development, Lima, ²IPSYD Innovacion Por la Salud Y el Desarrollo, Lima, ³DIRESA, Regional National Tuberculosis Program, Callao, Peru; ⁴Infectious Diseases & Immunity, Imperial College London, and Wellcome Trust Imperial College Centre for Global Health Research, London, UK. e-mail: marco.tovar@upch.pe

Background: Multidrug resistant tuberculosis (MDR-TB) is challenging TB control. Numerous assays have been developed to screen for MDR-TB. Despite this, MDR-TB rates are increasing and globally only 45% of people with MDR TB are estimated to be diagnosed. The Peruvian NTP uses Microscopic-Observation Drug-Susceptibility assay (MODS) as a universal MDR-TB screening test in patients diagnosed with TB disease. WHO endorses use of Xpert MTB/RIF® test for rapid DST in patients at high risk of MDR-TB. The MDR/XDR-TB Colour Test is a novel non-commercial direct DST that allows MDR-TB diagnosis and screening for extensively drug-resistant TB (XDR-TB).

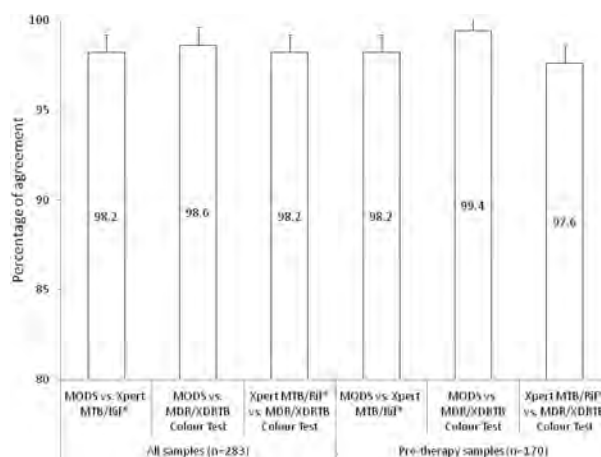
Objective: To compare the concordance of rifampin resistance testing in three DST assays: MDR/XDR-TB Colour Test, Xpert MTB/RIF and MODS.

Design/Methods: From February 2014 through October 2014, consecutive sputum samples of patients diagnosed at regional NTP clinics in shantytown communities of north Lima, Peru, were processed in the Research and Development Laboratory of Universidad Peruana Cayetano Heredia (LID). All patients signed a written, informed consent form. All samples were tested for rifampicin resistance concurrently by the three DST methods: MDR/XDR-TB Colour Test, Xpert MTB/RIF and MODS. Each assay was performed by staff who were blinded to the results of other assays. Concordance between the test results was analysed as percentage agreement compared by the z-test of proportions and McNemar's test.

Results: 762 samples were received and processed during the study period. 283/762 (37%) were culture positive and had an interpretable DST result in all 3 assays. The percentage agreement between MODS and MDR/XDR-TB Colour Test, MODS and Xpert MTB/RIF, Xpert MTB/RIF and MDR/XDR-TB Colour Test was: 98.6%, 98.2%, and 98.2%, respectively for all samples. When this analysis was repeated for the 170 sputum samples collected pre-treatment there was no significant change in the agreement between the three DST assays: 99.4%, 98.2%, and 97.6%, respectively. There were no statistically significant differences between the DST results for any samples groups.

Conclusion: There is high concordance between rifampicin resistance testing results for MDR/XDR-TB Colour

Test, Xpert MTB/RIF and MODS whether samples were collected pre-treatment or during therapy.



PC-1030-05 Exploring drug resistant tuberculosis profiles in the West Coast region of the Western Cape Province, South Africa

P Tshavhungwe,¹ R M Warren,¹ M Buckley,² T Dolby,³ P Van Helden,¹ J Simpson,³ K Jacobson,² E Streicher¹ ¹Biomedical Sciences, Stellenbosch University, Tygerberg, South Africa; ²Boston University, Boston, MA, USA; ³National Health Laboratory Services, Cape Town, South Africa. Fax: (+27) 938 9863. e-mail: phophi.tshavhungwe@gmail.com

Background: The West Coast, a rural district in the Western Cape Province, has one of the highest reported tuberculosis (TB) prevalence in the Province of 1225/100 000 population. Previous molecular epidemiological studies have demonstrated that the dynamics of TB transmission vary geographically. The dynamics governing TB transmission in this region are unknown, specifically that of drug resistance TB. The aim of this study was to describe the DR-TB epidemic and identify transmission hotspots within the West Coast region of the Western Cape, South Africa.

Design/Methods: We performed a retrospective cohort study, selecting one isolate from each of the patients diagnosed with drug resistant TB from 2008-2012 in the West Coast District. Isolates were received from all health facilities in the West Coast and incidence of disease as well as distribution of strains was described for sub-districts based on these locations. We genotypically characterised the isolates by the internationally standardised spoligotyping method and by Sanger sequencing drug resistance conferring genes.

Results: Isolates from 611 patients were genotyped and grouped according to their spoligotype pattern. Spoligotyping data revealed that X-family is the most dominant strain family (33 %), followed by the Beijing family (21 %). This is in contrast to previous studies in the rest of the Western Cape Province that found the Beijing strain family to be predominant in the province. Within the X-Family, 62 % of strains were MDR, 18 % pre-XDR, and

3% XDR. The X-family is the predominant strain in 3 of the 5 sub-districts in the region.

Conclusion: Even though spoligotyping is considered to have a low discriminatory power and could overestimate the extent of transmission, this study suggest an epidemic spread of MDR strains in the West Coast region of the Western Cape Province. Our findings also highlight the regional variation of outbreaks and the need for molecular epidemiologic studies in various regions to tailor interventions to curb TB and drug resistant TB spread.

PC-1031-05 Direct comparison of spontaneously expectorated sputum with sputum expectorated following mouth wash with water or with chlorhexidine

C Kleinhans,¹ M Hanekom,^{1,2} S Friedrich,² A Venter,^{1,2} A Diacon^{1,2} ¹TASK Applied Science, Bellville, ²Stellenbosch University, Tygerberg, South Africa. Fax: (+27) 219 389 317. e-mail: hanekom@sun.ac.za

Background: Mycobacterial sputum cultures are critical to score conversion from positive to negative in clinical trials of anti-tuberculosis regimens. Contaminated cultures do not allow clear scoring. We evaluated whether mouth wash with water or with antibacterial agents can reduce contaminated sputum culture results.

Design/Methods: Between December 2013 and February 2015 we asked Xpert MTB/RIF positive, sputum smear microscopy positive or negative, untreated HIV-infected adults to collect sputum A) expectorated spontaneously B) following a mouth wash with water, and C) following mouth wash with chlorhexidine solution (60 seconds, Corsodyl, South Africa) in that sequence with at least 30 minutes in between collections, once before initiation of anti-tuberculosis treatment and at 3, 7, 14, 28, 35, 56, 112 days thereafter. Sputum was transported to a central laboratory on the same day and processed for liquid culture in duplicate in routine fashion (MGIT960). Results of each sputum were reported as positive, negative or contaminated.

Results: We collected 93 sputum triplicates from 18 initially smear-positive ($n = 14$) and smear-negative ($n = 4$) patients. No adverse events were observed. A - Spontaneous B - Water C - Chlorhexidine Positive 68 73.1% 83 89.3% 78 89.3% Negative 18 19.4% 8 8.6% 15 16.1% Contaminated 7 7.5% 2 2.2% 0 0%. The odds for obtaining a valid result (not contaminated) were higher with a supervised mouth wash than without ($P < 0.01$). Mouth wash with water yielded the most positive cultures whereas mouth wash with chlorhexidine eliminated contamination, but those differences were not significant.

Conclusion: Water or a chlorhexidine mouth wash before sputum collection lowers the contamination rate in liquid culture. A greater number of samples is needed to determine whether water or chlorhexidine are more effective.

PC-1032-05 Molecular testing for tuberculosis in the United States: implications for national surveillance

L Armstrong,¹ T Dalton,¹ R Oatis,² J Higashi,³ S Allen,⁴ M Pecha,⁵ A Starks¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, ²State of Maryland Department of Health and Mental Hygiene, Baltimore, MD, ³San Francisco Department of Public Health, San Francisco, CA, ⁴Washington State Department of Health, Seattle, WA, ⁵Public Health-Seattle & King County, Seattle, WA, USA. Fax: (+1) 404 639 8959. e-mail: larmstrong@cdc.gov

Background: Rapid molecular tests for the detection of mutations associated with resistance to anti-TB drugs in *M. tuberculosis* are now available worldwide, but their use varies widely. The U.S. National Tuberculosis Surveillance System (NTSS) cannot currently incorporate results of these newer molecular tests, instead, relying on documenting drug resistance or susceptibility to anti-TB drugs using conventional growth-based drug susceptibility testing (DST).

Design/Methods: Confirmed tuberculosis (TB) cases were selected for further study if they were reported to NTSS as resistant to at least one of four first-line anti-TB drugs, isoniazid, rifampin, pyrazinamide, or ethambutol. Between the years 2011–2012, cases were abstracted for the states of Georgia (61 cases) and Maryland (27 cases); 2010–2013 for San Francisco County, California (42 cases); and 2011–2013 for Santa Clara County, California (80 cases); and 2009–2013 for Washington state (53 cases from King County and 46 cases from the remaining counties). All growth-based DST and molecular test results were abstracted from laboratory reports in patient medical records.

Results: A total of 309 drug-resistant TB cases were reported among project sites; 77 (25%) with molecular test results recorded in the medical record of which 57 (74%) had results detecting mutations associated with drug resistance. Most isolates were tested for genes associated with rifampin (67) and isoniazid (68) resistance (Table). Two cases had an isolate with a silent mutation (one in *pncA* and one in *embB*). Six cases had mutations associated with drug resistance without comparable growth-based DST results, including four cases with resistance to second-line injectable drugs (*tlyA*) or to fluoroquinolones (FQ) (*gyrA*), drug classes that define extensively drug-resistant TB. These cases were reported in NTSS as resistant to first line drugs, but either susceptible or not tested to second-line drugs. One case had results indicating resistance to FQ by growth-based DST and a *gyrA* mutation, but the growth-based FQ resistance was not reported to NTSS.

Conclusion: State and local TB programs have access to molecular tests for identifying mutations associated with drug resistance and sometimes, molecular results do not match those from growth-based assays. The inability of NTSS to capture these results has negative implications for complete and accurate reporting of drug resistant TB cases.

Table

Molecular test done	Result	Mutations associated with isoniazid* n (%)	<i>rpoB</i> n (%)	<i>pncA</i> n (%)	<i>embB</i> n (%)	<i>gyrA</i> n (%)	Mutations associated with 2 nd -line injectables† n (%)
Yes, n (%)	77 (25)	Mutation	53 (78)	26 (39)	7 (32)	9 (60)	7 (18)
No, n (%)	232 (75)	No mutation Silent	15 (22)	41 (61)	14 (64)	5 (33)	33 (83)
Total	309 (100)	Total	68	67	22	15	40

*Includes *katG* (32 cases), *inhA* (5 cases), *katG/inhA* dual mutations (10 cases), *katG/ahpC* dual mutation (1 case) and 5 cases with unspecified mutations associated with isoniazid.

† Includes *eis* (1 case) and *tlyA* (2 cases)

40. From safety to supply-chain: let's talk lab management

PC-1033-05 Containment of *Mycobacterium tuberculosis* in a Class II B biosafety cabinet during routine operations

G Daneau,¹ E Nduwamahoro,¹ K Fissette,¹ P Rüdelsheim,² D Van Soolingen,³ B De Jong,^{1,4,5} L Rigouts^{1,6} ¹Institute of Tropical Medicine, Antwerp, ²Perseus BVBA, Zwijnaarde, Belgium; ³National Institute for Public Health and the Environment, Bilthoven, Netherlands; ⁴Medical Research Council Unit, Fajara, Gambia; ⁵New York University, New York, NY, USA; ⁶University of Antwerp, Antwerp, Belgium. Fax: (+32) 3247 6333. e-mail: gdaneau@itg.be

Background: Guidelines for the manipulation of *Mycobacterium tuberculosis* (*M. tuberculosis*) cultures require a Biosafety-Level 3 (BSL-3) infrastructure and accompanying code of conduct, however the evidence on which these are based is limited. In this study, we aim to validate and apply detection-methods for viable mycobacteria from surfaces in a BSL-3 TB lab.

Methods: We evaluated phenotypic (RODAC plates) and molecular (propidium monoazide (PMA)-based PCR) approaches for the detection of viable mycobacteria, as well as the effect of 70% ethanol applied for 5 minutes for mycobacterial sterilisation, in a BSL-3 lab with a class II biosafety cabinet (BSC). For validation of the method, recovery of serial dilutions of *M. bovis* BCG from glass slides was measured. We stamped surfaces in and around the BSC after different technicians had manipulated high bacterial load suspensions from liquid or solid medium for routine drug susceptibility testing (1mg/ml, i.e. approximately 106 colony forming units/ml), without prior alert on time of stamping. Technicians had been trained on biosafety and specific techniques according to the good laboratory practices in place in our ISO15189-accredited lab.

Results: RODAC stamping could detect as little as three bacteria on slides stamped either 5 or 60 minutes after inoculation. No contamination was detected. PMA-based PCR, tested in parallel, did not pass validation. Mycobacteria were still detected after disinfection with ethanol 70% (applied 5 or 60 minutes after BCG inoculation). In the BSL-3, from 201 RODAC-stamped surfaces, *M. tuberculosis* was detected on four: three inside a BSC - on a tube cap and on operator's gloves - and one outside, on an operator's gown.

Conclusions: We show that RODAC plates, but not PMA-PCR, detect mycobacteria at low numbers of organisms, and can be applied to assess mycobacterial contamination on surfaces in TB environments. We also show that 70% ethanol does not reliably sterilize mycobacteria when applied for 5 minutes to a dried surface, and that a class II biosafety cabinet may be inadequate for strict containment of mycobacteria during manipulation of *M. tuberculosis* cultures.

PC-1034-05 Distribution and availability of essential tuberculosis diagnostic items in Amhara region, Ethiopia

M Sinishaw,¹ G Gebregergs,² M Balew¹ ¹Bahir Dar Regional Health Research Laboratory Center, Bahir Dar, ²Bahir Dar University, Bahir Dar, Ethiopia. Fax: (+251) 226 6701. e-mail: mulusewalemneh@yahoo.com

Background and challenges to implementation: Adequate supplies of tuberculosis laboratory reagents and consumables are necessary for tuberculosis diagnosis and monitoring of treatment response. This study was initiated to assess the distribution and stock levels of laboratory reagents and consumables used in tuberculosis control in public health centers of Amhara region, Ethiopia.

Intervention or response: A cross-sectional study was conducted in 82 health centers providing sputum microscopy services from April 28 to May 26, 2014. Stock levels were calculated and distribution of reagents and consumables assessed.

Results and lessons learnt: Thirty three (40.2%) health centers were under stocked for at least one of the key items for tuberculosis diagnosis at the time of visit. Fifteen (18.3%) health centers had no stocks of at least one of the key laboratory items (9 (11%) methylene blue, 9 (11%) carbol fuchsin, 7 (8.5%) acid alcohol and 3 (3.7%) sputum cups). Of the 82 health centers, 77 (93.9%) did not fulfill the criteria for effective distribution of tuberculosis laboratory reagents and consumables.

Conclusions and key recommendations: There were many health centers that had no or only low stocks of key tuberculosis laboratory reagents and consumables as a result of ineffective distribution system. This seriously hinders TB control in the area disrupting early diagnosis and treatment follow up services. It is necessary to strengthen supply chain management to ensure uninterrupted TB diagnostic service.

PC-1035-05 Trends in the rate of follow up sputum smear examination and conversion rate among smear-positive pulmonary TB patients in two regions of Ethiopia

J Seid,¹ N Demmelash,¹ W Gebrekirstos,² F Belachew,³ Z Dememew,¹ D Habte,¹ M Aseresa Melese,¹ P G Suarez⁴

¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, ²Amhara Regional Reference Laboratory, Bahar Dar, ³Oromia Regional Reference Laboratory, Addis Ababa, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: jseidmsh@gmail.com

Background and challenges to implementation: WHO recommends 2nd, 5th and 6th month follow up smear microscopy for sputum smear positive (SS+) patients. Smear conversion at these periods is used as an indicator for good adherence and strong directly observed TB treatment practice. Patients who failed to convert at these points are also likely cases of MDR TB and require close follow-up. At the beginning of the project, the complete examination rate of SS+ pulmonary TB patients was below the standard.

Intervention or response: USAID funded MSH/HEAL TB project supported Amhara and Oromia regional health bureaus of Ethiopia through various interventions. Heal TB trained staffs from health facilities on management of TB patients using the national guideline. The project supported the lab diagnostic and follow-up capacities of the health facilities by providing microscopes, trained laboratory professionals, and established a decentralized external quality assurance system. Standard of Care (SOC) monitoring was introduced to help district TB focal persons monitor each TB patient status including the status of sputum follow-up tests. Sputum follow up test monitoring tool/dashboard was also developed to be used by health facility TB focal persons.

Results and lessons learnt: We analyzed the routine data from health facilities in 10 zones that were included under the project support during the initial phase of implementation. The number of SS+ patients who gave sputum at the end of intensive phase has increased from 80 % (95%CI: 78% - 82%) at baseline to 96 % (95%CI: 95% - 97%) in 2014. It shows that only 4% of smear positive TB patients did not get follow up test at the end of intensive phase. In the last three years, smear conversion rate of SS+ TB patients at the end of 2nd month (intensive phase) has improved by 17 % [from 74% (95%CI: 71% - 76%) in 2011 to 91% (95%CI: 90%-92%) in 2014]. Similarly the sputum follow up at the end of the 5th month increased from 64% to 90% ($P < 0.001$) and the cure rate increased from 66 to 88% ($P < 0.001$)[Table 1]. For those who failed to convert at 2nd, 5th and 6th month, sputum was sent for culture and DST or GeneXpert to rule out MDR TB.

Conclusions and key recommendations: District level monitoring by health managers and local capacity building of laboratory and TB clinic staff plays a huge role towards ensuring quality service and treatment outcome. Indicator assisted close holistic support helps in

improving the performance of TB treatment follow up practice.

Table Trend of sputum follow-up at the end of intensive phase and smear conversion, Phase I zones of Amhara and Oromia regions, 2011-2014

Period	Smear conversion rate at end of intensive phase (%) ¹	Examined rate at 5 th month (%)	Cure rate (%)
Baseline	74	64	66
Year I/2012	82	80	77
Year II/2013	89	90	84
Year III/2014	91	90	88

¹The percentage shows that patients who converted to smear negative. The remaining could be still smear positive or sputum is not examined

PC-1036-05 The effect of triage in improving sputum-positive case detection in crowded out-patient settings: experience of 164 primary health centres in Bihar

S Mugudalabetta,¹ A K Pandey,¹ L V Ramana Rao,¹ S K Muthusamy¹ ¹Damien Foundation India Trust, Chennai, India. Fax: (+91) 044 2836 0496. e-mail: admin@damienfoundation.in

Background and challenges to implementation: In 2013, out of the estimated global annual incidence of 8.6 million TB cases, 2.3 million were in India. Bihar is second most populous state in India; Revised National TB Control Programme was implemented in the state in 2005. One of the major challenges faced by the state in TB control is poor case detection. Though it is estimated 203 TB cases of all types per 100 000 population, the State is not able to achieve even 35% of the target set by the programme. One of the main reasons was poor health infrastructure; each primary health centre covers a population range from 150 000 to 200 000. Health facilities are generally overcrowded with patients, doctors may not have enough time to take complete history from the patients attending outpatient clinics and many TB symptomatic cases can be miss the opportunity to undergo screening for TB.

Intervention or response: Damien Foundation India Trust is supporting Revised National TB Control Programme in 15 districts with less than 30 New Sputum Positive case notification per 100 000 population. One of the strategies to improve case notification is to promote triage approach for identification of TB symptomatic in crowded outpatient clinics at Primary Health Centres. Out of 293 microscopy centres in 15 districts, 209 DMCs were selected to implement triage approach based on high patient load. Lab Technicians were trained to visit the waiting area every hour and segregate patients with cough for sputum examination with the approval of doctor. By the end of 2014, complete data was available from 164 (78%) DMCs. The data was also collected for 2012 and 2013 from same microscopy centres for comparison.

Results and lessons learnt: There is significant improvement seen both in screening of TB symptomatic and sputum positive case detection in 2014 compared to

previous two years. It was observed that screening of TB symptomatic increased by 18% and 25% in 2014 compared to 2012 and 2013. Sputum positive case detection increased by 30% and 37% in 2014 compared to 2012 and 2013.

Conclusions and key recommendations: Implementation of triage approach can improve both screening of TB symptomatic and sputum positive case detection in crowded outpatient clinics.

PC-1037-05 The impact of seasonal factors on TB treatment loss to follow-up

A Mordovin,¹ C Acosta,² D Pashkevich,¹ S Sterlikov,³ I Danilova,⁴ L Migliorini,² M Dara² ¹World Health Organization, Moscow, Russian Federation; ²World Health Organization, Copenhagen, Denmark; ³Federal Research Institute for Health Organization and Informatics, Moscow, ⁴Moscow City Scientific and Practical Center for TB control, Moscow, Russian Federation. Fax: (+495) 787 2119. e-mail: a.mordovin@whorussia.org

Background: The Russian Federation is a country with difficult climatic conditions caused by extreme continental climate. We hypothesized the possible impact of seasonal factors on TB treatment loss to follow-up (LFU).

Design/Methods: We examined the proportion of LFU patients during the intensive phase of treatment and during the entire treatment course. In total, data was available on 19 923 new cases, including 5259 cases notified in quarter I (January-March), 2012, 5223 cases notified in quarter II (April-June), 2012, 4515 cases notified in quarter III (July-September), 2012, and 4926 cases notified in quarter IV (October-December), 2012. We determined Relative risk (RR) of LFU taking into account statistical significance ($P < 0.05$).

Results: For those patients treated during the intensive phase of treatment, there was a significant decrease in the RR of LFU among patients registered in Q1 compared to Q2 (RR=0.77) and Q3 (RR=0.76); there was a significant decrease in the RR among patients registered in Q4 compared to Q2 (RR=0.75) and Q3 (RR=0.74). During the whole course of treatment there was a significant decrease in the RR among patients registered in Q4 in comparison with Q1 (RR = 0.75), Q2 (RR = 0.70) and Q3 (RR = 0.85) ($P < 0.05$ for all).

Conclusion: Seasonal factors influence the frequency of LFU in the intensive phase and entire course of treatment. A decrease in the LFU RR during the intensive phase occurs at the beginning treatment in the cold season, when smear-positive patients start treatment in a hospital. A decrease in RR LFU over the entire course of treatment is associated with the continuation phase of treatment in the cold season, when patients have less opportunity to participate in seasonal work, which increases dependence on food packages, if issued. Since the RR of treatment LFU in the warm time of the year vs. the cold time is 1.2-1.4, it is advisable to reallocate resources accordingly.

PC-1039-05 The threat of human resource shortage to quality laboratory practice in Africa

T Maruta¹ ¹African Society for Laboratory Medicine, Addis Ababa, Ethiopia. e-mail: talkmoremaruta@gmail.com

Background: The shortage of health workers has been linked to poor health indicators with Africa estimated to have 2.3 healthcare workers per 1000 population. Of the 57 countries with critical shortage of healthcare workers, 36 are in Africa and as much as a 140% increase in healthcare professionals is required for them to achieve some of the MDG targets. Over the years, the role of the laboratory in the delivery of healthcare has increasingly been recognized and consequently its efficiency, cost-effectiveness, and quality of service has to be high. To ensure quality, laboratories implementing a quality management system (QMS). Implementing a QMS requires personnel that have a specific set of skills and knowledge about international standards like the ISO 15189 and their requirements. Given the already existing workforce shortage, limited personnel with competency in QMS has threatened the investments in laboratory system strengthening and quality of laboratory service.

Design/Methods: The ASLM developed a key strategic goal on workforce development; "Strengthen the laboratory workforce in Africa to achieve Millennium Development Goals for Health" by (1) Training and certifying 30 000 laboratory professionals and clinicians, (2) Advocating for national laboratory professional regulatory councils and (3) Developing standardized frameworks for workforce development, retention, and improving and maintaining pre-service training capacity.

Results: To date, ASLM has trained 30 Laboratory professionals in research and publication, 48 in laboratory mentorship, 60 in Laboratory quality management systems, 24 in accreditation preparedness, 88 certified as WHO auditors. 2 pre-service curricula have been reviewed and updated, 1 laboratory regulatory body established and 14 MOUs signed with laboratory associations

Conclusion: The availability of expert human resources continues to be a threat to provision of quality laboratory services. ASLM continues to provide advocacy for investment in building human resource capacity through its 2020 Strategic goal on workforce development.

PC-1040-05 Risk of acute lower respiratory tract infections in adults associated with household air pollution from solid fuel use: a systematic review

H Jary,¹ D Havens,¹ K Mortimer,¹ D Pope,² N Bruce² ¹Liverpool School of Tropical Medicine, Liverpool, ²University of Liverpool, Liverpool, UK. e-mail: hannah.jary@liverpool.ac.uk

Background: Acute lower respiratory infections (ALRI) in adults cause a large burden of mortality worldwide, particularly in developing countries. Exposure to household air pollution (HAP) is also high in many developing countries, as 2.8 billion people rely on burning solid fuels for essential domestic energy. HAP exposure is known to

be a risk factor for childhood ALRI, but the association in adults has not been confirmed and quantified. A systematic review in 2009 found just three studies investigating this relationship with inconclusive findings. We aim to update this systematic review from 2010 onwards to compile the evidence, for the purpose of informing future public health policy decisions regarding HAP interventions strategies.

Design/Methods: Searches were made of seven English language databases, using search terms that covered all sources of HAP and different forms of ALRI. Relevant studies were selected using a protocol driven process, and data was extracted and quality assessed using pre-defined forms.

Results: From 9238 titles, 4 studies were selected, including three cross-sectional studies and one observational natural experiment. All studies had methodological limitations and their results may have been affected by systematic biases. Significant methodological heterogeneity was seen between the four studies and so it was inappropriate to conduct a meta-analysis for calculation of an overall risk estimate. Of the studies providing a risk estimate, one found an increased risk of bronchitis with increased CO exposure (unadjusted odds ratio (OR) 1.66 (95% confidence interval (CI) 1.15-2.40) but the other two found no significant effect of reported biomass use or exposure on the risk of ALRI/bronchitis (OR 0.91, 95%CI 0.71-1.15 and OR 2.40, 95%CI 0.86-6.72).

Conclusion: The findings of this systematic review indicate that there is little robust evidence available and existing studies do not provide conclusive evidence regarding the effects of HAP on adult ALRI. Further prospective studies examining this relationship are warranted. To ensure comprehensive results, this systematic review is being extended to include non-English language databases and grey literature from 1960: final results expected by mid-2015. A thorough analysis of the existing evidence is essential to understand the contribution of HAP to the high burden of disease caused by adult ALRI, to facilitate targeted public health interventions if a need is identified.

41. Stepping up patient access and support

PC-1041-05 Enhancing accessibility and intensifying TB interventions with patient-centered care: BRAC experience

S Munim,¹ S Islam,¹ M Siddiqui,¹ M Akramul Islam,¹ M Rahman,² K Uddin¹ ¹BRAC, Dhaka, ²National Tuberculosis Programme, Dhaka, Bangladesh. Fax: (+88)02 8823542. e-mail: munim.s@brac.net

Background and challenges to implementation: Ever since 1984 BRAC has started TB control programme in Bangladesh and it has been waging this battle against tuberculosis, currently it serving 93 million populations. To improve case notification and overcome unfavorable treatment outcome, the organization introduced Com-

munity involvement and assessing the needs of TB patients is essential for universal access to TB care.

Intervention or response: BRAC design peripheral laboratory facilities with solar system in very remote areas and outreach sputum collection centers to improve access to diagnosis. BRAC's frontline health workers (Shasthya Sebika) disseminate TB messages in the community and refer TB presumptive for sputum examination at NTP designated laboratories during household visits and group meeting. Those persistent TB symptoms and negative smear referred to higher level health facilities for X-ray, FNAC and biopsy. Treatment for all TB patients is initiated by graduate medical doctors and daily DOT is ensured by Shasthya Sabika.

Results and lessons learnt: Additional 14,037 outreach sputum collection centers were held between January 2012 to December 2014 and established referral linkage with 4,967 additional graduate medical practitioners. A total of 11 peripheral laboratories with solar system were expanded to cover hard to reach areas. Significant number of DOT is ensured by these Shasthya Shebikas in BRAC covered area, service intensification result improved case notifications from 91 703 in 2011 to 1 24 286 in 2014. In 2013, among 1 01 555 pulmonary patients, 505 (0.5%) were lost to follow up and out of 1481 retreatment cases, lost to follow up 16 (1.1%) only, and treatment success rate reached 95%. Case notification of NSP in hard to reach areas also increased from 73/100 000 population in 2011 to 78 in 2014.

Conclusions and key recommendations: Patient centered approach by involving community people for showed better result in increased case notification, maintain high cure rate, reduce lost to follow up and DOTS expansion.

PC-1042-05 Community based MDR-TB management: BRAC experience from Bangladesh

S Munim,¹ S Islam,¹ M Basher,¹ M Siddiqui,¹ M Akramul Islam,¹ M M Rahman,² S Sultana³ ¹BRAC, Dhaka, ²National Tuberculosis Programme, Dhaka, ³World Health Organization, Dhaka, Bangladesh. Fax: (+88) 02 882 3542. e-mail: munim.s@brac.net

Background and challenges to implementation: National TB control programme (NTP) initiated programmatic management of DR-TB (PMDT) in 2008 with 24 months standard MDR-TB treatment regimen and BRAC is major implementing partner of NTP. NTP developed PMDT guidelines in 2009 and updated in 2013, and patient treated according to guideline. Shasthya Shebikas are front line health care providers of BRAC, ensures daily intake of medicine during ambulatory phase of treatment. They play significant role in community base MDR-TB management.

Intervention or response: Since 2013 BRAC has been providing diagnostic support to identify MDR-TB from presumptive, nutritional and other support to improve treatment adherence and outcome. Moreover, from 2013 NTP initiated community based programmatic management of DR-TB, treatment modality changes from 6-8

months to 1-2 months hospitalization and patients discharge to community from hospital. Outpatient DR-TB team trained and ready to provide community based DOT. Shasthya Shebikas receive basic orientation on MDR-TB management at community level, ensures daily intake of medicine in ambulatory phase and appropriate referral if any adverse drugs reaction occurs.

Results and lessons learnt: National DR TB patient enrolment increased of from 376 in 2012 to 717 in 2014 almost double. In 2012 total 336 patients have received ambulatory phases treatment at community level in BRAC supported areas. Out of 336 patients, 238 were successfully completed treatment in the community. Treatment success rate increased 71% in 2012 cohort from 68% in 2010 cohort and lost to follow up rate decreased to 15% in 2012 from 27% in 2008.

Conclusions and key recommendations: Community-based care is built on three tiers support: clinical care, socio-economic and psycho-emotional. Community based PMDT improves case notification and care for ensuring treatment adherence and outcome.

PC-1043-05 Improved treatment adherence among patients by making them aware of their rights and responsibilities through the TB charter

T Laha,¹ S Diwakar,¹ V Sameer,¹ P Bhat,¹ T Thomas¹ ¹The Catholic Health Association of India, Secunderabad, India. e-mail: sameer-valsangkar@chai-india.org

Background and challenges to implementation: Incomplete adherence to treatment has been identified as a major obstacle to the control of the disease. Tuberculosis (TB) is nearly always curable if patients are treated with effective, uninterrupted antituberculous therapy. Adherence to treatment is critical for cure of individual patients, controlling spread of infection and minimizing the development of drug resistance. This abstract makes an attempt to enumerate the barriers of treatment adherence and modes to encourage adherence through sensitizing patients on their rights and responsibilities.

Intervention or response: In the districts of Pakur, Jharkhand, India, TB patients were made aware about their Rights & Responsibilities through project Axshya, a Global Fund supported initiative. Through the project, trainings and Mid-media activities were organized for TB Patients on their Rights & Responsibilities and 180 TB Patients were made aware regarding the TB charter. Patients were identified from villages where completion rates were low and selection of patients was done through the help of TB Forum members involving local formal leaders.

Results and lessons learnt: Out of 180 TB Patients, 82% informed about difficulties in receiving medicine during the period of migration and they also informed that most of DOTS provider not ready to give medicine in advance before their departure to village. During their migration patients have to depend on Private Practitioner of the area and became irregular in taking medicine. Most of trained TB Patients started demanding necessary refer-

als before their migration following the sensitization with the TB charter.

Conclusions and key recommendations: Migration is a norm for better opportunities in Pakur district of India and this leads to interruption of treatment. Establishment of proper referral system in consultation with respective DOTS providers is required. There is a need for advocacy with policy makers for ensuring their regular treatment during the period of migration.

PC-1045-05 Experiences of delivering long-term injectables during TB treatment in Malawi

D Cohen,^{1,2} M Phiri,¹ H Banda,^{2,3} S B Squire,² N Desmond,^{1,2} I Namakhoma³ ¹Malawi Liverpool Wellcome Clinical Research Programme, Blantyre, Malawi; ²Liverpool School of Tropical Medicine, Liverpool, UK; ³REACH Trust, Lilongwe, Malawi. e-mail: danbcohen@yahoo.com

Background: Patients on treatment for recurrent or multidrug-resistant tuberculosis require long courses of injectable anti-tuberculous agents. There are various options for the daily delivery of injections, but each has major disadvantages. In order to investigate the feasibility of a novel model of care delivery, a clinical trial (The TB-RROC Study) was conducted in patients receiving Category II retreatment regimen at two central hospitals in Malawi. Hospital-based care was compared to a community-based approach in which guardians were trained to deliver injections to patients at home. In order to comprehensively evaluate this intervention, it is important to understand the experiences of those involved.

Design/Methods: A qualitative evaluation of the TB-RROC intervention was conducted, using phenomenographic methods to describe understanding and experiences of TB retreatment. TB-RROC trial participants were purposively sampled, and in-depth interviews were conducted with patients and guardians in both arms of the trial. Key informant interviews and observations in the TB wards and in patients' homes were also conducted. Thematic content analysis was used to derive analytical themes.

Results: 14 patients and 12 guardians were interviewed. 9 key informants including household members, potential trial recruits who declined to participate, nurses and TB officers were also interviewed. Three key themes relating to TB retreatment emerged: medical experiences (including symptoms, treatment, and HIV); the effects of the physical environment (particular distress caused by conditions on the ward, and disruption to daily routines and livelihoods); and trust (in other people, the community as a whole and in the health system). Experiences were affected by the nature of a person's prior role in their community and resulted in a range of emotional responses. Patients and guardians in the community benefited from better environment, social interactions and financial stability. Concerns were expressed about the potential for patients' health or relationships to be adversely affected in the community. These potential concerns were very rarely realised, and

overall participants described overwhelmingly positive experiences of community-based care.

Conclusion: Patients and guardians have a range of medical, social, financial and emotional experiences during TB retreatment. Overall, community-based care offered many advantages over hospital-based care.

PC-1046-05 Knowledge, attitudes and practices about home-based TB treatment support by community care workers in a South African urban informal settlement

T Collings,¹ A Von Delft,^{1,2} G Dhlomo,¹ B Khatry-Chhetry,¹ N Koen,¹ K Wilson¹ ¹University of Cape Town, Cape Town, ²TB Proof, Cape Town, South Africa. e-mail: vuzumsi@gmail.com

Problem: Tuberculosis (TB) rates in urban informal settlements in South Africa are amongst the highest in the world. Despite a renewed State focus on patient centred care, the optional utilisation of home-based TB treatment support (HTS) provided by Community Care Workers (CCWs) remains low.

Methods: A cross-sectional study was used to assess the knowledge, attitudes and health practices of community members in Langa, Cape Town, towards TB management and CCWs, and explore associations with uptake of HTS. An adapted KAP questionnaire was administered by medical students to community members with current and previous TB (TB exposed) and no history of prior disease. Participants were recruited from the Langa Community Health Centre and during home visits.

Results: 31.4% of the total 172 participants expressed a preference for HTS delivered by CCWs, but initial knowledge about what CCWs were was low (49.4%). Respondents interviewed at home ($n = 99$) were more likely to prefer HTS ($PR=1.75$, $P = 0.02$) compared to clinic respondents. There were no significant associations between demographic and socio-economic factors, HIV, previous TB, or levels of knowledge about CCWs or TB, and choice of HTS versus clinic-based support (CTS). The majority of current TB patients preferred HTS (52.6%, $P = 0.034$). Main reasons for preferring CTS were self-sufficiency and being able to travel (21.5%) and the belief in better services (15.7%). HTS was favoured if too old or frail (14.0%) or due to convenience (11.1%). Barriers to HTS included perceived stigma associated with CCWs (5.2%) and a lack of confidentiality (4.7%). The TB exposed group ($n = 53$) had better knowledge about TB ($PR=1.5$; $P = 0.03$) and CCWs ($PR=1.4$; $P = 0.02$) and had a greater preference for CCWs to wear civilian clothes (43.4% vs. 20.5%, $P = 0.001$). 34.3% of all respondents felt people with TB were treated differently by the community.

Conclusions: Despite the high burden of TB, preference for HTS remains low. Increased uptake among current TB patients is encouraging. Generally low knowledge about CCWs suggests more resources should be focused on promoting the benefits of and trust in patient centred care delivered by this cadre of workers. High self-reported HIV co-infection rates (70.0%) support current

efforts to integrate TB-HIV services. Subgroup analyses point to the complex interplay between TB and HIV exposure and perceptions of stigma, which requires careful exploration to render community-based services more acceptable.

PC-1047-05 Community involvement role in MDR-TB treatment in Tajikistan

A Ismayilov,¹ A Trusov,² O Norov,¹ P. Tabarov,¹ M Sianozova,³ S Odinaeva¹ ¹Project HOPE, Dushanbe, Tajikistan; ²Project HOPE, Millwood, VA, USA; ³Project HOPE, Yerevan, Armenia. Fax: (+992) 227 3646. e-mail: aismayilov@projecthope.org

Background and challenges to implementation: Tajikistan is among the 27 high burden multidrug-resistant tuberculosis (MDR-TB) countries in the world. It has one of the highest estimated TB cases (all forms) 142 (range 70-239) per 100 000 population incident number in the WHO European Region. According to the latest drug resistance survey in 2011, the prevalence of MDR is 13% among new and 54% among previously treated TB cases (WHO report, 2013). It has been a challenge to optimally manage MDR-TB treatment in civilian population living in remote and impenetrable districts.

Intervention or response: Medical and lab records were retrospectively analyzed for interim treatment results of two groups of MDR-TB patients enrolled since the third quarter of 2013. One group of patients (99) has been receiving the standard treatment for all Tajikistan settings, while the second group (114) has been supported by social workers and volunteers.

Results and lessons learnt: As the patients from cohort have not yet completed MDR-TB treatment, analyses were based on six months culture conversion and default rates. Culture conversion at six months in the group with community involvement was almost two times higher than conversion of MDR-TB patients under standard treatment. Groups / Cohort (3q 2013 – 3q 2014) Culture conversion at six months Default (including transfer out) Negative Positive Not known (including died) Standard Treatment / 99 45 (45.5%) 14 (14.2%) 27 (27.3%) 13 (13.1 %) Community DOT support 88 (77.2%) 8 (7%) 10 (8.8%) 8 (7%) Moreover, under the community surveillance group, there were no defaults during this period and no cases without lab results.

Conclusions and key recommendations: Community involvement in DOT has greatly positively influenced both culture conversion and default rates. Community DOT is proving to be an essential tool in achieving MDR-TB treatment success. It can be assured by involving the Community, particularly social workers and volunteers into TB control at household levels. NTP in Tajikistan should seriously consider expanding this example throughout the country.

PC-1048-05 Adherence to TB treatment among patients on supervised treatment approach in Tororo District

L Kwagonza,¹ M Ediau,¹ G Okure,¹ D Tuhebwe,¹ D Okumu,² E Buregyeya¹ ¹Makerere University, Kampala, ²Tororo District, Tororo, Uganda. e-mail: kwagonzaleo@gmail.com

Background: Supervision of TB patients during the treatment course is widely advocated for and forms part of the World Health Organization's Directly Observed Therapy, (DOT) strategy. The supervised treatment is aimed to ensure adherence to drugs as prescribed as also reduces chances of TB drug resistance. The aim of this study was to assess the level and factors associated with adherence to TB treatment in patients enrolled for TB supervised treatment in Tororo District.

Design/Methods: A cross sectional study was conducted among 105 TB patients enrolled on supervised treatment approach. Descriptive statistics and logistic regressions were done to determine the level and factors associated with adherence to TB treatment. Adherence was defined as taking the medication at prescribed time.

Results: The mean age of the respondents was 44 years (SD 1.3) ranging from 18 to 80 years. Eighty three percent (83.0%; 84/105) of the respondents were found to be adherent to TB treatment in this study. Among the adherent respondents: 75.0% (63/84) were female, and 76.6% (64/84) had attained at least primary level of education. 81.8 % had chronic illnesses. In addition, out of the respondents who adhered to TB treatment; 81.8% (68/84) were HIV infected, many (93.2%) reported that they had disclosed their TB status to their partners and 71.6% reported having been supported by their family members, and 61.9% reported travelling a distance of more than 5km to Health facilities. Married clients were more likely to adhere to TB treatment AOR=5.6, 95%CI (1.68 –18.6). Much as the study participants were registered as supervised treatment clients, only 34.3% (36/105) reported to have been supervised during treatment. Those who had a treatment supporter as part of supervision were more likely to adhere to TB treatment as compared to those who were not supervised during the treatment course OR 5.01, 95%CI (1.051-24.009).

Conclusion: Adherence to TB treatment was moderate, but still below 100% target adherence. Being married and having a supervisor or treatment supporter were associated with good adherence to TB treatment. In order to improve on TB treatment outcomes, particular attention should be put on clients who are single, due to reduced opportunity of being reminded to take their medication. TB control programmes should ensure that TB clients receive appropriate supervision as suggested by the Direct Observed Therapy short strategy.

PC-1049-05 Implementation of tuberculosis directly observed treatment in Kampala, Uganda

H Sempeera,¹ E Buregyeya,¹ A Kawooya^{3,4} ¹Makerere University School of Public Health, Kampala, ²International Health Sciences University, Kampala, Uganda. e-mail: hassardsempira@gmail.com

Background: Due to increasing slum population and HIV/AIDS, Kampala city (KC) is now responsible for about 20% of the Uganda's tuberculosis (TB) burden. In 2012, KC reported an increase (29%) of patients on TB directly observed treatment (DOT). Though DOT enhances treatment adherence and completion, KC registered a treatment completion of 45% and a default rate of 17%. This study assessed the implementation of TB DOT in Kampala.

Design/Methods: A cross-sectional study of quantitative and qualitative data collection was carried out in 2014 in Rubaga division (RD). Rubaga was chosen because in 2012 it reported the highest (70%) proportion of patients on TB DOT. Data was collected from division KC health facilities. 201 new TB patients on treatment for less than 16 weeks were recruited. Questionnaire and key informant interview guide were used to collect data from patients and health workers respectively. Stata version 12 was used whereas qualitative data was analysed manually.

Results: 66% of patients reported being DOT. Majority (82%) of the treatment supporters were relative/family members. Lack of caretakers was the main reason for not being on TB DOT ($n = 44$, 77%). 26% of all patients missed doses for at least one week. Lack of transport to collect medication and stock outs were the main reason for missing doses. In the adjusted regression analysis being married and positive attitude towards TB DOT were significantly associated with being on TB DOT, adj.PRR=1.4(1.1-1.6), adj.PRR=2.4 (1.6-3.6). Lack of independent community-based treatment supporters was the main barrier to the implementation of TB DOT in RD.

Conclusion: Over half of the patients were on DOT. Treatment supporters are mainly family members. A quarter of all patients did not adhere on treatment. The division lacks independent community-based treatment observers to support the poor and those without caretakers.

PC-1050-05 Equitable delivery and outcomes of tuberculosis treatment and care in the North West of England: analysis of North West TB Cohort Audit data

P Macpherson,^{1,2,3} B Squire,² P Cleary,⁴ C Wake,² K Dee,⁴ M Woodhead^{5,6} D Sloan,² On Behalf of the North West TB Cohort² ¹University of Liverpool, Liverpool, ²Liverpool School of Tropical Medicine, Liverpool, ³Cheshire and Merseyside Public Health England, Liverpool, ⁴Public Health England Field Epidemiology Service North West, Liverpool, ⁵Central Manchester University Hospitals NHS Foundation Trust, Manchester, ⁶University of Manchester, Manchester, UK. e-mail: p.macpherson@liverpool.ac.uk

Background: Individuals with TB in the UK predominantly come from the most socioeconomically deprived groups. However, the extent to which deprivation affects access to care and TB outcomes is unknown.

Design/Methods: Since 2011, the North West TB Cohort Audit has undertaken quarterly review of treatment and care outcomes against consensus-defined standards for all individuals notified with TB in the north west of England; the first region of the UK to undertake cohort audit across such a large geographical footprint. Socio-economic deprivation groups were constructed using quintiles of individuals' Index of Multiple Deprivation (IMD) scores measured at lower super output area of residence. Logistic regression and Cox proportional hazard models investigated associations between socio-economic deprivation group and adverse TB care outcomes.

Results: 1831 individuals notified with TB between 2011 and 2014 were included in this analysis. 62% (1131/1831) came from the most deprived national quintile, and socioeconomic deprivation group was associated with younger age group ($P < 0.001$), non-UK born status ($P < 0.001$) and having any social risk factors ($P = 0.061$). In single variable analysis, greater socioeconomic deprivation was not significantly associated with adverse TB care outcomes, including delay between symptom onset and treatment initiation (hazard ratio for most deprived vs. least deprived group: 0.91, 95%CI: 0.71-1.17); completion of standardized risk assessment to identify complex needs (odds ratio [OR]: 0.66, 95%CI: 0.24-1.86); having at least 90% of close contacts assessed (OR: 2.86, 95%CI: 0.79-10.31); all child contacts being assessed (OR: 1.30, 95%CI: 0.29-5.76); being offered an HIV test (OR: 0.70, 95%CI: 0.33-1.45); or completing treatment within 1 year in fully-sensitive cases (OR: 0.66, 95%CI: 0.43-1.01). On multivariable analysis, there remained no significant associations between socioeconomic deprivation and adverse TB care outcomes.

Conclusion: Despite high levels of socioeconomic deprivation in this population, across a range of TB care standards, TB patients in the most deprived group had similar care to more affluent individuals, suggesting that access to, and delivery of TB care in the North West of England is equitable. The extent to which the cohort audit process contributes to, and sustains this standard of care deserves further study.

42. Inside the belly of the beast: TB in correctional settings

PC-1051-05 The impact of Xpert® MTB/RIF and WHO-reviewed case definition on the number of TB relapse cases registered in the Azerbaijan penitentiary system

E Gurbanova,¹ K Blondal,² R Mekhdiyev,¹ R Tahirli,³ F Huseynov,¹ N Kerimova,⁴ F Mirzayev,⁵ A Altraja⁶ ¹Main Medical Department of the Ministry of Justice, Baku, Azerbaijan; ²Department of Communicable Disease Prevention and Control, Reykjavik Health Care Services, Reykjavik, Iceland; ³Laboratory of the Specialized Treatment Institution for Detainees with Tuberculosis, Baku, ⁴Project Implementation Unit, Main Medical Department of the Ministry of Justice, Baku, Azerbaijan; ⁵Laboratories, Diagnostics & Drug Resistance Unit, World Health Organization, Geneva, Switzerland; ⁶Department of Pulmonary Medicine, University of Tartu, Tartu, Estonia. e-mail: e.gurbanova@prisonhealth.az

Background: The Main Medical Department of Azerbaijan Ministry of Justice implements an exemplary TB Control programme in the penitentiary system (PS) providing up-to-date diagnostics and effective treatment for inmates with both susceptible and drug-resistant TB in the Special Treatment Institution (STI). The STI also houses a modern quality-assured reference laboratory that performs all WHO-recommended diagnostics of TB. In 2013, Xpert MTB/RIF assay was introduced as a routine diagnostic algorithm in STI along with adopting the reporting system to the Reviewed WHO Case Definitions Framework.

Objectives: To assess the impact of introduction of Xpert MTB/RIF assay to the diagnostic algorithm of TB and the impact of the use of the reviewed WHO definition of TB cases on the number of registered relapse cases in Azerbaijan PS. Design and methods: A cohort of all new and previously treated cases with pulmonary and extra-pulmonary TB that started treatment with the first line (FLD) and second line drugs (SLD) in the PS of Azerbaijan during 01.01.2007–13.02.2015 was included. The cohort was divided into 2 groups: Group 1: cases enrolled during 01.01.2007–31.12.2012 and Group 2: cases enrolled during 01.01.2013–13.02.2015 (i.e. before and after the Introduction of Xpert MTB/RIF to the diagnostic algorithm of TB and use of the new WHO Case Definition Framework (Table). Logistic regression analysis was used to determine the association of registered relapse cases with the introduction of Xpert MTB/RIF and use of the new definition.

Results: In the Group 2, 31% (57) out of all 180 relapse cases were due to diagnosis with Xpert MTB/RIF only ($n = 27$) and new WHO case definition introduction ($n = 30$). Among patients diagnosed with Xpert MTB/RIF only, the average duration between the end of most recent treatment course and the recurrent episode was 31 months. The number of relapse cases significantly increased in the overall cohort: OR 1.5 (95%CI 1.2-1.8, $P < 0.001$) and in patients on treatment with FLD: OR 1.5 (95%CI 1.2-1.9, $P < 0.001$). There was no

significant increase of relapse cases among the patients treated with SLD.

Conclusions: Introduction of Xpert MTB/RIF to the diagnostic algorithm of TB and use of the new WHO Case Definition Framework significantly increase the number of TB cases registered as relapse in the Azerbaijan PS.

Table. TB cases registered in Azerbaijan penitentiary system during 01.01.2007-13.02.2015

	Group 1 N (%)	Group 2 N (%)	Total N (%)
Total TB cases	4527 (100.0)	952 (100.0)	5479 (100.0)
On FLD treatment	3973 (87.7)	735 (77.2)	4708 (85.9)
On SLD treatment	554 (12.3)	217 (22.8)	771 (14.1)
Total Relapse-cases	611 (13.5)	180 (18.9)	791 (14.4)
On FLD treatment	474 (10.5)	128 (13.4)	602 (10.9)
On SLD treatment	137 (3.0)	52 (5.5)	189 (3.5)
Proportion of Relapse cases identified by Xpert MTB/RIF only	0	27 (2.8)	27 (0.5)
On FLD treatment	0	25 (2.6)	25 (0.4)
On SLD treatment	0	2 (0.2)	2 (0.03)
Clinically confirmed	0	30 (3.2)	30 (0.6)
On FLD treatment	0	30 (3.2)	30 (0.6)
On SLD treatment	0	0	0

PC-1052-05 Tuberculosis control services in prisons: patient care and referral in Bangladesh

K Uddin,¹ M Siddiqui,¹ D-U Mesbah,¹ S Islam,¹ K Khatun,¹ A Islam,¹ F Khanam² ¹BRAC, Dhaka, ²National Tuberculosis Programme, Dhaka, Bangladesh. Fax: (+88) 02988 8026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: Prison inmates are one of the high risk groups to develop infectious diseases like tuberculosis. Infected prison inmates spread the disease to others very easily and rapidly. BRAC, besides its community based TB services, started to work with prison inmates in 2004 covering 7 prisons and gradually expands the program in 41 prisons by 2011 under the stewardship of National TB Control Program (NTP). Entry examination, symptomatic screening and diagnosis of all forms of TB cases is a challenges to combat the deadly disease in this difficult setting. The objective of the study is to identify the tuberculosis status among prisoners in BRAC supported areas.

Intervention or response: To identify TB presumptive in prison, BRAC staff goes to prison everyday where laboratory facilities are available and two or three times in a month where laboratory facilities are not available. Prison authority also informs BRAC staff when new inmate enters the prison with sign symptom of TB. Diagnosed TB case is registered and managed following NTP guideline. Treatment initiated by medical officer and DOT is ensured by prison pharmacist. BRAC staff follows up patients weekly or fortnightly. Patients are transferred to other DOTS center with necessary documents, if needed, to continue the treatment.

Results and lessons learnt: In 2013, a total 148 cases were diagnosed in 41 prisons. Among them, 68% were new smear positive, 16 % new smear negative, 11% new extra pulmonary and 5% retreatment cases. Treatment success rate was 87% which is a bit lower than other population. Transfer rate from prison to prison and to outside the prison was as high as 12%. In 2014, a total 180 patients were diagnosed. Among them, 67% new

smear positive, 12% new smear negative, 14% new extra pulmonary and 7% were retreatment cases. Screening procedure should be in placed at the time of entry of inmate into the prison. Difficulty in securing follow up of TB cases who are released/ transferred before completion of their treatment.

Conclusions and key recommendations: Early detection of TB among prison inmates is crucial to control TB transmission and to have favorable treatment outcome. High transfer out and unknown treatment outcome causes low success rate. So, strong external referral linkage is essential to strengthen activity in special situation.

PC-1053-05 Effectiveness of an entry screening programme in the penitentiary sector in Georgia

N Lomtadze,¹ Z Avaliani,¹ M Madzgharashvili,¹ U Nanava¹ ¹National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia. Fax: (+995) 322 911 941. e-mail: nlomtadze@gmail.com

Background: TB in prisons has been a public health problem in Georgia, which is one among high X/MDR-TB burden countries globally. During 2010-2012 the TB notification rates per 100 000 inmates in Georgian prisons was 30 times higher compared to civilian sector, overcrowding being the major contributor. Since 2011, the 'Entry Screening' of every prisoner is performed using a standardized questionnaire, followed by sputum smear microscopy for those considered to have presumptive TB. An operational research aiming at assessing the validity and overall yield of entry screening within penitentiary sector has been conducted.

Design/Methods: A retrospective analysis of completed 'entry screening' questionnaires merged with data for each screened inmate regarding TB diagnosis was performed. The validity analysis of the screening questionnaire by assessing sensitivity, specificity, PPV and NPV for assessment of presumptive TB case was performed. The three year and annual yields of TB cases were assessed as proportion of cases identified due to screening among all TB cases detected within the corresponding period of time in the Prison sector.

Results: Overall out of 32 152 performed entry screenings, 1559 (5%) were assessed as "presumptive" TB case and remaining 30 593 (95%) as non-presumptive TB case. Out of presumptive TB cases 102 (6.5%) were diagnosed to have TB, while in 1457 (93.5%) TB was not confirmed, neither bacteriologically or clinically. Out of screened non-presumptive cases TB was never detected among 30 192 (98.7%) and TB was detected in 401 (1.3%) cases by intervention other than screening, such as self reporting with symptoms. The overall odds of having TB diagnosis for those who screened positive on screening questionnaire is 5.2 times greater compared to odds of having TB among those who screened negative using questionnaire with strong statistical significance: OR=5.2; 95% Confidence Interval (CI)=4.19-6.57; Chi2 (Mantel-Haenszel) χ^2 value <0.0000001. The sensitivity and specificity of the screening questionnaire were 20%

and 95%, while PPV and NPV were 6.5% and 99% respectively. The yield of entry screening in detecting TB cases in prison in during the period of 2011-2013 was 5%.

Conclusion: 'Entry Screening' with questionnaire that scores the patients based on symptoms, BMI and past TB history, proves to have high specificity but, low sensitivity, thus making the tool very effective method to rule out TB. Also overall yield of TB cases due to entry screening was 5%, which is in line with screening performance data internationally and in the range to prove the cost effectiveness.

PC-1054-05 RNTCP in prisons: special ACSM inputs in jails saved lives of vulnerable inmates in Chhattisgarh State, India

G Mallick,¹ M R Aggarwal,² S Chadha¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²Directorate of Health Services Chhattisgarh, Raipur, India. e-mail: gmallick@theunion.org

Background and challenges to implementation: More than 9.8 million people are detained in penitentiary services around the world. TB in prisons is a major public health problem in many settings, particularly in India with high incidence. Concomitant conditions, particularly HIV infection, injecting drug use, poor nutritional status, overcrowding and inadequate or inaccessible medical care put inmates at risk of infection and rapid progression from latent TB infection to TB disease. The situation is worsened by the emergence and spread of MDR- and XDR-TB. Many hard-core criminals including Left-wing ultra prisoners have posed perennial problems where 16 199/6482 inmates (three times of the capacity) are housed in 28/30 different high security jails in Chhattisgarh which is the most vulnerable Naxal-infested state in India.

Intervention or response: The five incarnations that factors TB in the prisons "Prisons receive TB, Prisons concentrate TB, Prisons disseminate TB, Prisons make TB worse and Prisons export TB" were prioritised in all 28 jails where intensified ACSM activities were conducted. Educational sessions like talks, videos, flipcharts, various educational materials, contests, question-and-answer games were done during the year. Few inmates were engaged as peer educators and treatment supporters who identified presumptive TB suspects. Regular sputum collection/test camps, close monitoring of diagnosed cases and their treatment has added credibility to the program outcome. Two groups of medicines "first-line anti-TB drugs and second-line parenteral agent (injectable anti-TB drugs) kanamycin, amikacin, capreomycin" were used for TB and MDR cases respectively.

Results and lessons learnt: 92 extensive ACSM events for 16 199 prisoners and 735 prison staff were conducted in 28 jails of the state during 2014. 124 diagnosed TB patients (96 positives, 28 negatives) and 3 MDRs were put on treatment from sputum examination of 1348 presumptive TB suspects that added about 1% to the state's 154 868 sputum examined during the year.

Table Revised National TB Control Program outcomes in different jails in Chhattisgarh state for 2014

Sl.No.	Name of Jail	Ca- pac- ity	Under lock- up (as on Jan'15)	With DMC facil- ity	No. of sensi- tiza- tion mtgs. held	Spu- tum exam done	TB+ MDR* on Rx
1	Central Jail, Raipur	1190	2804	DMC	6	106	12+1*
2	District Jail, Dhamtari	90	144	A2DTC	3	42	4
3	District Jail, Mahasamund	70	246	A2DTC	5	37	4
4	Sub Jail, Baloda Bazar	70	240	A2DTC	4	20	4
5	Sub Jail, Gariyaband	50	80	A2DTC	2	18	3
6	Central Jail, Jagdalpur	639	1591	DMC	5	82	25+1*
7	District Jail, Kanker	65	361	A2DTC	3	32	3
8	District Jail, Dantewada	150	547	A2DTC	2	87	6
9	Sub Jail, Sukma	50	0	Non-functional			
10	Sub Jail, Narayanpur	50	0	Non-functional			
11	Central Jail, Bilaspur	1028	2925	DMC	4	96	14+1*
12	District Jail, Raigarh	225	575	A2DTC	4	77	5
13	District Jail, Korba	110	265	A2DTC	4	52	5
14	District Jail, Janjgir	70	179	A2DTC	4	49	4
15	Sub Jail, Pendra Road	50	92	A2DTC	2	15	0
16	Sub Jail, Katghora	50	172	A2DTC	2	41	2
17	Sub Jail, Sarangarh	50	55	A2DTC	2	32	2
18	Sub Jail, Sakti	100	174	A2DTC	2	51	2
19	Central Jail, Ambikapur	975	1933	A2DTC	4	59	7
20	District Jail, Baikuntpur	148	152	A2DTC	3	48	2
21	District Jail, Jashpur	230	400	A2DTC	3	62	2
22	Sub Jail, Ramanujganj	130	323	A2DTC	3	45	0
23	Sub Jail, Surajpur	90	222	A2DTC	3	38	2
24	Sub Jail, Manendragarh	50	134	A2DTC	2	35	1
25	Central Jail, Durg	396	1763	A2DTC	4	57	6
26	District Jail, Rajnandgaon	116	299	A2DTC	4	68	4
27	Sub Jail, Sanjari	70	129	A2DTC	3	22	0
28	Sub Jail, Balod	70	85	A2DTC	3	21	1
29	Sub Jail, Dongargarh	50	176	A2DTC	2	34	1
30	Sub Jail, Bemetara	50	133	A2DTC	4	22	3
	Sub Jail, Kawardha						
Total		6482	16199		92	1348	124 (96/28) +3

Source: State Prison Office, Raipur; Central Jail – 5, District Jail – 10, Sub Jail – 15, Non-functional Jail – 2

*3 MDR patients were diagnosed and put on treatment – one each from Raipur, Jagdalpur and Bilaspur Central Jails

TB = tuberculosis; MDR = multidrug-resistant; A2DTC = Attached to District/sub-District Tuberculosis Unit.

Conclusions and key recommendations: Special ACSM efforts addressed early diagnosis and adherence to medication for 127 TB patients. Measures to reduce overcrowding and improved living conditions, integrating prison and national TB control to ensure treatment completion in the incarcerated population need to be viewed critically. A complementary political commitment must be built to establish and sustain effective TB control strategies in prisons

PC-1055-05 Xpert® MTB/RIF improves yield of bacteriologically confirmed TB in correctional services in Mozambique

A Mondlane,¹ I Manhiça,¹ I Chirime,¹ C Mutaquiha,¹ K Alberto,¹ S Hassamo,¹ L Nhocuana,¹ H Hamene¹
¹Ministry of Health, Maputo, Mozambique. e-mail: angelnvm1@gmail.com

Background: Mozambique prevails as one of 22 high burden countries for TB, with 37% case detection rate. The National TB control program (NPTC) faces challenges in the timely identification of TB, due to HIV prevalence (11.5% in 2009) and access to health services. TB-HIV co-infection is high, at 52% in 2014. The challenges are magnified for correctional services inmates who often face overcrowding, understaffing (health), high turnover, and therefore, passive case finding and inadequate follow-up of cases. A study conducted in correctional services in 2013 using smear microscopy, revealed 1.5% smear positive TB point prevalence and 24% HIV prevalence. In 2014, 2% of the 13 000 correctional inmates in the system were smear-positive TB by routine symptom screening. Current screening programs in correctional facilities involves a quarterly general TB awareness talk with verbal invitations for symptomatic inmates to provide sputum that is tested by microscopy.

Design/Methods: To estimate the proportion of undetected bacteriologically confirmed TB cases by current screening strategy in correctional services; To evaluate the yield of GeneXpert over routine practice (smear microscopy); smpptoms based screening was conducted in 5 correctional facilities located in South, Center and North region of the country, namely, Maputo, Sofala, Tete, Zambézia and Nampula, from 23 March 2015 to 10 April 2015. Every correctional inmate was screened for cough, fever, weight loss, night sweats of at least one-week duration. Onsite sputum collection was undertaken after instructions. HIV testing was offered for inmates with presumptive TB. Patients on TB treatment were not screened. Samples were analyzed using Xpert/MTB/RIF. Yields from this intervention were compared to yields from routine passive first quarter 2015 data (21 December to 20 March), to determine the proportion of bacteriologically confirmed cases missed by current approaches. Smear microscopy may under-diagnose and over-diagnose TB when used in active case finding in Southern Africa.

Results: From 5279 inmates in correctional services, 4969 (96.9%), were screened for TB. From the consent-

ing participants, 18.6% (927) were symptomatic. From 927 symptomatic inmates, were Xpert positive (2.7%). 315 were HIV Positive. Routine TB screening and passive case detection with smear had detected 13 TB cases (36%) in first quarte.

Conclusion: Active case finding and xpert MTB/RIF increases case detection by 63%.

PC-1056-05 High yield of mass screening for TB in police detention cells in Namibia

N Ruswa,^{1,2} A Evard,³ K Amufufu,³ F Mavhunga,¹ S S Nghoshi,³ J Ndahapele³ ¹Ministry of Health and Social Services, Windhoek, ²KNCV Tuberculosis Foundation, Windhoek, ³Ministry of Health and Social Services, Opuwo, Namibia. Fax: (+264)61 252 740. e-mail: ncruswa@yahoo.com

Background and challenges to implementation: A third of the nine million global cases of TB in 2013 were missed by health systems. In 2013, Namibia reported about 10 610 cases of TB, and it is estimated that Namibia missed 34% of its cases. The burden of TB in prisons in Namibia is unknown, and there are no dedicated health services for inmates in police detention cells. People living in the congregated setting such as prisons and police detention cells are at an increased risk of being infected with TB because these settings have poor ventilation, are often over-crowded, and have no system for screening inmates. Inmates in police cells are incarcerated for between a few days to a few years while awaiting trial. We present the results of a mass screening exercise for TB performed in a small town (Opuwo) in Namibia in March 2015.

Intervention or response: We used an adapted symptomatic screening tool from the Namibian TB guidelines, focusing on five questions (cough, weight loss, night sweats, fever, swollen lymph nodes) to interview inmates in the police cells in Opuwo. Two sputum specimens (spot-morning) were collected from participants who reported any one of the 5 symptoms. The specimens were sent for testing with smear microscopy and molecular testing with Xpert MTB/RIF at the district laboratory.

Results and lessons learnt: All 50 (100%) inmates, and 43 (36%) police officers were screened. 39 (78%) of inmates reported symptoms of TB and all of them had sputum tested. 3 (8%) were found to have active TB by smear and/or Xpert. 17 (34%) inmates knew their HIV status, of which 2 (12%) were HIV positive. None of the inmates or police officers were on TB treatment at the time of screening, but 5 (10%) of inmates and (1) 2% of officers had been treated for TB before. No TB case was identified among the police officers.

Conclusions and key recommendations: The prevalence of bacteriologically positive active TB among the inmates in Opuwo police holding cell is 8%. This is very high, considering none of these inmates were on treatment or had presented to health facilities. We recommend establishment mass screening of inmates for TB in police holding cells at regular intervals in Namibia.

PC-1057-05 TB-HIV integration in Gauteng correctional facilities

E Zishiri,¹ G Lekubu,² A Makhubela,² L Page-Shipp,¹ S Charalambous,^{1,3} G Gresak,¹ V Chihota^{1,3} ¹The Aurum Institute, Johannesburg, ²Department of Correctional Services, Johannesburg, ³University of the Witwatersrand, Johannesburg, South Africa. e-mail: ezishiri@auruminstitute.org

Background: South African national policy recommends integrating TB and HIV service delivery to improve health outcomes for co-infected patients. The Department of Correctional Services has taken up this recommendation and assimilated the TB-HIV integration model in their health centres. We describe health outcomes among inmates started on TB treatment in four correctional centres in Gauteng.

Methods: We conducted a retrospective record review of routine TB programme data for inmates started on TB treatment between April 2013-June 2014 in Modderbee, Leeuwkop, Krugersdorp and Boksburg correctional centres, Gauteng, South Africa. We collected data on demographic characteristics, details of TB diagnosis (method of TB detection, episode type, site of disease), TB treatment start date, treatment outcome and HIV care and treatment (date of HIV test, CD4 count testing, ART and Cotrimoxazole start dates).

Results: 186 inmates were started on TB treatment across the four centres (median age 33 years, all male, 5.9% re-treatment cases). HIV Counselling and Testing (HCT) was offered to 182 (97.8%) inmates, there was no documentation for 4 cases. 48 (25.8%) were known HIV positive at time of diagnosis and 134 were offered HIV testing. 129/134 (96.3%) agreed to undergo HIV testing resulting in 81/129 (62.8%) testing HIV positive. Overall 129 (69%) TB cases were co-infected with HIV. 104/129 (80.6%) co-infected inmates had a CD4 count documented (median CD4 count 119 cells/ μ l [IQR 41-303 cells/ μ l]). Among 129 TB cases co-infected with HIV, 36 (27.9%) were initiated on ART prior to starting TB treatment, 51 (39.5%) after starting TB treatment and 32 (24.8%) were documented as not having been initiated on ART and 10 (7.8%) had no record of ART initiation. Among the 51 TB cases initiated on ART after starting TB treatment, 30 (58.8%) were initiated within two months of starting TB treatment. Among the 32 cases documented as not having initiated ART, 17 (53.1%) had either been released or transferred out.

Conclusion: There is evidence of TB and HIV integration in correctional centres. Of the inmates started on TB treatment a large proportion were offered HCT and there was good uptake of HIV testing. The levels of knowledge of HIV status and the proportion starting ART are similar to the general population. The importance of TB-HIV integration is reinforced by the high co-infection rate. ART initiation remains a challenge especially where inmates are either released or transferred out.

PC-1058-05 Systematic review of the epidemiology of and programmatic response to TB in prisons and inmates in South Africa

F K Mukinda,¹ H Mahomed^{1,2} ¹Stellenbosch University, Cape Town, ²Western Cape Government, Cape Town, South Africa. e-mail: liesl.nicol@gmail.com

Background: South Africa's total prison population of 156 370 offenders is the largest in Africa and ranks ninth in the world. The South African prison population rate, estimated from a national population of 53.1 million in August 2013, was 294 per 100 000. The occupancy level of correctional facilities based on the official capacity was 131.7%. South Africa's prisons are overcrowded and represent a high-risk environment for tuberculosis (TB) transmission. Overcrowding, insufficient or lack of proper ventilation, poor nutrition, limited access to clean water, lack of TB preventive measures and failure to supervise and ensure adherence to treatment are major contributing factors to the occurrence of TB in prisons, especially in Sub-Saharan Africa, where high rates of TB in prison populations are reported. With the aim of contributing to evidence-informed TB policy development in South Africa this systematic review collated all relevant research on the epidemiology of and programmatic response to TB in South African inmates and prisons.

Design/Methods: A comprehensive search for both published and unpublished research was conducted in April 2015. Based on specific inclusion criteria, research investigating TB incidence, prevalence, risk factors, prevention, treatment and care in South African inmates and prisons was included in this systematic review.

Results: Three studies met the inclusion criteria of this review. Two studies reported on TB prevalence and one study reported on HIV-related health outcomes of inmates accessing antiretroviral therapy (ART). There are no studies investigating the programmatic response to TB in prison inmates. There are no studies investigating the occurrence of TB in prison employees (one study included prison employees but did not provide outcome data for the employees).

Conclusion: Inadequate TB management in prison will not only reduce the rate of cure, but will also be a risk for the emergence of drug-resistant strains that may affect other prisoners, and be spread through prison staff, visitors and via former inmates to the community. In this way, TB in prison becomes a public health threat. It is important that we determine accurately what the rates of TB are in prison, what interventions are effective in reducing the risk of TB transmission in prison settings as well as effective programmatic response to TB in South African prisons.

PC-1059-05 Tuberculosis control among prison population: what is the best approach?

H Kanyerere,¹ L C Chisuwu,¹ A Dimba,¹ R Banda,¹ J Mpunga,¹ L Kanyenda,² H Banda,³ K Kamoto⁴ ¹Ministry of Health, National Tuberculosis Programme, Lilongwe, ²United States Agency for International Development TB CARE II Project, Lilongwe, ³Research for Equity and Community Health Trust, Lilongwe, ⁴Malawi Prison Health Services, Lilongwe, Malawi. Fax: (+1) 301 941 8427. e-mail: asmitharthur@urc-chs.com

Background: Infectious diseases like TB pose serious threats in Malawian prisons and the world at large; and present significant challenges for prison and public health authorities. Since 1995 Malawi National TB Programme (NTP) has been collaborating with Prison Health Services in order to improve TB control in Malawian Prisons.

Intervention: The Malawi NTP developed a policy for TB control in prisons in 2007 and had put in place TB surveillance mechanism in all prisons. However, TB case detection in prisons remains low. As part of World TB Day (2015) commemoration activities, the NTP decided to commemorate the day by conducting mass TB screening at Mzimba Prison (medium size prison). The screening process included a standardised questionnaire, chest X-rays for everybody and sputum submission for those with TB related symptoms and/or abnormal chest X-rays. TB screening was conducted within the prison premises from 21st to 24rd March 2015. Those eligible for sputum examination were requested to submit spot and morning sputum specimens. All sputum specimens were examined using fluorescent technique on iLED microscopy and GeneXpert machines. All *M. Tuberculosis* positives on GeneXpert, Rif resistant and indeterminate results were repeated in order to confirm the results. All microscopy positive were reread by the second and third technicians blindly to confirm the results.

Results: During the 4 days of screening, there were 611 prisoners and 85 members of staff. 608 prisoners (99.5%; 604 males and 4 females) and 29 members of staff (34%; 20 males and 9 females) were screened for TB. 192 prisoners were eligible for sputum examination and 172 (89%) submitted sputum. Of these 172 who submitted sputum, 22 were HIV positive, 114 were HIV negative and 36 had unknown HIV status. Microscopy was done on all the 172 prisoners who submitted sputum. 161 had both microscopy and GeneXpert done. 71 prisoners (41%) were bacteriologically diagnosed with TB (7 were sputum smear microscopy positive only; 59 were positive on GeneXpert alone and 5 were positive to both microscopy and GeneXpert). Out of those that were GeneXpert positive, 5 prisoners had rifampicin resistance.

Conclusions and recommendations: The TB notification rate at Mzimba prison is very high at (11 620/100 000 population). Mass TB screening on regular basis could arrest the spread of tuberculosis in Malawi prisons. More efforts need to be made to do a similar intervention in all the prisons in Malawi.

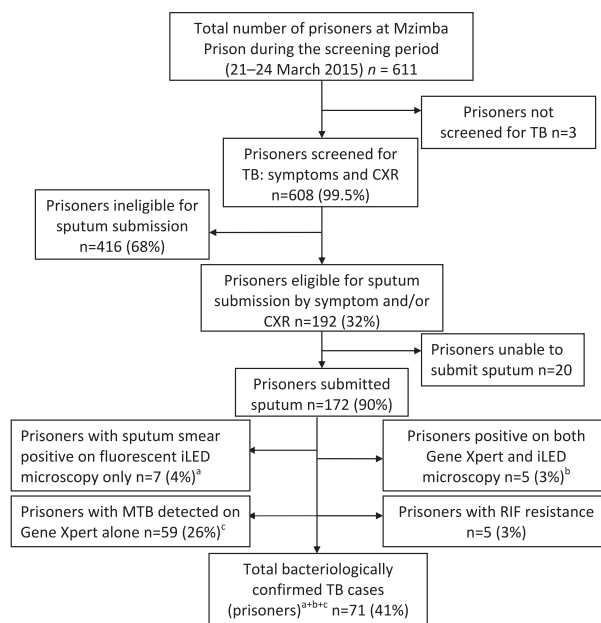


Figure TB screening at Mzimba Prison, Malawi-2015. CXR = chest X-ray; iLED = light emitting diode; RIF = rifampicin; MTB = *Mycobacterium tuberculosis*; TB = tuberculosis.

43. The urban-rural divide: different places, similar issues

PC-1060-05 Tuberculosis control in the state of São Paulo, Brazil: big cities and urban risk groups

V M Galesi,¹ V Souza Pinto,¹ S Fukasava,¹ N K Komatsu,¹ N Matsuda De Lima¹ ¹Tuberculosis Division, São Paulo State Health Secretary, São Paulo, SP, Brazil. Fax: (+55) 11 3082 2772. e-mail: veragalesi@uol.com.br

Background and challenges to implementation: Sao Paulo State is situated in the Southeast of Brazil with an estimated population of 44 million inhabitants in 2014 distributed in 645 cities. It was prioritized for this evaluation a big city with more than 1.2 million inhabitants and one megalopolis with more than 10 million inhabitants. In 2014 the state had about 19 000 TB new cases with an incidence rate (IR) of 37.4/100 000 inhabitants.

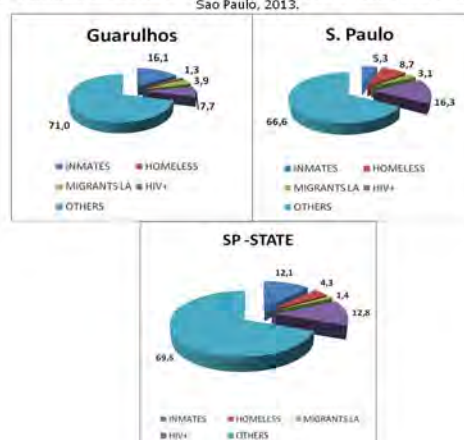
Intervention or response: Using data of TB Information System of Sao Paulo State (TBWEB) from Sao Paulo State, Sao Paulo municipality (SPO) and Guarulhos municipality (GRU) from 2006 to 2014 with the purpose to describe the disease occurrence and activities developed to TB control in the following risk groups: people living with HIV/Aids (PLWHA), inmates, homeless and Latin American immigrants.

Results and lessons learnt: In 2014 SPO and GRU discovered 5508 and 435 new TB cases with an IR of 46.3 and 33.2/100 000 inhabitants, respectively. Related to PLWHA were 1035 TB cases in SPO and 40 TB cases in GRU with 85.0% and 90.0%, respectively of HIV

testing. Related to inmates and homeless were 395 and 645 in SPO and 96 and 8 in GRU, respectively in 2013. On Figure 1 is shown the percentage of TB risk groups in the total of TB cases in each municipality. Concerning activities developed, in GRU was implanted the PAHO Project "TB in Great Cities" in the Health Districts of Pimentas and Jurema (2013) with the following activities: geoprocessing with mapping of community resources; DOTS training; Cultural & Health Fair for the Hispanic People aiming integration and matricial implantation of all TB and HIV cases referring to psychosocial care; awarding of health care facilities; implantation of rapid molecular test with 5379 done detecting 259 TB cases and 9 Rifampicin resistance. SPO works with the TB contingency actions for the cure project (PACTU) aiming the development of unique therapeutic project for the homeless with TB establishing intra and inter sector articulation intending social inclusion and develops activities according WHO recommendation in HIV polices. SPO done 14 143 molecular tests detecting 915 TB cases and 22 Rifampicin resistances.

Conclusions and key recommendations: TB control in great urban centers requires an ongoing evaluation process which includes analysis of active case finding and treatment cohort according risk groups, allowing to review strategies triggered from an initial situation analysis.

Figure 1 – Percentual distribution of TB risk groups in Sao Paulo Capital, Guarulhos and State of Sao Paulo, 2013.



PC-1061-05 Community interventions and patient-centered activities on the pacific coast of Colombia

B Gutierrez,¹ D Rodriguez,¹ N Gil,¹ E Varela,² A Palacios,³ M Rondón¹ ¹Organizacion Internacional para las Migraciones, Bogota, ²Instituto Departamental de Salud de Nariño, Pasto, ³Secretaria de Salud del Chocó, Quibdo, Colombia. e-mail: davidalejorod@yahoo.es

Background and challenges to implementation: The highest incidences are in dispersed rural populations, inaccessible, with high levels of Unmet Basic Needs. The 46 priority municipalities with a majority are African-descent and indigenous communities. In 2009, the

estimated incidence of TB in all forms is 131 per 100 000 population and the cohorts in 2008 were 70% successful treatment, 11% of default, 3% failures, 4% of deaths and 12% not evaluated. There were not infections

Control in Health Care Setting.
Intervention or response: Improve scope of bacteriological diagnosis and TB treatment under DOTS in the community, a network of Community Health Workers (CHW) is formed, on diagnosis, treatment and monitoring, initially with 25 CHW, who were monitored by 7 nurses who were moving between urban and rural, where the Program control TB had identified TB cases in previous years. CHW went where TB cases came Sputum Smear Frotis Positive SSF(+) with difficult geographical access. CHW identified respiratory symptomatic, taking sputum samples were extended and smear reading, report it to the health authorities and identify a community leader. We set up support networks for drugs supply with the help of the community, who also took part in the cases registration and supervision, which were also linked to the bacilloscopy carried out by CHW. Bacilloscopy was after confirmed by the network laboratories and the Public Health Laboratory. Patients residing in poverty belts surrounding urban areas also benefited from this project. The Infection Control Plan was implemented in healthcare institutions and was successful in 34 health centers in 34 out of the 46 municipalities. In 2013 recommendations for administrative, environmental and personal control measures were incorporated.

Results and lessons learnt: 53% of the cases were male, 34% from indigenous peoples, 54% African descendants, 9% had some degree of disability, 49% were householder who brings to the family income, 36% had steady work, the average income is 200 USD. 27% received state subsidies, 15% reported that he had forced displacement. A 94% success rate was reported in new sputum smear positive (+) cases within the DOTS strategy in the community in 2012.

Conclusions and key recommendations: The community-based DOTS contributed to increase success in treatment by 11%. In 46 municipalities the success rate reached 81%. In Chocó and Nariño success rates of 88% and 94% respectively were reported

PC-1062-05 TB literate villages: is this the way to garner politico-administrative support and empower marginal and vulnerable communities?

O Bera,¹ M Chandge,² S Kamble,³ S Nayak,¹ S Chadha,¹ B Pawar³ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²District TB Office, Mumbai, ³State TB Office, Pune, India. e-mail: oprakash@theunion.org

Background: With low TB knowledge in communities and sub-optimal political and administrative commitment followed by lack of proper integration with general health system case detection, adherence and treatment outcomes remains low. A multipronged advocacy,

communication and social mobilization approach is desirable but difficulties associated with planning and field level implementation remains a major hindrance to achieve desired awareness level and community ownership. The objective of the intervention study was to assess commitment and awareness level of tuberculosis and impact of ACSM intervention package amongst local leaders and community members of 25 villages in Latur district, Maharashtra.

Intervention: Latur district has a population of 2.6 million with more than 700 villages having Gram Panchayats constituted by elected people representatives and public servant. At the onset in Jan 2014, 5 low performing designated microscopy centres (DMC) were identified within a low performing tuberculosis unit Ausa with regards to case detection and treatment adherence. Mapping was done and 10 villages were finalised which were located more than 10 kilometres from DMCs. It was followed by interventions which lasted for around 5-7 days within a village which were conducted by trained community volunteers and communication materials from Project Axshya. At first, political representatives were sensitized on symptoms, diagnosis and treatment of TB followed by two to three community meetings at common areas within the village and at least one school children sensitization meeting. Also intensive house to house communication campaign was conducted followed by presumptive TB referral and symptomatic sputum collection and transport. Two oil paintings were painted at prime locations within the village and 10 running lines were painted throughout the village. Baseline KAP evaluations and end line evaluations was conducted after an observatory period of 6 months among new random batches of 500 villagers and 10 political representatives with semi structured, pre tested questionnaire in local language.

Results: A total of 8000 village members and 50 people representatives were sensitized on TB symptoms, diagnosis and treatment during the entire campaign within 25 villages. Of the 500 villagers interviewed, in the base line survey only 35.6% had heard of TB as compared to 88.4% at end of 6 months. Significant ($P < .05$) increase in knowledge was observed at end of 6 months in variables such as cough of two week as major symptom (90%), sputum testing as method of diagnosis (69.9%), spread of TB (55.9) high chance of acquiring TB in HIV patients (44.5%), contact examination (63%) free treatment at all government health facilities (92.1%), DOTS as preferred treatment (90%), TB is curable (95.2%). A positive change of attitude regarding decreased stigma associated with TB (20.1%), increased sharing of TB Status (23%) and increased acceptance of TB treatment at Government health facility and increased practice of covering face while coughing or sneezing (25.3%). Amongst 10 political leaders, there was significant increase in knowledge with regards to cough of two weeks as main symptom (72%), sputum testing (71%), free DOTS provision (79%), free treatment (83%) and TB is curable (92%). Also there was commitment of assured DOT provider within each village from the local leaders.

Conclusions: Political and administrative commitment remains one of the most important pillars for TB control. The study has brought into light the importance of decentralizing TB education and screening activities at village level. With the vision of reaching the unreached, TB literate villages has provided a common platform for roping in politicians, government officers and local people for the cause of TB control.

Table Comparative analysis of baseline, end line KAP survey among villagers.

Variables	Baseline KAP Study (Total=500) n (%)	End line KAP Study (Total=500) n (%)
Knowledge		
Heard of TB	178 (35.6)	442 (88.4)
*Cough of 2 weeks as symptom of TB	54 (30.3)	401 (90.7)
*TB spreads when a person having TB cough or sneezes	30 (17)	247 (55.9)
*Sputum testing as method of diagnosis	32 (30.4)	309 (69.9)
*HIV increases the chances of having TB	9 (5.1)	197 (44.5)
* Knowledge of TB contact examination	43 (24.2)	278 (63)
*DOTS as TB treatment	11 (6.2)	398 (90)
*TB treatment better in private health facility	124 (69.7)	227 (51.4)
*TB Treatment free in nearest government health facility.	101 (56.7)	407 (92.1)
Attitude		
* TB is curable	114 (64)	421 (95.2)
*TB creates stigma	102 (57.3)	89 (20.1)
*TB status sharing	39 (21.9)	102 (23.1)
Practice		
*Cover your face with cloth while coughing	27 (15.2)	112 (25.3)

*These questions are only for those 'who have heard of TB'

PC-1063-05 Training TB patients: a strategy for a better treatment adherence

G Martelli,¹ M Tadolini,¹ E Vanino,¹ P Viale,¹

G Lombardi,² S Ianniruberto,¹ P Dalmonte,²

A Gramegna¹ ¹Infectious Diseases Unit, S. Orsola-Malpighi University Hospital, Bologna, ²Microbiology Unit, S. Orsola-Malpighi University Hospital, Bologna, Italy. Fax: (+39) 0516 363 802. e-mail: giuliamartelli84@gmail.com

Tuberculosis (TB) remains a major public health concern predominantly affecting low and middle-income countries. However in high-income countries TB epidemiology is characterized by a low rate of transmission in native population and higher incidence in certain vulnerable groups, especially migrants. Therefore current public health strategies must address these targeted groups. The metropolitan area of Bologna, a city in northern Italy, is a low TB incidence setting, but has a high rate of immigration. The Infectious Diseases clinic of St.Orsola-Malpighi University Hospital notifies around 90 new TB patients per year and nearly 75% of them are foreign born. The majority is initially admitted and started on treatment and then followed-up at out-patient level. At the first post-discharge visit patients are

interviewed about compliance to treatment: several mistakes had been observed (i.e. wrong type or number of pills taken, wrong timing) especially among migrants, mostly due to language barriers or illiteracy. It must be noted that direct observed therapy (D.O.T.) is usually not implemented in western countries, except in very limited cases and treatment is self-administer at home. In addition, in Italy 4 drugs fixed-dose combination only is available posing challenges in all those cases where standard treatment cannot be utilized (due to side effects or resistance). From the beginning of 2014 we introduced an “educational project” involving both nurses and doctors aimed to improve the adherence to anti-TB treatment (ATT). During their stay in the ward, all TB patients started on treatment receive the boxes of oral drugs and a leaflet (see fig.1) outlining the time and the numbers of pills they must take. Every day the nurse instead of merely distributing the pills, asks the patients to self-administer the drugs under direct observation and corrects potential mistakes. Before being discharged patients need to demonstrate to be able to take the medication correctly and autonomously. At the post-discharge follow-up, adherence to treatment at home is verified with a standardized questionnaire. After one year of this experience we observed a reduction of proportion of patients making mistakes in taking ATT from 16.2% to 7.5%. Treatment adherence is critical to guarantee the control of TB. Simple tools like the example described might prevent lack of adherence and reduce onset of resistance, especially among vulnerable groups.

		h 8	h 16	h 20
Rifadin 600 mg			0	
Nicozid 200 mg			00	
Etapiam 400 mg		00		
Piraldina 500 mg		00		
Benadon		0		
Rimstar			00	
Benadon		0		

PC-1064-05 Effectiveness of innovative TB case finding strategies to reach the unreachable slum population in the urban areas in Nepal

S C Baral,¹ P Shrestha,¹ S Khanal,¹ S Kandel,¹ M Pandey,¹ B Lamichhane,² M Puri¹ ¹Health Research and Social Development Forum (HERD), Kathmandu, ²National Tuberculosis Centre, Bhaktapur, Nepal. Fax: (+977) 1 410 2016. e-mail: sushilbaral@hotmail.com

Background and challenges to implementation: Low case detection among poor and marginalised, particularly the urban poor is one of the primary strategic challenges faced by NTP. The urban poor comprise 25.2% of the total urban population of Nepal (UN, Habitat, 2005). Of the 25.2% of the urban poor, 60.7% population reside in slums and 7% is from marginalized group (Lumanti, 2001). The poor socio-economic conditions, health seeking behaviour and accessibility to health services of the urban poor make them vulnerable population for TB. **Intervention or response:** HERD under TB REACH implemented intensified case finding activities using GeneXpert MTB/RIF in 22 districts of Nepal. To reach the slum groups, door-to-door screening for cough more than 2 weeks was done by urban health volunteers. Identified presumptive TB patients were brought to mobile clinics or static clinic and were evaluated for TB following the NTP algorithm (annex). Sputum samples of those presumptive TB patients not visiting clinics were collected by volunteers during home visits and submitted in the clinics. Besides these, various awareness about mobile clinics were conducted in urban areas.

Results and lessons learnt: Over the period of one year, a total of 74 187 people were screened in the slum population of which 4982 (7%) were symptomatic. Out of those symptomatic 4016 (81%) were microscopy tested (using both Xpert and microscope). Of those tested microscopically 1509 (30%) were tested using gene expert (30%). In total, 277 (6%) were identified as positive cases. Inadequate participation in the screening camps, demand for direct benefits for attending the camps and unavailability of people at home for screening due to their working hours were some of the challenges faced during the screening process. Also, due to low awareness amongst the people in the slum, they neglected the symptoms of TB and were reluctant to give their sputum for testing

Conclusions and key recommendations: Mobilization of the urban health volunteers and door to door screening in the urban slums though comes with some challenges is an effective strategy to reach and improve early diagnosis of TB in the urban slum population.

PC-1065-05 Profile and determinants of unsuccessful tuberculosis outcome in rural Nigeria: implications for tuberculosis control

K Ukwaja,¹ S Oshi,² I Alobu,³ D Oshi² ¹Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, ²Centre for Development and Reproductive Health, Enugu, ³National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, Nigeria. e-mail: ukwajakingsley@yahoo.co.uk

Background: Rural residence can be a marker for poverty and, thus vulnerability to tuberculosis (TB). Previous studies demonstrate that rural TB patients often do not recognize TB symptoms. This has resulted in prolonged delays in seeking care for TB as well as inability to complete treatment once started. The aim of this study was to investigate the treatment outcomes of TB and the determinants of adverse outcomes in rural Nigeria.

Design/Methods: Adult rural TB patients treated during 2011 and 2012 in two healthcare facilities were retrospectively reviewed. Determinants of unsuccessful outcomes were analyzed using a multivariable logistic regression analysis.

Results: Of 1180 rural TB patients enrolled, 494 (41.9%) were females. The overall treatment success rate was 893 (75.7%), death, loss-to-follow-up, and treatment failure rates were 10.9%, 8.5%, and 1.5% respectively. Independent predictors for unsuccessful outcomes were; public (urban) facility-care (adjusted odds ratio [aOR] = 2.9), smear-negative TB (aOR 1.3) and extrapulmonary TB (aOR 2.7), HIV co-infection (aOR 2.1), and receiving the 8-month regimen (aOR 1.3).

Conclusion: Treatment success among rural TB patients in Nigeria is low and receiving care at an urban public facility, smear-negative or extrapulmonary TB, HIV co-infection, and receiving the eight-month regimen were predictors for unsuccessful outcomes. We recommend that: 1) urgent measures should be adopted to reduce loss-to-follow-up and deaths among TB patients especially TB-HIV patients, 2) there is need to further expand quality TB education, services and TB-HIV collaborative activities in rural Nigeria, 3) targeted interventions to reduce unsuccessful outcomes for patients in the high-risk groups should be implemented, and 4) further studies to identify additional determinants of outcomes including socioeconomic and clinical factors should be conducted; and the impact of socio-economic interventions on outcomes for rural TB patients assessed.

PC-1066-05 Improving outcomes in a remote, low-resource tuberculosis DOTS program, East New Britain Province, Papua New Guinea, 2012-2013

D Ulaia,^{1,2} M O'Reilly,² B Pavlin^{2,3} ¹Nonga Hospital, Nonga, ²Field Epidemiology Training Programme Papua New Guinea, Port Moresby, ³World Health Organization, Port Moresby, Papua New Guinea. e-mail: moreilly24@yahoo.com

Background and challenges to implementation: Papua New Guinea has the fourth highest TB prevalence in WHO's Western Pacific Region. Multi-drug resistant TB

(MDR-TB) is an emerging problem in PNG. Directly Observed Treatment Strategy (DOTS) was initiated in quarter four of 2011 at Nonga Hospital in East New Britain Province. Nonga is a remote, low resource setting. At the time of initial roll out of DOTS, many elements of the TB program, including contact tracing and data management, were chaotic. Early post-DOTS performance fell short of expectations: in 2012, cure rate was at 28%, defaulter rate was unknown, and only 49.8% of sputum specimens were processed by the laboratory within a week. New case detection identified only a fraction of the estimated number of new TB cases within the catchment area. We undertook a study to assess trends in TB program performance, designed an intervention, and reassessed performance in order to evaluate the intervention.

Intervention: Our interventions were designed in fall 2012, and implemented from the end of 2012 throughout 2013. Interventions included a local radio TB awareness campaign, training for health care workers on TB screening, and development of weekly rosters to facilitate case follow-ups and contact tracing. We identified strategic areas of the hospital to provide ongoing reminders to staff about TB program referrals and protocols. We trained TB program staff in patient documentation. We provided feedback to laboratory staff on sputum processing performance. The lab assigned one technician to our program.

Results and lessons learnt: In 2013, post-intervention, TB detection increased from 6 to 18 cases per quarter. The cure rate increased from 28.0% to 50.0%; successful sputum diagnosis improved from 49.8% to 98.0%; the mortality declined from 9.9% to 2.0%. The defaulter rate was unchanged: 52.0% to 50.0%. The radio campaign first aired during the second quarter of 2013 was replayed throughout the remainder of 2013.

Conclusions and key recommendations: Post interventions, TB cure rate, new case detections, and successful sputum diagnosis improved, although cure rate still lagged national target of 80%. Mortality rate declined. Defaulter rate remains unchanged, which is concerning given the emerging MDR-TB. Further work is required to understand and address the high defaulter rates and to confirm programmatic gains. Our next step is to assess MDR-TB prevalence in our setting.

PC-1067-05 Role of community-driven mobile clinics in the detection and management of smear-tositive tuberculosis in underserved areas in Sudan

A Ali¹ ¹Geisinger Medical Center, Danville, PA, USA. e-mail: abbaskhid@hotmail.com

Background and challenges to implementation: Res Sea State in Sudan is a marginalized state with extreme poverty and high prevalence of tuberculosis. The community participation to curtail TB in Sudan is limited
Intervention or response: This project is funded by Khider Ali Mustafa organization, a philanthropic organization established to mobilize local resources to

support TB patients and remove the associated stigma (www.khiderali.org). A truck is modified to work as a mobile clinic, equipped with a laboratory, a portable X-ray machine, a digitizer and DICOM software to utilize the new technology of tele-radiology (Fig 1 and 2). The objective is to have a free walk in mobile clinic with no direct or indirect fees. Red Sea State has ten districts. The first campaign covered Dordaib district.

Results and lessons learnt: Mobile walk in clinics were held in the eight villages of the district. A total of 364 patients were examined by the physician, 111 ZN smears were done and 33 chest x rays were done. All patients received free treatment. One patient turned out to be smear positive. The patient received free treatment and monthly supplies of flour, sugar, tea and cooking oil. The local medical assistant reports monthly to the organization about the patient's health.

Conclusions and key recommendations: The mobile clinic is able to bring the health service to the underserved TB patients at their homes and encouraged them to step forward without being stigmatized. The organization will continue to cover all the state districts without additional costs to the government or international community. All smear positive patients will receive treatment and will be incentivized by nutritional support.

44. Paediatric TB: MDR

PC-1068-05 Drug-resistant tuberculosis among extra-pulmonary samples in children at a national reference laboratory in India

A K Verma,¹ G Kumar,¹ J Arora,¹ R Singhal,¹ M Bhalla,¹ V Myneedu,¹ R Sarin¹ ¹National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India. e-mail: akv_680@yahoo.co.in

Background and challenges to implementation: Tuberculosis (TB) in children has been less discussed and extrapulmonary tuberculosis (EPTB) is rarely addressed in the public health literature as a childhood problem. In this study we aimed to estimate the drug resistant mycobacterial strains among EPTB samples in children at a tertiary care referral centre of India retrospectively.

Intervention or response: EPTB samples from 109 children (≤ 15 years) suspected of TB were received in the laboratory for culture and drug susceptibility testing (DST). Laboratory data was analysed retrospectively for a period from April 2012 to December 2014. Samples were processed and cultured in Mycobacterial Growth Indicator Tube (MGITTM). All identified positive cultures were subjected to DST against streptomycin; 1 μ g/ml, isoniazid 0.1 μ g/ml, rifampicin 1 μ g/ml and ethambutol; 1 μ g/ml as per manufacturers recommendations.

Results and lessons learnt: The distribution of various extrapulmonary samples was: pleural fluid (62; 56.88%), lymph-node aspirate (34; 31.19%), tracheal aspirate (5; 4.58%), synovial fluid (1; 0.91%), urine (6; 5.50%) and cerebrospinal fluid (1; 0.91%). The samples were categorised as failure (62), new cases (19), relapse

(15), follow up (07), defaulter (04), and chronic (02). The mean age of male child in this study was 11.28 ($\pm$ SD 3.63) and female child was 11.99 ($\pm$ SD 3.29). Of 109 cultures, 34 (31.19%) were positive for *Mycobacterium tuberculosis* complex, 72 (66.05%) were negative for mycobacterium, and 3 (2.75%) were non tuberculous mycobacterium. Drug sensitivity results showed that 7/109 (15.6%) strains were sensitive to all 1st line drug and 23 (21.11%) were multidrug resistant and (3/109) were monoresistant to isoniazid.

Conclusions and key recommendations: This study showed the stunningly high occurrence of EPTB in children being isolated at the referral centre. It may be a hidden contributory factor in the transmission of drug resistant strains and reason for partial effectiveness of tuberculosis control program especially in developing countries.

PC-1069-05 Drug resistant *Mycobacterium tuberculosis* among pulmonary samples from children at a reference hospital

J Arora,¹ A K Verma,¹ G Kumar,¹ M Bhalla,¹ R Singhal,¹ R Sarin,¹ V Myneedu¹ ¹National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India. e-mail: arojyoti@gmail.com

Background: 246 children who attended the outpatient department (OPD) during the study period of 2011-2013 and whose sputum sample was received at Department of Microbiology for liquid culture and DST were analyzed retrospectively.

Design/Methods: The mean age of the children included in the study was 12.94 years with majority of children, 213/246 (86.6%) in the age group of 11-15 years. There was high prevalence of disease in females (73.98%; P value ≤ 0.0001) with male to female sex-ratio 64/182 or 0.35. Samples received were processed by NaLC-NaOH method and cultured using MGIT 960 system (Middlebrook 7H9 broth-based Mycobacteria Growth Indicator Tubes; Becton Dickinson, Sparks, MD) in a BSL III laboratory. Drug susceptibility to four first line drugs was performed on 184 positive cultures by MGIT 960 liquid culture system at the following critical concentrations: rifampicin 1.0 μ g/ml, isoniazid 0.1 μ g/ml, streptomycin 1.0 μ g/ml, ethambutol 5.0 μ g/ml as per manufacturer's instructions. 54 MDR isolates were also subjected to DST for four second line drugs at the following critical concentrations: kanamycin 2.5 μ g /ml, amikacin 1.0 μ g /ml, capreomycin 2.5 μ g /ml, ofloxacin 2.0 μ g /ml.

Results: Ziehl Neelsen smear microscopy was positive for acid fast bacilli (AFB) in 155/264 (58.7%) whereas culture was positive for 193 (78.4%) samples. DST was conducted for 184 isolates of which 46 (25%) isolates were sensitive to all four first line drugs. 137 (74.4%) isolates were resistant to at least one drug and 116 (63%) were resistant to both isoniazid (H) and rifampicin (R); i.e. multidrug resistant [MDR]. Isolates of 54 MDR patients were also subjected to second line drugs as requested by clinicians. 16 (29.62%) were sensitive to all four drugs. 29 (53.7%) isolates were resistant to

ofloxacin alone. 3(5.55%) patients showed resistance to one of the aminoglycoside. 6 (11%) patients were resistant to both ofloxacin and all the aminoglycosides (XDR).

Conclusion: Since childhood tuberculosis is a measure of recent transmission of *M. tuberculosis* and an indicator of the effectiveness of TB control programmes, high rate of drug resistant tuberculosis in the present study is alarming. Large scale surveillance studies are needed to estimate the prevalence of drug resistance among children. Active tracing and screening of household contacts at high risk would allow children with disease to receive a diagnosis earlier.

PC-1070-05 Isoniazid monoresistance among culture-positive *Mycobacterium tuberculosis* from children aged 0–14 years in Pakistan: implications for preventive therapy

S Shakoar,¹ F Malik,¹ R Hasan¹ ¹Aga Khan University, Karachi, Pakistan. e-mail: sadia.shakoar@aku.edu

Background: In Pakistan, where annually 275 new cases of tuberculosis (TB) occur per 100 000 population, children are at high risk for infection. Isoniazid preventive therapy (IPT) is recommended by the national childhood TB guidelines to arrest progression of latent to active TB. However, children infected with isoniazid (INH)-resistant TB may fail IPT. We present INH monoresistance rates among *Mycobacterium tuberculosis* (*M. tuberculosis*) isolates cultured from children 0–14 years, during 2003–2012 in Pakistan.

Design/Methods: Data from the Aga Khan University (AKU) laboratory was retrieved and analysed in MS Excel. The AKU mycobacteriology laboratory is a technical partner of Pakistan National TB Program and part of the WHO Supra-national Laboratory Network for tuberculosis. We receive samples from all over Pakistan through over 200 collection units. Duplicates in the data were removed and resistance rates and proportions were calculated. χ^2 values for trends were calculated with the EpiTools software (epitools.ausvet.com.au).

Results: From 2003 to 2012, 2841 cultures were received from children aged between 0–14 years. Of these, 27% ($n = 767$) were culture-positive for *M. tuberculosis*. INH monoresistance was found in 42.9% ($n = 329$) of these *M. tuberculosis* strains. Of INH monoresistant *M. tuberculosis*, 88.8% ($n = 292$) strains were pulmonary while 11.2% ($n = 37$) were extrapulmonary. Analysis of trends in isoniazid monoresistance among all *M. tuberculosis* isolates from children demonstrated a significant upward linear trend ($\chi^2 = 5.7911$; $P = 0.016$) from 2003 to 2012. Analysis of trends in INH monoresistance among extrapulmonary isolates also demonstrated an increase in resistance ($\chi^2 = 14.4742$; $P = 0.0001$); however, trends showed a non-significant downward slope for pulmonary isolates ($\chi^2 = 0.0022$; $P = 0.96$). Figure 1 shows proportions and regression lines from 2003 to 2012 for INH resistance among pulmonary, extrapulmonary and total pediatric isolates.

Conclusion: The proportion of INH resistance among children is increasing. However, year-to-year variation in proportions may indicate underutilization of laboratory services to diagnose tuberculosis among children and therefore may be an underestimation of true population proportions. High INH resistance demonstrates the need to explore performance of alternative regimens to treat latent TB infection among children in high burden settings.

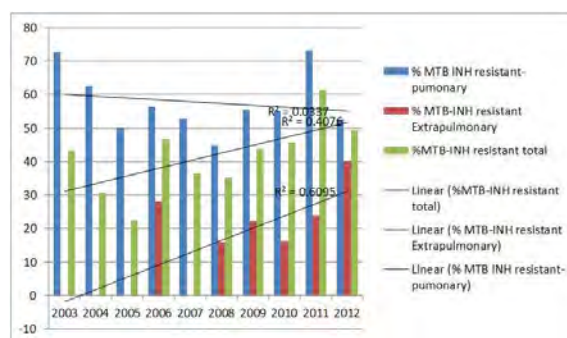


Figure: Proportion of isoniazid (INH) resistant isolates among MTB isolated from children 0–14 years in Pakistan, 2003–2012.

PC-1071-05 To treat or not to treat? Outcomes of an observation programme for children with a DR-TB diagnosis not started on treatment in South Africa

M Loveday,¹ V B Sunkari,² G Osburn,² I Master,² J Brust³
¹South African Medical Research Council, Cape Town, ²King Dinuzulu Hospital, Durban, South Africa; ³Montefiore Medical Center & Albert Einstein College of Medicine, New York, NY, USA. Fax: (+27) 865 126 019. e-mail: marian.loveday@mrc.ac.za

Background: KwaZulu-Natal South Africa has a high burden of drug-resistant TB (DR-TB). Children diagnosed with DR-TB are referred to the specialist DR-TB hospital in the province for treatment initiation. A number of children referred to this hospital with a laboratory diagnosis of DR-TB are clinically well, but because DR-TB therapy causes frequent and serious adverse events, some children are not started on treatment but enrolled in an observation programme. The decision to defer therapy is based on several criteria: chest X-ray, HIV status, body mass index (BMI), contacts, previous history of TB and clinical signs and symptoms of TB. We reviewed the outcome of children enrolled in this programme after 2 year of follow-up.

Methods: Between January and December 2011, 43 children diagnosed with DR-TB were enrolled in the observation programme. We reviewed medical records for baseline demographic and medical characteristics including HIV status and previous TB history. We also collected clinical data from the 2 year follow-up period including results of sputum culture and drug susceptibility testing, weight, signs and symptoms of TB and details of DR-TB treatment if it was commenced.

Results: Of the 43 children enrolled in our study, the median age was 3 years (IQR 1.5, 6.5) and 17 (40%) were female (Table). Twenty-nine (68%) of the children had MDR-TB; 9 (21%) mono-resistant TB of whom 7 (16%) were rifampicin resistant only; 1 (2%) pre-XDR-TB and 4 (9%) XDR-TB. Of the entry criteria for the observation programme, all children (100%) had a clear chest X-ray and were asymptomatic, 83% were HIV negative and 7% had a close contact with MDR-TB (Table). The median length of time in the observation programme was 549 days (IQR 159, 622). At the final evaluation, 34 (80%) of the children were well, 7(16%) had been lost to follow up, 1 child (2%) had started DR-TB treatment and 1 child had died of causes unrelated to TB.

Conclusions: This exploratory study showed that 80% of the children enrolled in the observation programme did not need DR-TB treatment, as they were well at the end of the observation programme. We are currently exploring reasons as to why these children did not need treatment including whether contamination in the laboratory or transient secretion had a role. In addition we are refining the selection criteria for entry into the programme.

Table: Baseline demographic and clinical characteristics of children included in study

Characteristic	Number (%) N=43
Female	17 (40)
Median age (years), (IQR)	3 (1.5 – 6.5)
Weight <3 rd percentile for age (malnutrition)	9 (21)
TB history	
Presently on TB treatment	18 (42)
Negative chest radiograph	15 (35)
Contact history: Close MDR-TB source case	43 (100)
Pulmonary/Sputum positive MDR-TB	3 (7)
Extrapulmonary positive MDR-TB culture	42 (98)
HIV and ART status	1 (2)
HIV-infected, n/total tested (%)	
HIV unknown	7/41 (17)
On ART, n/total HIV-infected (%)	2 (5)
Drug-resistance profile	4/7 (57)
Mono-resistant TB	
MDR-TB	9 (21)
Pre-XDR-TB*	29 (68)
XDR-TB**	1 (2)
	4 (9)

* Pre-XDR-TB: MDR-TB with resistance to either the fluoroquinolone or the injectable agent.

**XDR-TB: MDR-TB with resistance to both the fluoroquinolone and the injectable agent.

PC-1072-05 Children treated for drug-tuberculosis in academic hospitals differ from those treated in the provincial referral hospital, Gauteng Province, South Africa

M Van Der Walt,¹ J Lancaster,¹ N Ndjeka,² L Erasmus,³ S Masuku,¹ R Odendaal¹ ¹Medical Research Council, Cape Town, ²South Africa National Department of Health, Pretoria, ³National Health Laboratory Services, Pretoria, South Africa. Fax: (+27) 866 193 784. e-mail: karen.shean@gmail.com

Background: Children with drug-resistant tuberculosis (DR-TB) in South Africa should be referred to specialized DR-TB hospitals for treatment. However, not all DR TB hospitals have facilities to accommodate babies or very young children, and little is known about the epidemiology and treatment of them elsewhere. In Gauteng the DR hospital only admit children >2 years, while it is known that some children are treated in

academic hospitals. The purpose of this investigation is to compare a cohort of children and adolescents treated in the DR-TB hospital with those treated in academic hospitals to inform practices for inclusion of all children in surveillance systems.

Design/Methods: Retrospective record review of children and adolescents enrolled for DR-TB treatment from 2005-2010 at the specialized DR hospital with those treated in an academic hospital. Data sources were individual patient files, site-specific and provincial registers. Demographic, treatment, clinical and drug-resistant variables were collected. Patients included in the project had a culture-confirmed diagnosis of drug-resistant tuberculosis and received treatment with second-line drugs between 2005 and 2010.

Results: Of 320 children, 53% were treated in academic hospitals, 65% of children with a known HIV status were infected. Children treated in the academic hospital were significantly younger (range 0.5-7.3) compared to the DR hospital's (4.5-14.4), and had worse outcomes among which more had unknown outcomes. Signs and symptoms differed significantly between the two groups. Diagnosis of DR TB takes place at primary health care level, but we could not determine why some children were referred to the provincial DR hospital and others to the academic hospital.

Conclusion: the epidemiology, response to treatment and clinical presentation of children treated outside of the national DR hospital network differ significantly from those included in the network. Provinces should seek mechanisms to integrate surveillance and treatment with all facilities treating children, and have dedicated facilities for treating children not suitable for DR hospitals.

PC-1073-05 Presentation and outcome of children with culture-confirmed isoniazid-resistant, rifampicin-susceptible tuberculosis

A Garcia-Prats,¹ L Du Plessis,¹ W Burger,² H R Draper,¹ J Seddon,³ K Zimri,¹ A Hesselings,¹ H S Schaaf¹ ¹Desmond Tutu TB Centre, Stellenbosch University, Tygerberg, ²Brewelskloof Hospital, Western Cape Department of Health, Worcester, South Africa; ³Imperial College London, London, UK. e-mail: garciaprats@sun.ac.za

Background: Isoniazid (INH)-resistant/rifampicin (RIF)-susceptible (HRRS) tuberculosis (TB) is the most common form of drug-resistant TB. However, the clinical presentation, treatment regimens and outcomes are poorly described in children. Children with HRRS-TB may be at risk of poor outcomes, given frequent use of a 3-drug intensive phase (INH, RIF, pyrazinamide [PZA]), which may be inadequate. Based on limited evidence, current guidelines suggest adding a fluoroquinolone in cases of severe disease.

Design/Methods: A retrospective cohort study of children <14 years of age with culture-confirmed HRRS-TB was conducted at 3 hospitals in the Western Cape, South Africa from 2006-2012. Baseline demographic and clinical characteristics were extracted from medical

records; treatment and outcomes are described where available.

Results: 72 children were included (median age 4.1 years; range 0.1–14.2); 42% were male. 12 (17%) were HIV-infected; 7 (10%) had unknown HIV-status. Only 44 (61%) had a documented TB source case; of the 21 source cases with available drug susceptibility test results, 10 had HRRS-TB, 7 had multidrug-resistant TB, and the rest had other resistance patterns. 15 children (21%) had previous TB episodes; outcomes from previous episodes included 4 treatment failures and 2 lost to follow-up (LTFU). Thirty-four (47%) children had pulmonary TB (PTB) only, 26 (36%) had extrapulmonary TB (EPTB) only, and 12 (17%) had both PTB and EPTB. 54 (75%) children had severe TB using a standard classification. 46 children had information on treatment regimen and outcome; 41 (89%) had successful outcome while 2 were LTFU, 1 died, 1 failed treatment and acquired RIF resistance, and 1 transferred care. The median treatment duration was 11.5 months (IQR 9.0–13.0); 13 received INH/RIF/PZA for >1 month including the child with acquired RIF resistance, while 39 received a fluoroquinolone for the majority of their treatment.

Conclusions: Few children with HRRS-TB had documented exposure to a confirmed HRRS-TB source case, highlighting the importance of bacteriological confirmation in children. Treatment outcomes were good despite a high proportion with severe disease, possibly related to prolonged treatment regimens and frequent inclusion of a fluoroquinolone. The impact of HRRS-TB in children deserves additional investigation, especially as the increasingly utilized Xpert MTB/RIF tests for RIF resistance only. Optimal regimens need to be formally evaluated in children.

PC-1074-05 Assessment of treatment practices for pediatric drug-resistant tuberculosis in three provinces of South Africa

S Smith,¹ L Erasmus,² B Moore,¹ M Van Der Walt,³ R Odendaal,³ N Ismail,^{2,4} N Ndjeka,⁵ S Morris¹ ¹US Centers for Disease Control and Prevention, Atlanta, GA, USA; ²National Health Laboratory Service, Johannesburg, ³South African Medical Research Council, Pretoria, ⁴University of Pretoria, Pretoria, ⁵South Africa National Department of Health, Pretoria, South Africa. Fax: (+1) 404 718 8308. e-mail: uyi7@cdc.gov

Background: The aim of this study was to assess effectiveness of key drug groups and regimens used to treat pediatric drug-resistant tuberculosis (DR TB).

Design/Methods: This was a secondary analysis of a retrospective cohort study of children (<13 years) and adolescents (13–17 years) diagnosed with and treated for DR TB, 2005–2008, at DR TB hospitals in three South African provinces¹. A drug was defined as effective if drug susceptibility test (DST) results did not show resistance to the drug. Considering cross resistance, a drug was defined as effective if DST results did not show resistance to any drug in the drug group. Resistance patterns and treatment outcomes have been previously

defined^{1,2}. Multivariate logistic regression was used to estimate odds ratios (aOR) and 95% confidence intervals (CI) of treatment success adjusting for age, sex, province, HIV status, and weight category.

Results: Of 399 eligible children and adolescents, patients' median age was 11 years (interquartile range 6–15), 46% were male, 49% were HIV-positive, and 51% were underweight. Of 363 patients with DST results, 83% had MDR, 9% had XDR, 5% had pre-XDR and 4% had other DR TB. Of 359 with a treatment outcome, 77% of patients were successfully treated while 23% had poor outcomes (death or treatment failure). In multivariate analysis, patients receiving 4–5 effective drugs (aOR=7.6; 95%CI 3.4–17.3) and those receiving 6–8 effective drugs (aOR=8.6; 95%CI 3.3–22.2) had greater odds of treatment success than those receiving 1–3 effective drugs. However, treatment outcomes for those receiving 6–8 effective drugs was not statistically different from 4–5 effective drugs. Those receiving an effective second-line injectable and those receiving an effective fluoroquinolone had 6.4-fold (95%CI 2.2–18.4) and 4.4-fold (95%CI 1.3–14.9) increased odds of treatment success, respectively. Considering cross resistance, those receiving an effective second-line injectable and those receiving an effective fluoroquinolone had greater odds of treatment success (aOR=8.9; 95%CI 3.4–23.1 and aOR=11.4; 95%CI 3.9–32.9, respectively).

Conclusion: Children with DR TB who received an effective second-line injectable, effective fluoroquinolone, or ≥4 effective drugs had greater odds of treatment success. Susceptibility to first- and second-line drugs should be determined quickly for children with DR TB in order to develop a regimen containing ≥4 effective drugs.

References

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Table Effective treatment and treatment outcomes of pediatric DR TB in three provinces of South Africa

Effective treatment	Treatment success vs. death/failure n/N	aOR* (95%CI)
Each additional effective drug	351	1.69 (1.33–2.14)
1–3 effective drugs	49/351	1.0 reference
4–5 effective drugs	196/351	7.64 (3.37–17.31)
6–8 effective drugs	106/351	8.58 (3.32–22.17)
Effective SLI	281/302	6.37 (2.21–18.36)
Effective SLI (excluding potential cross-resistance)	269/302	8.90 (3.43–23.11)
Effective FQ	303/320	4.35 (1.27–14.93)
Effective FQ (excluding potential cross-resistance)	293/320	11.35 (3.92–32.87)

*Multivariate models contained age, sex, HIV status, province, and disease severity.

SLI = second-line injectable; FQ = fluoroquinolone aOR = adjusted odds ratio.

PC-1075-05 Predictors of unfavorable outcomes among children and adolescents with drug-resistant tuberculosis in three provinces in South Africa

D Burton,¹ M Pinto,¹ M Van Der Walt,² S Smith,¹ L Erasmus,³ B Moore¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²South African Medical Research Council, Cape Town, ³National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa. e-mail: dburton@cdc.gov

Background: There is a high burden of drug-resistant tuberculosis (DR-TB) among children (<13 years) and adolescents (13 to <18 years) in some settings in South Africa, with potential for high morbidity and mortality. Identifying predictors of unfavorable outcomes among pediatric patients with DR-TB may lead to opportunities to improve patient care.

Design/Methods: We conducted a retrospective review of medical records at designated multidrug-resistant (MDR) TB treatment facilities and identified 487 children and adolescents treated for any form of DR-TB in three provinces in South Africa from 2005-2008. Data were abstracted on demographics, clinical presentation, treatment course and outcomes. Completion of DR-TB treatment or documented cure were considered favorable outcomes, whereas death or documented treatment failure were considered unfavorable outcomes. Characteristics independently associated with unfavorable outcomes of DR-TB treatment were examined using multivariate logistic regression modeling, controlling for province and calendar year. Patients with unknown outcomes (n = 96) were analyzed separately as an alternative category of unfavorable outcomes.

Results: Of 361 children and adolescents with DR-TB for whom treatment outcome was known, 277 (76.7%) had favorable outcomes and 84 (23.3%) had unfavorable outcomes, including 80 deaths. In multivariable analysis, factors associated with increased odds of an unfavorable outcome included male gender (adjusted odds ratio [aOR] 4.0, 95% confidence interval [CI] 1.8-8.9), HIV infection (aOR 3.8, 95%CI 1.3-10.7), being severely underweight (aOR 6.5, 95%CI 2.7-15.8), and having extensively drug-resistant TB (aOR 10.5, 95%CI 3.4-32.5) compared to MDR TB. Presenting complaints associated with increased odds of an unfavorable outcome were non-specific constitutional symptoms (aOR 5.9, 95%CI 2.2-16.2), neurologic symptoms (aOR 5.2, 95%CI 1.1-24.5), and cough (aOR 4.0, 95%CI 1.6-9.6). Children aged 8 to 12 years had lower odds of an unfavorable outcome (aOR 0.25, 95%CI 0.1-0.7) compared to adolescents aged 13-17 years. Only drug resistance was significantly associated with unknown outcome (aOR 5.1, 95%CI 1.9-13.6 for mono- or poly-resistance compared to MDR).

Conclusion: A large proportion of children and adolescents treated for DR-TB in our study sites in South Africa had unfavorable outcomes. Close monitoring should be provided for pediatric DR-TB patients at increased risk of unfavorable outcomes.

PC-1076-05 Treating children for drug-resistant tuberculosis in Tajikistan with Group 5 medications

A Swaminathan,¹ J Seddon,² P Du Cros,³ S Quinnell,¹ O Bobokhojev,⁴ K West,³ Z Dusmatova,⁴ J Achar³ ¹Médecins Sans Frontières, Dushanbe, Tajikistan; ²Imperial College, London, ³Médecins Sans Frontières, London, UK; ⁴National Tuberculosis Programme, Ministry of Health and Social Protection, Dushanbe, Tajikistan. e-mail: philipp.ducros@london.msf.org

Background: Treatment of drug-resistant tuberculosis (DR-TB) in children is challenging. Besides limited treatment options, the side-effect profile of many drugs, in particular the group-5 anti-TB drugs (like linezolid, clofazimine, amoxicillin/clavulanate and clarithromycin), are not fully known when used for a long term in children for pre extensively drug resistant (pre-XDR) and extensively drug resistant (XDR) tuberculosis. MSF runs a comprehensive paediatric tuberculosis programme in Tajikistan in coordination with the Ministry of Health (MoH) that since 2011 has enrolled and treated 45 DR-TB patients, including children and their household contacts.

Design/Methods: We conducted a retrospective review of eight children with multidrug resistant (MDR) TB and resistance to one fluoroquinolone or at least one injectable (pre-XDR TB); or XDRTB (MDR+resistance to one fluoroquinolone and ≥ 1 injectable) who were treated between October 2012 and January 2015 with ≥ 1 of the four group 5 drugs available in the programme: linezolid (Lzd), amoxicillin-clavulanate (Amox/Clav), clofazimine (Cfz) and clarithromycin (Clr); in addition to first and second-line drugs. We examined interim outcomes (sputum conversion; or good clinical response in case of extrapulmonary TB at 6 months), final outcomes (if attained) and adverse effects.

Results: One child was cured, six achieved favorable interim outcomes and one died due to extensive disease not responding to treatment. Adverse effects attributable to Lzd occurred in one child warranting stoppage of the drug; there were no significant adverse effects of the other group 5 drugs.

Conclusion: Our early results suggest that group 5 anti-TB drugs, when used appropriately, are safe and may be effective for pre-XDR and XDRTB in children. With proper monitoring and aggressive management of adverse effects, the safety profile of these drugs might be acceptable, even in long-term use; however, current evidence remains limited. Choice of a drug depends on availability in the country, paediatric-friendly formulations, efficacy, safety, co-morbidities, drug-drug interactions and facilities for monitoring adverse events. With the advent of new anti-TB drugs there is a need for increased evidence and guidelines regarding appropriate selection and careful use of these drugs in children.

45. Paediatric TB: training, BCG and pharmacokinetics

PC-1077-05 Capacity building program for doctors and health care workers increased the child TB case detection rate in Bangladesh

S Ahmed,¹ A L Kabir,² R Amin,³ A Mollah,^{3,4} M Shahidullah,⁵ A H Khan⁶ ¹Shaheed Suhrawardy Medical College, Dhaka, ²Sir Salimullah Medical College, Dhaka, ³Dhaka Shishu Hospital, Dhaka, ⁴Dhaka Medical College, Dhaka, ⁵Bangabandhu Sheikh Mujib Medical University, Dhaka, ⁶Director General Health Services, Dhaka, Bangladesh. e-mail: shakildr@gmail.com

Background and Challenges: Diagnosing child TB is a challenge in 22 HBCs including Bangladesh. WHO estimates the case detection rate should be 6-10% of total TB cases. Recent publication shows it 4-22%. In Bangladesh, case detection was 3.1% in 2011, 2.85% in 2012 and it was 2.74% in 2013. One of the important reasons is lack of clinical skills of doctors and awareness of health care workers on child TB. To build capacity of these stakeholders (adults are difficult learner), no andragogy training modules were available. We planned to build capacity of doctors and Health Care Workers (HCW) of Dhaka Division (population 47 428 421) of 122 sub-district district hospitals, 17 district and medical colleges in 2013-2014.

Intervention: To develop capacity among these groups of stakeholder, we developed generic interactive training modules, training video, flip chart and other training aids on Child TB. By using these tools, a capacity building program was conducted between November 2013 and July 2014. This was done with support from USAID under NTP-Bangladesh with Bangladesh Pediatric Association as technical & implementing partner. After the training, data were collected on child TB from NTP source on cases up to 31st December 2014. Data of 2014 were compared with 2010 to 2013 of Dhaka division and other divisions.

Results and lessons learnt: After development of 39 facilitators, 1181 doctors and 8345 HCW have been trained. Pre- and post-test analysis showed significant ($P < 0.001$) improvement of knowledge of the participant irrespective of age, qualification and portfolio of doctors. Trend of case detection of Dhaka division showed significant increase in Dhaka division: 2010- 1849 (3.26%), 2011-2119 (3.74%), 2012- 2187 (3.60%), 2013- 2299 (3.84%) and 2014-2881(4.33%). Age aggregated data shows increase in cases between 0-4 years increased by 156% (456/291) between 2014/2013, while it was 116% (291/251) between 2013/2012 while it was 121% and 104% between 5-15 yrs. No significant increase was noticed in 6 other divisions of Bangladesh except Chittagong Division.

Conclusions: The generic training modules made a significant change of knowledge across age, qualification and portfolio of doctors. Since no other intervention was undertaken during this period in Dhaka Division, it can be assumed that the increase in the case detection rate was due to this capacity development program. This can

be implemented in other divisions of Bangladesh and probably in other HBCs.

PC-1078-05 Assessment of risk and benefit of BCG vaccine program in Taiwan

Y-J Shih,¹ H-H Lin¹ ¹National Taiwan University, Taipei, Taiwan. e-mail: diana820111@gmail.com

Background: Recent active surveillance revealed a high incidence of Bacille Calmette-Guerin (BCG) associated osteomyelitis (2-9 per 100 000 per year) in Taiwan. On the other hand, the incidence of tuberculosis (TB) meningitis and miliary TB among those under five was low (0.1-0.2 per 100 000 per year) under the continued decline of TB incidence nationwide. We assessed the risk (increase of under five TB meningitis and miliary TB) and benefit (decrease of BCG-related osteomyelitis) of stopping BCG vaccination in Taiwan.

Methods: We obtained the incidence rates of TB and BCG-related osteomyelitis under five years old from the notification system and active surveillance program of Taiwan CDC. Assuming BCG can prevent 80% of under five TB meningitis and miliary TB, we projected the (counterfactual) incidence of TB meningitis and miliary TB if the vaccine program was stopped completely. We further estimated the incidence of TB meningitis and miliary TB at the county level by assuming a constant ratio between incidence of all TB and incidence of under five TB meningitis and miliary TB across all counties. We then projected the (counterfactual) incidence of TB meningitis and miliary TB if the vaccine program was stopped in low risk counties (those with all-age TB incidence <50 per 100 000).

Results: For the 2008 birth cohort, if BCG had been stopped completely, the five-year cumulative incidence of TB meningitis and miliary TB would have increased from 0.5 to 2.7 per 100 000, while the incidence of TB osteomyelitis would have decreased from 5.9 to 0 per 100 000. The number needed to vaccine to prevent one case of TB meningitis or miliary TB was 46 892, and the number needed to harm to cause one case of BCG-osteomyelitis was 17052. If BCG had been removed only from low risk counties, the five-year incidence of TB meningitis and miliary TB would have increased from 0.5 to 1.6 per 100 000, while the incidence of TB osteomyelitis would have decreased from 5.9 to 2.0 per 100 000. The number needed to vaccine to prevent one case of TB meningitis or miliary TB was 34273.

Conclusion: The decision to continue or discontinue BCG vaccination should consider and balance the benefit and risk of BCG vaccine.

PC-1079-05 The use of ethionamide and prothionamide in childhood tuberculosis

S Thee,^{1,2} A Garcia-Prats,² P Donald,² A Hesselings,² H S Schaaf² ¹Charité, Universitätsmedizin, Berlin, Germany; ²Desmond Tutu TB Centre, Stellenbosch University, Cape Town, South Africa. e-mail: stephanie.thee@charite.de

Background: Ethionamide (ETH) and prothionamide (PTH) are important components of treatment regimens

for multidrug-resistant tuberculosis (MDR-TB) and disseminated forms of drug-susceptible (DS)-TB, however there is limited specific guidance for their use in children. In order to inform treatment recommendations for ETH and PTH, and to highlight knowledge gaps for priority research in children, we performed a scoping review to assess the existing evidence for ETH and PTH use in the treatment of paediatric TB, with a focus on pharmacokinetic (PK) and safety data.

Table Literature review on ethionamide adverse events in children with tuberculosis

Study	TB disease	Number	Dose	Adverse effects
De Voogd, 1963	PTB LN-TB	59	ETH 10-30mg p.o./rectally	No severe hepatotoxicity
Freour 1965	PTB LN-TB	30	ETH 15 (12-35mg/kg) rectally	In 3 (10%) children mild GI-intolerance
Guimard, 1966	PTB LN-TB	107	ETH 20mg/kg p.o.	In 7 (6.5%) children ETH stopped: skin reaction and fever (n=1), severe GI-intolerance (n=6)
Donald, 1987	TBM	56	ETH 20mg/kg p.o.	46 (82%) children had grade 1 or 2, and 3 (5.3%) grade 3 elevated liver enzymes
Thee 2011	MDR-TB	137	ETH 15-20mg/kg	79/137 (58%) children with abnormal thyroid function tests; higher risk in HIV-infected children and concomitant treatment with PAS; 18 (7.5%) children received thyroxine supplementation
Seddon 2014	MDR-TB	137	ETH 15-20mg/kg	Thyroxine supplementation in 32 (23.4%) children based on elevated thyroid-stimulating hormone and low free thyroxine levels
Van Toorn, 2014	TBM	184	ETH 20mg/kg p.o.	8 (5.6%) children with grade 3 hepatotoxicity, following interruption and normalisation of liver enzymes original regimen was restarted without recurrence

PTB= pulmonary tuberculosis, LN-TB= lymph node TB, TBM= tuberculous TB, MDR-TB= multi-drug resistant TB

GI= gastrointestinal

Methods: We searched PubMed for English, French, Spanish, Italian and German language articles, without

date restriction. Abstracts were reviewed and full text articles retrieved for studies with relevant information. The reference lists of identified articles were searched for additional relevant reports.

Results: We included information from 113 articles. ETH and PTH have significant activity against *Mycobacterium tuberculosis*, including a bactericidal effect at higher doses, and prevent drug resistance in companion drugs in clinical studies. The mode of action and mechanisms underlying ETH/PTH resistance show that combination of high-dose isoniazid and ETH provides at least one active drug for most MDR-TB strains. We identified 6 studies of ETH PK in adults and 2 in children. There were 2 studies of PTH in adults, and no studies in children. In children, ETH at doses of 15-20mg/kg achieves maximum serum concentrations found in adults following oral doses associated with good outcome in MDR-TB treatment and in disseminated DS-TB. Information on optimal pharmacodynamic targets is lacking. The effect of crushing/breaking ETH/PTH tablets has not been assessed, despite a lack of child-friendly formulations. Seven studies reported on ETH adverse effects in children (Table), which commonly included dose dependent gastrointestinal disturbances, mild liver enzymes elevations (5-20% of children), and hypothyroidism during long-term therapy (>40% of children). These are rarely life-threatening and seldom necessitate cessation of ETH therapy. Data on PTH safety in children is limited.

Conclusions: The existing limited data suggests the recommended dose of ETH is adequate, however additional data on PK and pharmacodynamic targets and on safety in children are needed to inform paediatric TB treatment.

PC-1080-05 Isoniazid hair concentrations in children with tuberculosis

V Mave,^{1,2} A Kinikar,¹ N Gupte,^{1,2} A Kagal,¹ H Horng,³ G Ramachandran,⁴ K Dooley,² A Gupta^{1,2}

¹Byramjee-Jeejeebhoy Medical College Clinical Trials Unit, Pune, India; ²Johns Hopkins School of Medicine, Baltimore, MD; ³University of California, San Francisco, CA, USA;

⁴National Institute of Research in Tuberculosis, Chennai, India. e-mail: vidyamave@gmail.com

Background: Measurement of adherence and adequate exposure to drugs for tuberculosis (TB) are difficult among children. We propose an innovative non-invasive therapeutic drug monitoring (TDM) tool among children with TB by measuring anti-TB treatment (ATT) drug concentration of isoniazid (INH) in hair samples that estimates an average level of drug exposure over weeks to months.

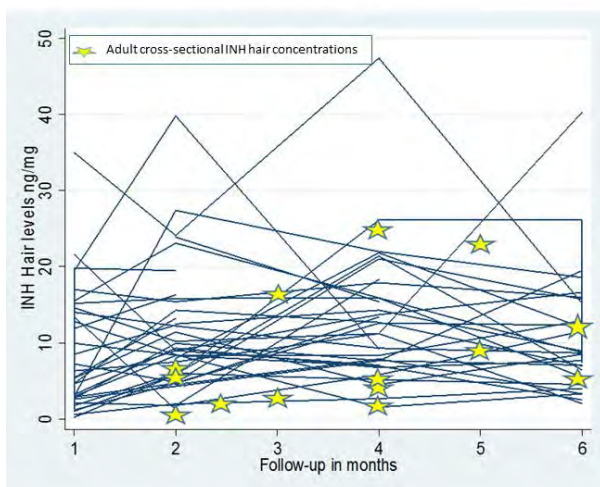
Design/Methods: We prospectively enrolled HIV-infected and uninfected children <12 years of age initiated on thrice weekly ATT drugs including INH at 10mg/kg for 6 months for a new diagnosis of TB. INH hair concentration was measured using liquid chromatography-tandem mass spectrometry at 1, 2, 4 and 6 months of ATT. The median (interquartile range (IQR)) isoniazid (INH) levels in hair was calculated for months on ATT and for children, <2 years, 2-<5 years, 5-12years. Univariate

and multivariate random effects models were constructed to assess the difference in INH levels over months on ATT, sex, and age groups.

Results: Of 38 children enrolled, the median age was 5.3 (IQR, 2–7.5) years; 18 (47%) were female, 3 (12%) had HIV co-infection and 14 (48%) had pulmonary TB. All caregivers reported >95% adherence to ATT. The overall median INH concentration was 8.9 (5.15–15.20) ng/mg in hair and showed higher concentrations for females at month 1 ($P = 0.03$), a trend for higher levels at 4 months on ATT ($P = 0.08$), and a trend for lower concentrations in 2–<5 years age group ($p = 0.05$) (Table). Figure represents intra-individual INH hair concentrations among children (spaghetti lines) and comparisons to cross-sectional adult hair levels (stars). The multivariate random effects model adjusted for age, sex and type of TB showed that INH levels at month 4 were significantly higher compared to other months ($P = 0.002$).

Conclusion: INH drug concentrations in hair can be measured in children on ATT and the concentrations tend to increase over time. The average concentration and variability of INH concentration in hair in highly-adherent children getting thrice-weekly ATT is now established. Therefore measurement of INH hair concentrations may be an innovative TDM tool to assess drug exposure to ATT.

Isoniazid (INH) hair concentrations (spaghetti lines) among children <12 years of age on anti-TB treatment (ATT)



PC-1081-05 Pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol in South African infants at revised WHO-recommended dosing guidelines

A Bekker,¹ H S Schaaf,¹ H R Draper,¹ L Van Der Laan,¹ S Murray,² L Wiesner,³ H McIlleron,³ A Hesselings¹

¹Stellenbosch University, Cape Town, South Africa; ²Global Alliance for TB Drug Development, New York, NY, USA;

³University of Cape Town, Cape Town, South Africa. e-mail: adrie@sun.ac.za

Background: The World Health Organization (WHO) recommended higher dosing of first-line TB drugs in

2009. Limited pharmacokinetic (PK) data are available for rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) in infants (< 12 months) who have high TB-related morbidity and mortality, and developmental changes that may influence drug disposition.

Objectives: To determine the PK of RMP, INH, PZA +/- EMB at doses of 10 (10-15), 15 (10-20), 35 (30-40), and 20 (15-25) mg/kg/day, respectively in infants, and to describe the related effects of age, weight, prematurity and ethnicity. Liver toxicity was assessed.

Methods: Intensive PK sampling was conducted in infants routinely initiating first-line TB therapy (fixed dose combination tablets) in Cape Town, March 2014 - March 2015. Samples were collected at baseline (0 hours), 1, 2, 4, 6 and 8 hours following dosing. Regulatory approved single TB drug formulations were used on day of PK sampling, including two RMP formulations.

Results: Thirty-nine infants (26 male; 29 black) were included and sampled, 14 (36%) with culture-confirmed TB. Fifteen (38%) infants were premature (< 37 weeks); 5 (13%) were HIV-infected. The mean corrected age was 6.6 months (SD; 3.3), and mean weight 6.45 kilograms (SD; 1.67). All 39 were receiving RMP, INH and PZA; 16 (41%) were also on EMB. The median maximum drug concentration in serum (C_{max}) for RMP, INH, PZA and EMB were 2.17, 8.08, 40.4 and 1.35 $\mu\text{g/ml}$; concentration-time curve (AUC_{0-8}) 9.36, 23.35, 217.21 and 5.61 $\mu\text{g}\cdot\text{h/ml}$; and half-life ($t_{1/2}$) 1.84, 1.87, 7.59 and 3.04 hours, respectively. C_{max} and AUC_{0-8} differed for two RMP formulations used. RMP was associated with a short time to C_{max} (T_{max}) and $t_{1/2}$ in African infants, and delayed absorption was noted in HIV-infected infants. No significant differences due to age, weight, prematurity or ethnicity were observed for INH, PZA or EMB. Alanine aminotransferase (ALT) values were abnormal in 2 infants (one 7 x and the other 2 x elevated) at PK sampling, which normalized without intervention.

Conclusions: WHO-recommended dosing resulted in very low RMP exposures in infants, even if dosed at 15 mg/kg/day. PZA and INH concentrations compared well to proposed adult target concentrations. EMB exposure was lower than suggested adult target concentrations, but equivalent to other paediatric studies. The low RMP concentrations in infants require further investigation, especially with consideration of future treatment shortening trials in children.

PC-1082-05 Impact of drug-resistant tuberculosis on the education outcomes of school children in the Northern Cape, South Africa

P Pholoholo¹ ¹Department of Health, Kimberley, South Africa. Fax: (+27) 538 300 655. e-mail: phyllisb018@gmail.com

Background and challenges to implementation: Drug Resistant TB (DR-TB) has been declared a threat to the gains made globally in the control and management of TB. The number of DR-TB patients in the Northern Cape

(NC) has increased three-fold between 2004 and 2014 and school children are reported to be among these cases. There is uncertainty on access to education support to school children diagnosed with DR-TB and the impact of the DR-TB on their education outcomes.

Intervention or response: This is a retrospective, quantitative and partly qualitative study of children diagnosed with DR-TB in the NC Province between 2012- 2014, aged 7-18 years and attending school at time of diagnosis. Existing files and EDRWeb data were used to extract age, sex and treatment outcomes. The children were followed to determine whether any education support was received during treatment period, whether they returned to school during or after treatment and if they completed the school grade they were enrolled at the time of diagnosis.

Results and lessons learnt: Twenty five (25) children were diagnosed with DR-TB during 2012 - 2014. Three (3) children were in primary school aged 7-12 years and 20 were in high school aged 13-18 years at the time of diagnosis. Three (3) children died and 2 were lost to follow-up. Smear positive sick children were unable to attend school for up to 6 months. Only children (28.5%) who received education support in any form passed their grades at the end of the year. School peers played a significant role in sharing learning material. More than 70% of the children who returned to school during the same year had poor end of the year results. A high proportion (83.3%) of children who were in the last two years of schooling (grade 11 and 12) at the time of diagnosis did not complete their high school education. DR-TB diagnosis, prolonged treatment and poor education support are strongly associated with poor education outcomes of school children.

Conclusions and key recommendations: Education support to school children diagnosed with DR-TB is important in ensuring good education outcomes. Peers, parents and teachers can play a meaningful role in supporting the infected children during treatment and integrating them into the school system once they are declared non- infectious. Education of children can contribute toward breaking the cycle of poverty associated with high TB prevalence rate.

PC-1083-05 Treatment outcomes and tolerability of the revised WHO anti-tuberculosis drug dosages among children living in high HIV prevalence settings

M Nansumba,¹ E Kumbakumba,² P Orikiriza,¹ Y Boum,^{1,2} N Kyomugasho,¹ D Nansera,² J Kiwanuka,² M Bonnet^{1,3} ¹Epicentre Mbarara Research Centre, Mbarara, ²Mbarara University of Science and Technology, Mbarara, Uganda; ³IRD L'Unité Mixte Internationale 233 Recherches Translationnelles sur le VIH et les Maladies Infectieuses, Institut Nationale de la Santé et Recherche Médicale, Montpellier, France. e-mail: margaret.nansumba@epicentre.msf.org

Background: In 2010, WHO revised the dosages of anti-tuberculosis drugs for children increasing rifampicin to 15mg/kg, isoniazid to 10mg/kg and pyrazinamide to

35mg/kg. We assessed the treatment outcomes and safety, particularly liver toxicity of children treated with the new recommendations.

Design/Methods: Tuberculosis (TB) child suspects (1 month to 14 years) attending Mbarara Regional Referral Hospital, with confirmed TB microbiologically, or probable TB based on clinical and/or radiological grounds, were treated with the new recommended dosages. There was monitoring of alanine aminotransferase (ALT) at weeks 2, 4 and 8 of treatment. TB relapse was monitored for after 6 months of treatment.

Results: Between April 2012 and January 2014, out of the 396 TB suspects enrolled, 144 (36.4%) were started on treatment. Of these, 18 (12.5%) were TB confirmed microbiologically and 126 (87.5%) were probable TB. They were categorized by age as follows; 64 (44.4%), 42 (29.2%), 23 (16.0%) and 15 (10.4%) for <2, 2-4, 5-10, and > 10 years respectively. 48 (33.3%) were HIV positive and 48 (32.6%) were moderately to severely malnourished (weight for height Z score). Treatment outcomes at 24 weeks were 116 (80.5%) treatment success, 3 (2.1%) failures, 4(2.8%) defaulters, 19 (13.2%) deaths and 1(0.7%) transferred-out. There was no TB relapse. Among deaths, 10 (52.6%) were severely malnourished and 9 (47.4%) were HIV infected. Median time to death was 10 days (IQR 10-40). Thirty (20.1%) children had serious adverse events including 1 grade 3 increased of ALT (5xULN) at week 8 which resolved. Median (IQR) ALT values at baseline, weeks 2, 4 and 8 of treatment were 24.5 (16-39), 26 (18-38), 28.5 (21-40) and 27 (19-38) UI/L respectively.

Conclusion: Despite increase in pill burden due the increased of the dosage of anti-tuberculosis drugs, the new TB recommended drug dosages did not result in high proportion of defaulters and treatment was well tolerated. More than 80% of children achieved treatment success. However, the high proportion of deaths, especially among malnourished and HIV TB co-infected children are a serious concern. It highlights the importance of early and better management of comorbidities in children with Tuberculosis in high HIV prevalence settings.

PC-1084-05 A theory-informed approach to identifying barriers to use of guidelines for diagnosis of childhood tuberculosis in health centers in Kampala, Uganda

A Katamba,¹ J Ggita,² I Ayakaka,² P Turimumahoro,² F Mugabe,³ M Sekadde,³ L Davis,⁴ A Cattamanchi⁵ ¹Makerere University College of Health Sciences, Kampala, ²Makerere University-University of California Research Collaboration, Kampala, ³National Tuberculosis and Leprosy Control Program, Kampala, Uganda; ⁴Yale School of Public Health, New Haven, CT, ⁵Curry International Tuberculosis Center, San Francisco, CA, USA. e-mail: akatamba@yahoo.com

Background: Tuberculosis (TB) in children remains under-diagnosed in high burden countries. We conducted a mixed methods study at primary health centers in Uganda to 1) Evaluate the number and proportion of

pediatric TB diagnoses and 2) Evaluate barriers to implementation of evidence-based guidelines (Union Desk Guide) for pediatric TB evaluation.

Design/Methods: The study took place at 5 public, primary health centers in Kampala, Uganda. We abstracted data from TB laboratory and treatment registers to ascertain the number of childhood and total number of TB cases identified in 2013 and 2014. We then conducted a qualitative study informed by the Behavior Change Wheel, a synthesis of 19 behavior change frameworks, to elicit health center staff perspectives on barriers to implementation of childhood TB diagnosis guidelines. Thematic analysis of de-identified focus group discussion (FGD) and interview transcripts was performed to identify barriers related to capability, opportunity and motivation.

Results: In 2013 and 2014, 3.7% (27/739) and 3.0% (47/1545), respectively, of all new smear-positive TB cases were among children <15 years. The 56 health workers who participated in 4 FGDs and 16 in-depth interviews included 10 medical officers, 18 clinical officers, 21 nursing officers, 1 laboratory technologist, 4 counselors and 2 community health workers. Barriers were primarily in the following theoretical domains: 1) Psychological capability: lack of awareness of clinical algorithms for childhood TB diagnosis; 2) Physical opportunity: lack of tests/equipment, high staff workload, lack of visual aids on childhood TB diagnosis; and 3) Reflective motivation: beliefs that clinically diagnosing TB should be done by a specialist and TB medications could make children suffer. Because of these factors, clinicians consider TB mainly in children with prolonged cough, and refer most children who cannot produce sputum to the National Referral Hospital.

Conclusion: TB in children is under-diagnosed at primary health centers in Uganda. In addition to education and training, our findings indicate that successful Desk Guide implementation will require additional interventions that use communication to stimulate action (persuasion); create an expectation of reward or cost; make more resources available for childhood TB diagnosis; model positive examples of desired childhood TB evaluation practices and outcomes; and/or utilize technology or other means to reduce workload (enablement).

PC-1085-05 Four-SNP NAT2 genotyping panel identifies slow but not rapid isoniazid metabolizer phenotype in Ghanaian children with tuberculosis

X Tang,¹ A Dompheh,² J Zhou,^{1,3} A Topletz,¹ E Ahwireng,^{2,4} S Antwi,^{2,4} M Court,⁵ A Kwara^{1,6} ¹Brown University, Providence, RI, USA; ²Komfo Anokye Teaching Hospital, Kumasi, Ghana; ³Hunan Normal University, Changsha, China; ⁴Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; ⁵Washington State University, Pullman, WA; ⁶The Miriam Hospital, Providence, RI, USA. e-mail: xiaoli_tang@brown.edu

Background: Isoniazid is primarily metabolized by hepatic N-acetyltransferase type 2 (NAT-2) and polymorphisms in the NAT2 gene influences isoniazid

pharmacokinetics (PK). The 4-SNP NAT2 genotype panel infers acetylator phenotype with high accuracy experimentally. This study examined the relationship between the 4-SNP NAT2 acetylator predicted phenotype status and isoniazid PK in Ghanaian children on anti-TB treatment.

Design/Methods: PK samples were collected at times 0, 1, 2, 4, and 8 hours post-dosing in children with TB on standard first-line antituberculosis therapy for at least 4 weeks. Drug concentrations were determined by validated methods and PK parameters calculated using non-compartmental analysis. Genotyping for NAT2 SNPs rs1801279 (191G>A), rs1801280 (341T>C), rs1799930 (590G>A) and rs1799931 (857G>A) was performed using validated TaqMan® real-time PCR assays. Samples homozygous wild-type for all SNPs were classified as rapid, those heterozygous for any one of the SNPs were classified intermediate, and those homozygous variant for one or more SNPs or heterozygous for two or more SNPs were classified slow acetylator genotypes. One-way ANOVA on ranks was used to compare PK parameters between the three genotypic groups. Where significant ($P < 0.05$), post hoc multiple pairwise comparison analysis was performed to identify groups that were significantly different from each other. **Results:** Of 59 patients with PK and genotype data available, 5 (8.5%) had rapid, 28 (47.4%) intermediate and 26 (44.1%) had slow acetylator genotypes. There were no differences in baseline characteristics and isoniazid dose between the genotypic groups. Isoniazid area under the concentration-time curve time 0-infinity ($AUC_{0-\infty}$) was 27.3 vs. 12.5 vs. 15.4 $\mu\text{g} \cdot \text{hr/mL}$, half-life was 2.8 vs. 1.5 vs. 1.7 hours, and apparent oral clearance (CL/F) was 5.1 vs. 10.3 vs. 14.6 L/hr for patients with slow, intermediate and rapid acetylator genotype, respectively ($P < 0.001$). A significant difference in $AUC_{0-\infty}$, half-life and CL/F was observed between slow and intermediate acetylator genotypes, but there were no differences between slow and rapid or intermediate and rapid acetylator genotypes. Half-life was also different between slow and rapid genotypes.

Conclusion: Acetylator status inferred by the 4-SNP NAT2 genotyping panel identified children with slow acetylator phenotype. This economical genotyping panel could be used to identify children at risk of reduced isoniazid elimination and high plasma exposure.

PC-1086-05 Do childhood TB guidelines provide optimal guidance to providers of child health services in the identification and management of childhood TB?

R Thetard,¹ C Lijinsky,² C Powell,² K Sawyer¹

¹Management Sciences for Health, Arlington, VA, ²Office of Sustainable Development, Bureau for Africa, United States Agency for International Development, Washington DC, USA. e-mail: rthetard@msh.org

Background: WHO's 2014 Guidance for National Tuberculosis Programs on the Management of Tuberculosis in Children notes that "many countries developed

national policies and strategies to address childhood TB. Practical implementation of these strategies, however, has not always been achieved". African countries still face challenges with identifying, diagnosing, and treating children with TB, as well as with notifying cases to the National TB Program. Sick children are unlikely to present to TB clinics, so in addition to following technical standards, an effective service delivery model would require organizational structures linking TB and child health services at community and primary care levels. We assessed whether Childhood TB Guidelines adequately guide health workers in the "who", "what", "where" and "when" required for practical implementation of service delivery aimed at increasing access by children to TB care.

Design/Methods: Data were extracted from childhood TB guidelines from 13 English speaking countries in Africa. Data extraction was guided by an assessment of technical elements of TB service delivery with the organizational elements that support effective implementation. Technical questions included diagnostic criteria, approach to disease confirmation and treatment of TB in children. Organizational questions explored reference to integration with maternal and child health services (IMCI and nutrition programs), incorporation of indications for referral and hospitalization, and description of roles and responsibilities across all levels of the health system.

Results: Ten countries describe when a child should be suspected with TB; thirteen emphasize a systematic clinical evaluation approach. Six countries include diagnostic algorithms. In contrast, only one country incorporates a statement with recommendations for screening for active TB while two refer to IMCI and one refers to screening for TB in children with under-nutrition. Twelve countries describe the practical aspects for treatment monitoring while nine describe monitoring of IPT. Eleven countries incorporate referral guidelines; six refer to service provision by level of service delivery or task allocation by cadre

Conclusion: Future versions of guidelines should strengthen content about the organizational aspects of service delivery, especially linkages with maternal and child health services. This could contribute to increased efficiency and effectiveness of TB care for children.

46. Harmful effects of second hand smoke

PC-1089-05 Comprehensive assessment and study on the results of the Tianjin Tobacco Control Act

G H Jiang,^{1,2} W Li,^{1,2} W Zheng,^{1,2} Z L Xu,^{1,2} D Z Wang,^{1,2} Y Pan,² C F Shen,^{1,2} X D Xue,^{1,2} Y Yang,² W D Shen^{1,2}

¹Tianjin Centers for Disease Control and Prevention, Tianjin,

²Tianjin Medical University, Tianjin, China. e-mail:

jiangguohongtjcdc@126.com

Background: Tianjin Tobacco Control Regulation was formally implemented on May 31, 2012. Regulation

covered 13 categories indoor area. To evaluate the integrated effects of tobacco control by the comparison of before and after implementing Tianjin Tobacco Control Act in successive 4 years.

Design/Methods: The case data of myocardial infarction was collected by Tianjin Surveillance System of New Case Registry. The representative sample size of indoor work place and public place where we developed observation survey and PM2.5 monitoring was selected with the calculation of The Survey System, and the representative sample size people was involved in the survey of interview by Door to Door and Intercept.

Results: Before and after implementing Tianjin Tobacco Control Act, the post of No Smoking Sign was much more improved in hospitals, schools, governmental building and the waiting areas of public transportation. The great reduction of smoking phenomenon was in the nine types main public places excepting for hotel and public bath room. The average level of PM2.5 decreased about 39% in the main public places and workplaces ($P = 0.00$). The awareness rate about the harm of smoking and SHS increased dramatically, such as the awareness rate about smoking can cause stroke and heart disease reached 66.2% and 75.0% respectively (25.2% and 58.0% before the implementation of the Regulation). Second Hand Smoke Exposure declined 18% ($P < 0.05$) compare to before implementing ACT in work place and public place. The cases to hospitals with myocardial infarction declined with years in the indoor workers while the cases grow up in the entire population in Tianjin ($\beta = -0.0974$, $P = 0.0002$; $\beta = 0.0267$, $P = 0.0153$). **Conclusion:** Tianjin Tobacco Control Act decreased the smoking in public places and has already protected people from SHS. Once again proves that tobacco related disease is preventable, controllable. Smoke-free laws can create a smoke-free environment to reduce the burden of disease. And it is the effective measures to improve the public health. It should disseminate the health effect and social benefits of tobacco control are another way we should do in the future, so that the Act would be implemented comprehensively.

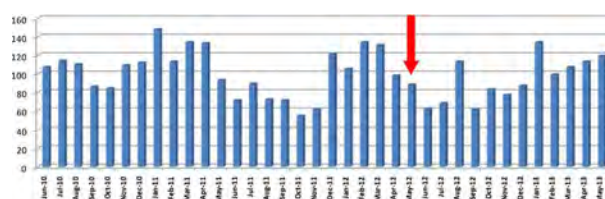


Figure 1. The case data of myocardial infarction before and after the implementation of Tobacco control Regulation

PC-1090-05 Maternal active and passive tobacco smoking during pregnancy: a retrospective cohort study

V Vivilaki,¹ A Diamanti,^{1,2} M Tzeli,¹ D Bick,³ E Patelarou,³ K Lykeridou,¹ P Katsaounou⁴ ¹Technological Educational Institute of Athens, Athens, ²Gaia Maternity Hospital, Athens, Greece; ³King's College London, London, UK; ⁴Evangelismos Hospital, Athens, Greece. e-mail: ath.diamanti@gmail.com

Background Active and passive maternal tobacco smoking during pregnancy are recognized as high risk factors for adverse pregnancy outcomes. There is good evidence that change in maternal health behavior can improve pregnancy outcomes of either stopping or reducing the amount of smoking a woman does in pregnancy. Both active and passive maternal smoking are generally held responsible for a number of adverse outcomes.

Methods: 337 women were invited to complete a questionnaire specially developed for the study. Data on active and passive maternal smoking status in the first, second and third trimesters of pregnancy, maternal environmental tobacco smoke exposure at home and work, pregnant women's experiences and beliefs towards smoking cessation during pregnancy, were collected using self-administered questionnaires. Descriptive statistics were used to illustrate the demographic data of pregnant smokers and quitters in order to reveal their smoking and passive smoking behaviors. We compared risk perception, attitude toward smoking during pregnancy, smoking behaviors, and behaviors for avoiding passive smoking between smokers and quitters using chi-square tests of association and t-test.



Figure 1. Active and passive smoking during and after pregnancy

Results: Around 3/4 of the women ($n = 221$, 73.7%, $n = 65$, 21.7% of whom were pregnancy quitters) chose not to smoke during pregnancy. Most pregnant smokers did not stop smoking because they felt unable to do so ($n = 78$, 55.8%), they did not want to stop ($n = 76$, 25.6%) or they did not consider it was an important health behavior intervention ($n = 28$, 9.3%). There were statistically significant differences between smokers and non-smokers in pregnancy and fetal problems ($\chi^2=11.41$; $df=5$; $P < 0.05$), newborn problems ($\chi^2=6.41$; $df=2$; $P < 0.05$) and smoking status of the partner ($\chi^2=14.62$; $df=1$; $P < 0.001$). The mean EPDS score for smokers was 9.72 (SD=6.28; Std Error Mean 0.52) and for quitters 8.04 (SD=5.17; Std Error Mean 0.41). Smokers had signifi-

cantly more depressive symptomatology as measured using the EPDS than quitters.

Conclusion In this sample, many women chose to stop smoking during pregnancy, however many continued to be exposed to passive smoking environments. It is essential that pregnant women, their partners and close relatives are educated on the health risks of active and passive smoking to fetal and infant outcomes as well as the pregnant women themselves. Only smoke-free environments will sufficiently promote optimal perinatal health for both the woman and her fetus/newborn.

PC-1091-05 High prevalence of secondhand smoke: a major challenge to achieve a smoke-free community in Shimla

D Singh¹ ¹Indira Gandhi Medical College, Shimla, Shimla, India. e-mail: dsdhadwal@gmail.com

Background and challenges to implementation: Second hand smoke (SHS) is also known as environmental tobacco smoke (ETS). Exposure to SHS leads to increased risk of contracting lung cancer, coronary heart disease, lower respiratory tract infections and asthma. Women and children are the most vulnerable groups to SHS and yet they are helpless in reducing this risk.

Intervention or response: The present study was done to assess the smoking and SHS patterns and awareness regarding ill effects of smoking and SHS amongst people of Boileauganj, urban field practice area of Department of Community Medicine, IGMCM Shimla.

Results and lessons learnt: In spite of the fact that 77% of smokers knew about harms of SHS, 70% still reported to smoke in room at office or home. 58% had heard of ban on smoking in public places and 53% knew that Himachal Pradesh has been declared as a no smoke state. Only 50% of the participants had heard of COTPA act. All the smokers (100%) were males and admitted to smoking inside their homes or inside offices. Only 23% females knew about harmful effects of SHS though 90% of them knew about ill effects of active smoking.

Conclusions and key recommendations: Reinforcement of smoking ban in public places can have a major effect on reducing SHS. Aggressive media campaigns educating people about harmful effects of SHS need to be started. Involvement of local communities, Resident welfare societies and women organizations in raising awareness as well as taking stand against SHS in their localities and homes is the need of the hour. 'Say No to SHS' campaigns need to be launched with help of prominent female & youth celebrities.

PC-1092-05 Hoshiarpur, a 'Total Tobacco Free City': a district headquarter city with comprehensive compliance with COTPA 2003

S Surila,¹ R Gupta,² J Singh Bains,³ S Goel⁴ ¹Social Network of Education and Health Awareness, Mohali, ²Directorate of Health and Family Welfare Punjab, Chandigarh, ³Directorate of Health and Family Welfare Punjab, Chandigarh, ⁴Postgraduate Institute of Medical Education & Research Chandigarh, Chandigarh, India. e-mail: surin3006@gmail.com

Background and challenges to implementation: Tobacco consumption is very harmful to human body. Indian Government spends lacs of rupees annually to cure the diseases caused by it. The Government spends annually more than one lac crore of INR on the treatment of such diseases besides the loss of above 8 lacs of precious lives. To control this, Indian Anti Tobacco Act, COTPA-2003 is in force since Oct. 2008. Objective: Head Quarter City of Hoshiarpur has been recently identified as to potential comprehensively implementing COTPA-2003. Hence study is being done: 1) To measure the level of compliance of Sec-5, Sec-6a Sec-7, 8 and 9 of the Act at POS across the municipal limits of the City Hoshiarpur. 2) To measure the level of compliance of Sec-6b of the Act in educational institutions across the municipal limits of the City.

Intervention or response: Enforcement of COTPA 2003 through health and family welfare department- tobacco control cell Punjab at district Hoshiarpur and social activist and district administration year 2013-14.

Results and lessons learnt: "No Active Smoking in Public Places" and other provisions of Section-4 were observed in 99% of visited places. "Points of Sale" complied 98.5% with displaying of Signage's and other provisions under the Sec-6a of the Act. There was no Advertisement found anywhere in the city except as per Sec-5 of the Act. Eateries, Hotels and Restaurants and Point of Sale complied 100%. There was no violation of sec- 7, 8, 9 of the Act with the packages of tobacco products being sold. No imported tobacco products were being sold there.

Conclusions and key recommendations: The comprehensive compliance of COTPA-2003 in Section-4, 5, 6a and 6b, 7, 8 and 9 has been observed is above the level considered to be the minimum bench mark of declaring city as "A Comprehensive Tobacco Free City". There is 100 % awareness level of the COTPA-2003.

PC-1093-05 Community-led tobacco control initiative combatting secondhand smoke at home in a North Eastern State, Tripura, India

G Tripathi,¹ A Singh,² R J Singh,³ P Tripathi⁴ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ²Government of India, Agartalla, ³University of Delhi, New Delhi, India. e-mail: tripathi.govind@gmail.com

Background and challenges to implementation: Integrating Tobacco control programme with Village Health Sanitation Nutrition Day (VHSND). A unique initiative

for reducing tobacco use by involving community through increased level of awareness. VHSND is a Governmental Flexi Programme across the country being run for providing health, sanitation and nutrition services at the doorstep. Tripura State (Population 3.7 million) integrated VHSND with Community Led Tobacco Control Initiative (CLTCI), a unique intervention at the community level to prepare the people for quitting tobacco by changing the behavioural aspects.

Intervention or response: Community Led Tobacco Control Initiative (CLTCI) using VHSND platform run by Community and Health workers to work against tobacco use. Here, community gets repeated doses of the counselling, discussions and reach at cessation centers for quitting tobacco. As a result, significant reduction noticed in second hand smoke at household's level. Particularly youth and women groups have played vital role through direct, peer group/family. A Cross sectional survey of randomly selected 2856 households in 6 administrative blocks of West Tripura district was done in the month of Jan-Feb, 2014 by the trained investigators using the pretested checklist. The core parameters of evaluation were: Presence of some IEC material, Interaction with children, absence of active smoking, absence of smoking aids, absence of tobacco litter and absence of tobacco smell at the house hold level.

Results and lessons learnt: Some IEC material found at 70% places, negative report from children about smoking at home found around 82 % places, 84.50% House holds found without active smoking. 82.69% households found free from Smoking aids like ashtrays, & lighters. More than 83 % of sampled sites didn't have any tobacco litter (cigarette butts and bidi ends). Over 85% of sampled sites we're having no evidence of recent smoking smell.

Conclusions and key recommendations: Second hand prevalence substantially reduced from the level of the 71.10 percent (GATS- 2009-10) to around 30 percent, which is reduced by 60 percent. District has achieved high level of success against SHS at household level. A pro-active district administration approached with community driven initiation and established historic achievement.

PC-1094-05 Prevalence of exposure to smoking and indoor air pollution among the general population in 30 districts across 6 states of India

S Pandurangan,¹ S Mohanty¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 11 46 05 40 30. e-mail: sripriya14@gmail.com

Background: Tuberculosis (TB) is one among the important public health challenges and accounts for about 300 000 deaths per year in India. Lack of awareness and exposure to various risk factors are the main causes for Tuberculosis. Levels of these risk factors vary from time to time. Assessing the levels of risk factors is an important step in addressing the issue in the country.

This study attempts to evaluate the information on exposure to different risk factors of TB such as smoking, drinking and living conditions in urban and rural areas. **Methodology:** Two rounds of cross sectional community based survey was conducted adopting multistage systematic random sampling in 30 districts of 6 states of India. The estimated sample size was 2426 from 30 districts in the 6 states considering 5% change in two years. A structured pretested questionnaire was administered to capture information on respondent's exposure to different risk factors of TB like smoking, drinking and living.

Results: The study showed that 45.6 % of target group exposed to smoke due to unsafe fuel usage for cooking. Out of them 18 % are from urban and whereas nearly 3 out of 5 rural respondents reported using unsafe fuel for cooking purpose. Over 85 percent of respondents reported to have a safe kitchen and the remaining reported having an unsafe kitchen (defined as a kitchen located in the living room). A similar proportion (80%) of respondents reported to be living in safe housing conditions (defined as house with windows and doors). About 19.8% of rural and 19 % of urban respondents reported to be living in a closed living room. Usage of unsafe heating methods is also seemingly high in rural areas with a proportion of rural respondents more than double (11.5%) the proportion reported by urban respondents (4.7%). Nearly 16 % of respondents said that they smoke and about 19 % said that they consume alcohol. A difference of 4-6 percentage points were found between urban and rural respondents with respect to smoking and drinking patterns.

Conclusion: This study highlights the risk factors of tuberculosis that are prevalent in rural and urban areas. The remedial measures for these risk factors are mainly socio economical in nature. However some behavioural change strategies could be initiated on factors such as usage of unsafe fuel, smoking and consumption of alcohol. These changes could result in the reduction of incidence and prevalence of tuberculosis in the country.

PC-1095-05 Reactions to smoke-free policies in the Republic of Georgia and to messaging strategies in support and opposition: results from a national survey

C Berg,¹ M Topuridze,² N Maglakelidze,² L Sturua,² M Shishniashvili² ¹Emory University, Atlanta, GA, USA; ²National Centers for Disease Control, Tbilisi, Georgia. e-mail: carlajberg@gmail.com

Background: Despite the ratification of the Framework Convention on Tobacco Control, the Republic of Georgia has limited tobacco control policies in place, particularly in the area of smoke-free public policies. This implies a substantial rate of secondhand smoke exposure (SHSe). Thus, we examined: 1) the adoption and enforcement of smoke-free policies in personal settings, 2) reactions toward public smoke-free policies, and 3) the persuasiveness of messaging strategies related

to smoke-free policies in bars and restaurants among Georgian adults.

Design/Methods: We conducted a national household survey of 1163 Georgian adults aged 18-65 years conducted in Spring 2014. A multi-stage, clustered sample design was used to produce representative data with stratification done by region. We assessed the aforementioned variables and conducted bivariate and multivariate analyses.

Results: Our sample was on average 42.41 years old (SD=13.58), 51.1% male, 43.2% urban, 65.6% married or living with a partner, and 53.0% had children in the home. They had an average of 12.78 years of education (SD=2.85), and 40.0% were employed. Current tobacco use prevalence was 54.2% among men and 6.5% among women. Overall, 38.8% indicated that someone smoked inside their home on a daily basis, and only 14.3% had a complete smoke-free home policy. However, only a minority of participants opposed a smoke-free policy in most public settings. Less than 15% opposed smoke-free public policies on school grounds (indoor or outdoor), on college/university campuses, in workplaces or offices, in public transportation, in taxis, or in vehicles with children present. The greatest opposition was in relation to outdoor seating areas of restaurants, bars, pubs, or clubs (38.7%). Notably, only 33.3% and 35.1% opposed smoke-free restaurants and bars, pubs, or clubs, respectively. Less than 25% opposed smoke-free policies in common areas of multiunit housing or individual apartments. Those who were older and female were more likely to have smoke-free homes and were more receptive to public smoke-free policies ($P < .01$). Messaging with arguments regarding the health and economic impact of smoke-free policies were most persuasive both in support of and opposition to such policies.

Conclusions: In Georgia, efforts must promote smoke-free policies, particularly among male smokers, in order to reduce SHSe, smoking rates, and ultimately the related morbidities and mortality.

47. Monitoring the tobacco industry: promotion and advertisements

PC-1096-05 Tobacco control: a messed up agenda in India due to conflicts of interest

A Phull¹ ¹Daily Post, Shimla, India. e-mail: archanaphull@yahoo.com

Background and challenges to implementation: Health is a priority, but it is often a loser in the tug of war with tobacco promotion in India. According to WHO Tobacco kills up to half of its users. Around six million people are killed each year in the world due to tobacco use. More than five million of those deaths are the result of direct tobacco use. The WHO data says that Tobacco use causes 22% of the global 8.2 million deaths due to cancer and 71% of the global lung cancer deaths. Nearly 60-70% of all cancer cases in men are due to tobacco.

The scenario is dismal in India as about one million people die of tobacco use every year in the country. As per GATS, tobacco users in India are 34.6 % (majority of them using smokeless tobacco), while the average age of initiation of tobacco use is 17-18 years. Gutkha is found to be the major tobacco hazard in the country. But all this does not seem to wake up the country's policy makers. And why would it? Conflict of Interest: The visible conflict of interest within the Indian government on the issue has led to deliberate official callousness towards the gaps in tobacco control. The implementation of Cigarettes and other Tobacco Products Act, 2003 (COTPA) and National Tobacco control programme has not been effective, all for want of spirited work. India is the third largest producer of tobacco in the world and over 38 million people in the country are now directly or indirectly dependent on Tobacco industry for livelihood. A Tobacco Board, instituted under the Union Commerce Ministry, has been there since 1975 to promote tobacco industry. The Tobacco Board is in contrast with the tobacco control commitment of Government of India. The controversy over the Parliamentary panel on subordinate legislation examining the provisions of COTPA, 2003 corroborates it. The panel's conclusion that there was no need to enhance health warnings on tobacco products from 40 to 85 % on retail pack size and the argument by a panel member that there was no Indian study to link tobacco with cancer is self-explanatory. Not surprisingly, two Members of (Indian) Parliament on the panel are directly associated with Tobacco industry.

Conclusions and key recommendations: Tobacco or Health? The policy makers in India will have to set the priorities to save the generations next from the ills of tobacco.

PC-1097-05 Assessment and implementation of prohibition of tobacco advertisement, promotion and sponsorship at point of sale in Delhi, India

S Arora¹ ¹Public Health Wing-1, Directorate of Health Services, Government of Delhi, New Delhi, India. e-mail: aroradsk7@yahoo.com

Background information: Tobacco industry interferes with anti-tobacco activities through POS (point of sale) advertisement and promotion of tobacco products. Tobacco used pattern has been shifted from adult to minor and women group due to aggressive advertisement strategy of tobacco companies. At present 14% students (upto age 15 years) currently use any tobacco products where 4% currently smoke and 12% use tobacco products other than cigarettes. Chewable tobacco use is also increasing despite the fact that the gutka has been banned in Delhi since September 2012. Section 5 of cigarette and other tobacco products act (COTPA) prohibits tobacco advertisement, promotion and sponsorship at point of sale.

Methods: Cross-sectional analysis using observation checklist was conducted in 331 shops in different areas/

districts of Delhi state. Inspection of shops done for presence of advertisement, its type, size of board, presence of mandatory board regarding prohibition of sale of tobacco to minor (less than 18 years of age) & interviews of tobacco vendors. **Result:** the advertisements were observed at 79 (24%) places. among them at 32 places big stickers & at 20 places small paper pamphlets displays observed. At 27 (41%) places big hoarding boards were displayed, out of which 13 (48%) were backlit. The size of all 27 boards were more than 60X45 cm. Products display were observed at 72 places. Mandatory board regarding prohibition of sale of tobacco to minor (less than 18 years of age) were seen in 223 (67%) shops. 50 (63%) were aware that it is illegal. Tobacco companies had distributed these as free attractive gifts. **Strategy adopted:** all advertisements removed on the spot with warnings. 12 court cases initiated against the repeated offenders. media was used strategically for masses, tobacco vendor associations sensitized. Tobacco companies were instructed to remove all such displays from entire Delhi and stop distributing these gifts in future, failure will attract strict actions against them. Meeting with the municipalities, police department and other stakeholders was conducted and municipalities and police department were instructed to remove all such displays from entire Delhi. For awareness among public & tobacco vendors, IEC activities were performed through different media.

Conclusions and recommendations: Challenges regarding tobacco industry interference needs to be tackled strategically using all stakeholders with repeated & extensive awareness along with rigorous enforcement.

PC-1098-05 Pan masala and mouth freshener surrogates for tobacco product advertisements in India?

A Mangla¹ ¹Shimla Municipal Corporation, Shimla, India. e-mail: manglaindia@gmail.com

Background: Article 13 of FCTC and Indian tobacco control legislation (COTPA) prohibit direct and indirect advertisement of tobacco products in any media. However, tobacco industry is circumventing the law and adopting below the belt strategies; there are several advertisements of non-tobacco products such as pan masala (a non-tobacco product containing areca nut) and mouth fresheners having same brand name and similar packaging design to tobacco products seen in Indian print and television media. Current study was carried out to know whether advertisements in Indian print and television media were for the intended products or serve as a surrogate for tobacco products.

Design/Methods: Investigators did a cross sectional survey using a pre-tested checklist in Shimla city in April-June, 2014. Three vernacular newspapers were scanned, selected 30 matches of Indian Premier League (Cricket) telecasted live on a Sports TV channel were observed for any advertisement of pan masala and mouth freshener. Total 286 tobacco shops in Shimla city were

also surveyed for availability of these products in the market.

Results: Total 13 advertisements (of four brands) of pan masala and mouth fresheners were observed in the newspapers. On an average, four advertisements of pan masala/mouth fresheners (of three brands) were aired in each of the 30 IPL matches telecasted in a Sports TV channel. Field survey revealed that the advertised non-tobacco products and tobacco products of same brand name and package design are also available in the market. Total 223 (78%) shops were selling at least one brand of pan masala/ mouth fresheners and zarda (raw tobacco product) of same brand name and package design. Overall, total 12 brands of pan masala/ mouth fresheners and zarda (including the advertised brands) were available in the market.

Conclusion: The advertisements in Indian print and television media is serving dual purpose. Tobacco industry is advertising the non-products (pan masala and mouth fresheners) but also the tobacco product (zarda) of same brand and packaging design, which otherwise under the law was totally banned. Pan masala and mouth fresheners advertisements become surrogate for tobacco products (zarda) in India. There is an immediate need for enforcement of complete ban on such advertisements.

PC-1099-05 The first tobacco advertisement-free point of sale state in India: the Kerala experience

P Kumar¹ ¹Kerala State Government Health Services, Trivandrum, Kerala, India. e-mail: aspkscet@yahoo.com

Background and challenges to implementation: In Kerala, smoking prevalence was high and stringent tobacco control was needed for further progress in TB control since smoking has linkages with TB disease. State health department carried out vivid activities during 2011 to 2013 to build capacity of department officials and to sensitize the community to create favourable environment for smooth implementation of tobacco control laws. Department mobilized community leaders, civil society groups, NGO, academia and other government departments. Over 23 500 notices were issued to remove advertisement boards non complying legal restrictions at point of sale. But shop owners did not remove them since tobacco industry gave support. After gaining political support, two search campaigns, serial monitoring and legal actions were planned.

Intervention or response: About 3000 health workers were trained and organized a week long search campaign in January 2014 to check shops along with community leaders, civil society representatives and police to remove illegal boards and issue legal notice. Of the 19 455 shops checked, illegal advertisement boards were detected in 48.8% shops and all of them were found to be violating legal specifications. About 65% boards were removed on the spot and correction notices issued to others. Another search campaign conducted in May 2014 found that about 90% of left over boards were still present but

modified by removing or masking all text messages including brand name. All of them were given legal notice and conducted monthly monitoring at different levels. Evaluation was conducted by an NGO through 90 trained volunteers using pretested questionnaire during November 2014. Study was conducted in 84 wards selected by stratified random sampling method from the whole state and collected information from 22 344 point of sale by observing seven components namely big boards, promotional materials, display of cost, display of tobacco products, open sale of single cigarette, supply of smoking aids and discount sale.

Results and lessons learnt: Overall compliance of all seven components was 95.3%. Big hoardings were absent in 98.5% sites and promotional materials were not seen in 96.7% sites. Discount sale could not be seen anywhere. Other components were absent in about 90% sites. There was no significant difference between districts.

Conclusions: Kerala became the first tobacco advertisement free point of sale state in India in November 2014.

Table District wise compliance of components (%)

District	Big Hoardings	Promotional materials	Display of cost	Display of tobacco products	open sale of single cigarettes	Supply of smoking aids	Discount sale	Overall
TVM	99	98	97	89	94	97	100	95.9
KLM	99	96	96	87	93	89	100	94.1
PTA	99	98	100	94	98	97	100	97.6
ALP	96	94	98	89	90	95	100	93.7
KTM	97	96	96	92	94	97	100	95.4
IDK	99	98	96	94	93	91	100	96.1
EKM	99	96	94	91	90	90	100	94.5
TSR	99	98	98	95	95	98	100	97.4
PKD	99	97	98	89	89	94	100	95.0
MLP	98	96	96	90	91	91	100	95.2
KKD	97	92	97	86	85	89	100	91.8
WYD	99	99	99	96	91	93	100	97.0
KNR	99	98	96	91	94	89	100	95.4
KSD	100	97	98	90	88	88	100	95.0

PC-1100-05 Compliance level with Section 6A of the Cigarettes and Other Tobacco Products Act to protect minors from tobacco in Karnataka, India: a cross-sectional study

Mahamad P,¹ P Poojary¹ ¹State Anti Tobacco Cell-Karnataka, Bengaluru, India. e-mail: bimahamad.kar@gmail.com

Background: India's Tobacco Control Legislation "Cigarettes and Other Tobacco Products Act (COTPA), 2003" Section 6 A of COTPA prohibits the sale of tobacco products to and by minors. Since its inception, Section 6A has not achieved success in banning the access of a minor to tobacco products in India. In order to find the compliance of COTPA, an observation was conducted regarding inception of section 6 A in Karnataka.

Design/Methods: In the year 2014, a Cross-Sectional Observation Study was conducted on compliance mon-

itoring. Out of 30 Districts of Karnataka, 08 districts were selected using a structured, pre-tested checklist-based assessment method. A total of 3084 Point of Sale (PoS) were observed at the estimated compliance of 50%, confidence interval of 95% and at 5% margin of error. This survey was conducted using the cluster sampling.

Results: Out of 3084 PoS observed, 373 (11.88%) PoS were found to have displaying a mandatory signage's used to indicate that "sale of tobacco products to a person below the age of eighteen years is a punishable offence". In about 423 (14.19%) of the PoS, the vendor was a minor; it was observed that 906 (28.3%) buyers were minors visibly below the age of 18 years. In very few cases the vendors enquired the age of the buyers in borderline cases 184 (5.9% of vendors). This clearly points out the failure of COTPA in curbing the buy and sale of tobacco products to and by minors. Hence, the compliance level of Section 6A of COTPA is fairly low in Karnataka.

Conclusion: A majority of the PoS are not complying to the COTPA presently, and those who are following the norms are not abiding completely to the specifications. The basic and most primary reason is that people who are supposed to follow the rules are not even aware of the presence of such rules and laws. And the vendors are least bothered about it, as most of them are profit oriented and no such restrictions are also levied on them during the time of license sanction. Therefore, Efforts must be made to make such laws more effective & easy to understand and interpret the importance of Law by common people who are essentially the target group of the laws that are being passed.

PC-1101-05 Countering tobacco industry interference in government policy on bidi tax

S V Itty¹ ¹Kerala Voluntary Health Services, Kottayam, India. Fax: (+91) 984 781 9080. e-mail: sajuitty@rediffmail.com

Background and challenges to implementation: Beedi are the popular smoking form of tobacco in the state of Kerala. According to the GATS data 4.9 % of adult population are (above 15 years) smoke beedi. Kerala has the 13th highest beedi smokers in India. Kerala established the first beedi manufacturing unit under the co-operate sector with the support of govt. in 1969. This corporate beedi making unit and trade unions working in it influenced all government policies on tobacco control especially on smoking tobacco products. As per the GATS data in the state 1 53 7936 people are exposed to beedi smoking. Last four year our advocacy to increase beedi tax was failed due to the intervention of beedi industry lobby. As a result beedi had no tax up to 2015 March. This year government first time in history imposed 14.5% tax on beedi.

Intervention or response: Kerala Voluntary Health Services made some unique strategies to counter the tobacco company tactics. The year-long campaign planned just after the 2014- 15 budget: Systematically assess the previous years' campaigns and identify the challenges and loop holes. Recruited special team for

study the Beedi company details including their profit, welfare measurers, promotion tactics, management system, linkage with political leaders etc. Prepare case studies on promotional tactics of beedi companies. Conduct advocacy at political and administrative front. Mass Action by civil society coalition. Prepare and conduct follow up campaign. Use media in strategic way. **Results and lessons learnt:** The government changed its non-tax policy on Beedi and imposed 14.5% tax on all beedies. As a result the cost of Beedi packet rose from 25% to 30%. The point of sale study shows that 15 to 20% reduction in consumption and 4% shift from Beedi to cigarette.

Conclusions and key recommendations: Kerala VHS will continue its efforts in this year also, targeting a 40% to 60% tax imposition on Beedi. Long term planning and focused intervention needed for successful advocacy campaign.

PC-1102-05 How good is compliance with legislative provisions on TAPS, protection of minors and pack warnings in Himachal Pradesh, India?

R Sharma,¹ R Thakur,² R Badrel,³ R J Singh¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi; ²Department of Health and Family Welfare, Government of Himachal Pradesh, Shimla; ³Himachal Pradesh Voluntary Health Association, Shimla, Himachal Pradesh, India. e-mail: rsharma@theunion.org

Background: The Northern state of Himachal Pradesh was declared Smokefree by state Health Minister on 2nd July 2013 based on a compliance assessment study. The government and civil society resolved to make the state fully compliant to all provisions of Cigarette and Other Tobacco Products Act (COTPA) namely prohibition of TAPS, prohibition of sale to and by minors and around 100 yards of educational institutes and mandatory display of pack warnings on all tobacco products. This paper presents a baseline compliance assessment conducted in 2013 to know the level of compliance before tobacco control interventions were instituted. An end line compliance assessment is planned in June 2015 and the final paper will also outline the progress made in infrastructure set-up, strengthening of enforcement of COTPA and variance in level of compliance in 2013 and 2015.

Methodology: The assessment was conducted at all 12 districts and 34 blocks headquarter towns of the state. The sampling was done using protocols developed by The Union and its partners. A mapping of Point of Sales (PoS) and Educational Institutes (EI) was done and finally 1645 PoS and 693 EI were assessed in the survey. The investigators were trained by the Union technical staff for data collection using an observational check list based on various provisions of COTPA.

Results: Violations of legislative provisions of TAPS ban was highest in Kangra and Solan and least in Kinnour district. Product showcase was most common type of TAPS violation found at 54.8% PoS and promotional activities were noticed only at 5.2% PoS. The visibility of

tobacco products to minors was highest in Kullu and Una and lowest in Shimla (50.2%). Majority of PoS boards were not as per specification of COTPA and violated its norms in size, colour, text and picture. Tobacco products were being sold within 100 yards of educational institutes in 88% of institutes surveyed and enquiry for proof of age in borderline children was done only in 0.6% cases. The tobacco products without pack warnings were mostly observed at tourist destinations where illicit products didn't have warnings.

Conclusion: The baseline assessment showed gross violations of above three provisions of COTPA on TAPS, protection of children and pack warnings. A comprehensive mechanism was instituted to strengthen enforcement across the state in 2013. The baseline results will be compared with end line compliance due in June 2015 and presented in the conference.

PC-1103-05 Point-of-sale tobacco promotion and risk of smoking amongst youth: a meta-analysis

L Robertson,¹ C Cameron¹ ¹University of Otago, Dunedin, New Zealand. e-mail: l.robertson@otago.ac.nz

Background: Several countries have now implemented bans on PoS tobacco promotion, yet this form of marketing remains extensive in many jurisdictions. Two systematic reviews have indicated a positive association between exposure to PoS tobacco promotion and smoking amongst children and young people. We aimed to provide an estimate of the effect size of this association.

Methods: Inclusion criteria were quantitative observational research published in a peer-reviewed journal between 1 January 1990 and 23 June 2014 that included self-reported or objective measures of exposure to POS tobacco promotion, and either behavioural or cognitive smoking-related outcome measures. Studies were eligible if the samples included children and adolescents aged 18 years old or younger. We used random effects models to provide effect size estimates for 1) behavioural outcomes and 2) cognitive outcomes. Subgroup and sensitivity analyses were conducted to take into account the extent of PoS tobacco promotion in the study location, study quality and sample size.

Results: Thirteen articles were judged to have met the inclusion criteria; 11 of these reported associations for behavioural outcomes and 6 reported associations for cognitive outcomes. Eight studies were conducted in the US, 3 in Europe, 1 in New Zealand and 1 in Japan. Two were cohort studies and the remainder were cross-sectional. For the eleven studies examining behavioural outcomes, the pooled odds ratio (OR) was 1.61 (95% confidence interval (CI): 1.33- 1.96), and for those examining cognitive outcomes the pooled OR was 1.32 (95%CI: 1.09 – 1.61). Sub-groups analysed indicated higher odds ratios in study jurisdictions where the only form of promotion was the “powerwall” of tobacco.

Conclusion: The evidence indicates a small to moderate positive association between exposure to PoS tobacco

promotion and smoking risk amongst children and youth. This suggests that prohibiting PoS tobacco promotion would lead to important reductions in youth smoking at the population level. The “powerwall” of tobacco products appears to be particularly salient to young people where no other form of retail tobacco promotion is present. Therefore partial restrictions on PoS promotion are inadequate; policies should prohibit all forms of retail tobacco advertising and display.

PC-1104-05 Monitoring the tobacco industry's compliance with the Russian Federal Tobacco Control law in Krasnoyarsky krai

I Berezhnova,¹ E Terskih,² E Zeynalova,² D Trufanov³

¹International Union Against Tuberculosis and Lung Disease, Moscow, ²Krasnoyarsk Regional Organization Center for Health Promotion, Krasnoyarsk, ³Center for Sociological Research Public Opinion Monitoring, Krasnoyarsk, Russian Federation. Fax: (+7) 495 984 7408. e-mail: iberezhnova@theunion.org

Background: Art 5.3 FCTC provisions are well reflected in the Federal Tobacco Control (TC) Law (Art 8 and 16) of the Russian Federation though they may not be fully comprehensive and well enforced by the federal enforcement agencies. Experts of the Center for Sociological Research “Public Opinion monitoring” and Krasnoyarsk regional public organization “Center for Health Promotion” carried out TC Legislation’s (№15-FZ) Art. 8 on Tobacco Industry (TI) transparency and accountability, Art. 16 on TAPS and Art. 19 on POS compliance monitoring from September to December 2014 in the Krasnoyarsk territory.

Design/Methods: Observation and desk research were used for data collection. Indicators included violations of TAPS, PoS bans, and sales regulations and others. Areas of monitoring included urban environment (outdoor advertising, outdoor events, promotions, contests in public places, Internet, Social networks, media (after 2013 - films, videos, audio, radio, and TV content) and press (newspapers, magazines).

Results: The monitoring revealed 191 facts of violation of the Federal Law 15-FZ Articles 16 and 19 in the Krasnoyarsk territory. The most frequent violations included: ban on PoS – 55 cases; violations of TAPS – 41 (including Internet advertisement); and brand stretching - 30 cases. Forth most common type of violations was deviation of usage and placement of the trademark – 20 cases. And the fifth is violation of the ban on tobacco companies’ promotional activities, including lotteries and competitions, with terms provided for purchase of cigarettes – 20 cases. Monitoring of the official sources of information revealed that Art. 8 on transparency of government interaction with the tobacco industry has not been observed.

Conclusion: Despite adoption of the Federal Tobacco Control Legislation in Russia, the tobacco industry continues to apply new and traditional marketing strategies to promote tobacco consumption in Russia. Statistical analysis of the monitoring data was conducted on TI activity levels from September to December 2014

in Krasnoyarsk city and region. The analysis concluded that a daily level of 1.57 TI activities contained violations of articles 16 and 19 of the Russian Federal legislation. In our opinion, these findings demonstrate a high level of violation of the Tobacco Control Law.

48. Enforcement of smoke-free legislation

PC-1105-05 Assessment of the establishment of smoke-free venues in national chronic disease demonstration areas and tobacco control activities

Y M Bai,¹ Y Zhang,¹ N Ji,¹ F Mao,¹ S Deng,² Y Fan,³ L H Wang,¹ J X Ma¹ ¹National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, ²Xinjiang Center for Disease Control and Prevention, Urumqi, ³Nanchang Center for Disease Control and Prevention, Nanchang, China. Fax: (+86) 106 302 2350. e-mail: bym0057@sina.com

Background: In order to further strengthen NCD prevention and control work in China, the construction of national demonstration areas (hereinafter referred as “NDAs”) of NCD comprehensive prevention and control was launched in 2010 by the National Health and Family Planning Commission. By the end of 2014, 265 districts or counties have been named NDAs (Figure). In order to control tobacco use, a program “Integrating tobacco control into the implementation strategy of the National Plan on NCD Control and Prevention in China” was carried out under the support from The Union, aiming to improve tobacco control capacity building and tobacco control policy intervention in the contexts of NDAs. Objective To collect baseline data and understand the present tobacco control work in NDAs.

Methods: The data between 2010 to Jun 2011 were collected from the work reports and the community diagnosis reports of the 39 NDAs. And the data in 2013 were collected from the questionnaire of the 39 NDAs.

Results: Tobacco control activities In 2013, execution rates of the MPOWER strategies in the 39 NDAs from high to low were as below: W (warning about the dangers of tobacco use) 84.6%, P (protecting people from secondhand smoke) 82.1%, E(ensuring the ban on tobacco advertising, promotion and sponsorship) 53.8%, M(monitoring tobacco use and prevention countermeasures) 48.7% and O (providing services on smoking cessation) 48.7%. While the R, which means raising taxes on tobacco products, is unavailable since it is beyond certain county or district's power. The coverage rate of tobacco-free health institutions Among the 39 NDAs, 32 (82.1%) achieved that all health institutions went smoke free. Geographically, 20 out of 24 NDAs (83.3%) in the eastern region, 6 out of 8 (75.0%) in the central region, and 6 out of 7 (85.7%) in the western region achieved that all health institutions go smoke-free. Tobacco-free environments outside health system Thirty

(76.9%) out of 39 NDAs provided the information on the creating of tobacco-free environments outside health system. The median of the number of tobacco-free environments outside health system is 12.5 and the interquartile range is 30.75.

Conclusion: The outcomes showed that, indicators on tobacco control in the evaluation system applied in national demonstration area were not specific enough. Further amendments were needed to complete the evaluation system in order to achieve the goal of decreasing the adult smoking prevalence to 25% by 2015.



PC-1106-05 How capable is the health system of tobacco control through current policies

G Chauhan¹ ¹ Postgraduate Institute of Medical Education & Research, Chandigarh, India. e-mail: drgopal7475@yahoo.co.in

Background and challenges to implementation: Tobacco control is a health regulatory issue thus implementation of tobacco control laws (COTPA) and FCTC framework policies falls within the domain of health system at national and sub national level in India. Eventually health system functions are preventive, promotive and curative. The manpower within the health system encompasses the inherited characters of the above streams. Health system also regulates prevention of female feticide, food safety standards, drugs and cosmetics through food safety officers and drug inspectors but they are not from the health streams. As tobacco control involves all skills like search, seizure, enforcement, court cases/prosecutions, and legal formalities so implementation through current health system remains a question.

Intervention or response: Police has undefined role in health regulations in India. On the request of the State head of the police in the high level meeting in the Himachal Secretariat on 5.5.09 a separate body was established with the mandate to enforce all the health regulations. The body is headed by an senior level administrator with specialized manpower and legal experts with capacity to exercise powers over other departments too. In the last 5 years more than 80 000 violators has been panelized but the health authorities

contribution is less than 5% as law enforcers and the story is even worst in rest of India.

Results and lessons learnt: Enforcement of the law is the likely solution of tobacco control India. The Health is the nodal /regulatory agency for tobacco control with poor capacity The role of police is minimally defined as supporter for tobacco control Police has contributed >95% in enforcement The key strategies like raising tax on tobacco is beyond preview COTPA and health system

Conclusions and key recommendations: Regulation means enforcement. Awareness as a part of program can be well taken care within the health system but enforcement is beyond its current capacity. Health regulatory body at national /state level for law enforcement is the possible solution subject to the stake of enforcers in it.

PC-1107-05 Comparative study on the enforcement of smoke-free legislation in Bengaluru Rural District, Karnataka

Mahamad P,¹ R J Singh,² P Poojary,¹ J Purushothama¹

¹State Anti Tobacco Cell- Karnataka, Bengaluru,

²International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India, e-mail: bimahamad.kar@gmail.com

Background: Section 4 of India's tobacco control legislation "Cigarettes and Other Tobacco Products Act (COTPA), 2003" comprehensively prohibits smoking in public places. A comparative observation was done regarding inception of section 4 in Bangalore rural district.

Objectives: The objective of the comparative observation was to assess the level of compliance to Section 4 of COTPA in Bangalore Rural and assess the level to which COTPA has been implemented in Bangalore rural to declare it as smoke free. **Methodology:** A comparative observation was conducted before and after the effective enforcement of section 4 of COTPA in Bangalore Rural. An observation checklist was used for compliance monitoring. A total of 348 public places were observed at the estimated compliance of 50%, confidence interval of 95% and at 5% margin of error. This survey was conducted using the cluster sampling.

Results: 1) Before the Effective implementation of section 4: 4.2% of the public places had the "NO SMOKING" signage as per COTPA. In terms of active smoking being observed at various places, no public smoking was observed in 73.2% of the public places during the time of investigation. In about 67.6% of the public places smoking aids which encourage smoking were not found. In about 65.8% of the public places visited, there was no smell of cigarette or bidi suggesting that someone had smoked recently. 2) After the Effective implementation of section 4: 87.35% of the public places had the "NO SMOKING" signage as per COTPA. In terms of active smoking being observed at various places, no public smoking was observed in 87.64% of the public places during the time of investigation. In about 88.21% of the public places smoking aids which encourage smoking

were not found. In about 91.95% of the public places visited, there was no smell of cigarette or bidi suggesting that someone had smoked recently.

Conclusions: As a result of effective implementation of Smoke Free Legislation, Display of COTPA Section 4 Signage had been increased up to 87.35%, No smoking in public places has been increased to 87.64%, Smoking aids were not found in public places increased from 67.6% to 88.21%, Over all, a majority of the places are complying to the COTPA presently, and those who are following the norms are also abiding completely to the specifications as evident by the results. Approximately, more than 3 lakh people have been protected from Second Hand Smoking in Bangalore Rural District.

PC-1108-05 In-school prevention of tobacco use through life skills development: the super army model

R Kadam¹ ¹Salaam Bombay Foundation, Mumbai, India. Fax: (+91) 222 034 809. e-mail: devika@salaambombay.org

Background and challenges to implementation: Tobacco is the single largest preventable cause of death in the world today. In India, approximately 14.6% of youth (13-15 years) use tobacco products. Some children start using before the age of 10. In response to India's tobacco epidemic, Salaam Bombay Foundation has developed the Super Army School Leadership Programme to prevent tobacco use and build advocacy skills among children and youth.

Intervention or response: The Super Army School Leadership Programme uses a life skills development model in schools for the 7th – 9th grades. The Super Army includes two modules – Awareness (tobacco and its health effects) and Advocacy (community-based advocacy). Through the modules, the programme develops life skills including leadership, communication and self-empowerment. The program uses a variety of teaching methods, including arts and theatre, to develop students' knowledge and skills. In the 8th and 9th grade, students conduct advocacy with local stakeholders (including education and police officials) on tobacco control, learn about government and tools to enact social change. To date, more than 530 000 students have participated in the Super Army programme from 230 schools in Mumbai.

Results and lessons learnt: In 2010, researchers from the Harvard School of Public Health conducted an evaluation of the Super Army¹. They found that Super Army students were half as likely to report tobacco use - 4.1% of 8th standard Super Army students, compared to 8.7% of control school students (OR = 0.51). Super Army students were also significantly more knowledgeable about tobacco and related legislation and had stronger life skills.

Conclusions and key recommendations: The Super Army is an effective model for low-cost tobacco prevention and life skills development in schools in low- and middle-income countries.

1 Sorensen G, Gupta P C, Nagler E, Viswanath K. Promoting life skills and preventing tobacco use among low-income Mumbai youth: effects of Salaam Bombay Foundation Intervention. *PLoS ONE* 2012; 7(4): e34982.

PC-1109-05 District level administration can be a role model for countries in becoming smoke-free

R Choudhary¹ ¹Shikshit Rojgar Kendra Prabandhak Samiti, Jhunjhunu, Rajasthan, India. e-mail: srkpsijn@gmail.com

Background and challenges to implementation: India has been very conscious of the harmful effects of tobacco use, disease burden and related social and economic costs of health care. Government of India enacted COTPA 2003 in May 2003 with a view to protect public health by prohibiting smoking in public places. But, due to high market integration of tobacco based industries, prevalence of smoking is increasing day by day in all parts of the country.

Intervention or response: SRKPS initiated the tobacco control program (Enforcement of section 4, 5 & 6 under COTPA 2003) in Jhunjhunu district of Rajasthan in the year 2005 and worked jointly with district administration towards creating a smoke free environment at public places as well as sensitized the vendors, public place managers, school/college principal, all the head administrators in hospitals, hotels, government offices, etc. about the ill effect of smoking and other tobacco products on the society. For this, one to one meeting with stakeholders was conducted with all district level officers (District Collector and CMHOs, District Education Officers, etc.). District level committee has been formed to take lead role in taking necessary action for ensuring effective implementation of COTPA. All block level officers (SDM, BDOs, CDPOs, BEEOs, etc.) and village level health workers (ANMS, ASHA and AWW), Educational institution heads, government officials and other partners were oriented to increase the outreach of the program up to village level in sustained participatory mechanism. Also, the implementation mechanism (Challan & violation reporting) has been activated with the help of district administration. More than 4500 educational institution heads, 5497 NSS students, 580 health workers and 93 members of NGOs and 888 CBOs were oriented for making smoke-free society.

Results and lessons learnt: With efforts of SRKPS and support of District Administration, Jhunjhunu was declared as the first Smoke-Free district in Rajasthan and forth in India, on 31st May, 2012. After the successful intervention in Jhunjhunu, SRKPS with support of 'The Union' replicated the strategy in other two districts Jalore and Pali in Rajasthan on 13th November, 2013. As a result, in a short period, Pali and Jalore become Smoke-free districts on 26th January, 2015 and many districts are in progress.

Conclusions and key recommendations: If the GOs and NGOs work jointly with this effort, we can make the world Smoke-free and Tobacco-free.



PC-1110-05 Does enforcement of smoke-free rules in hospitality venues harm tourism? A case study from three tourist states in India

R Thakur,¹ P Lal,² R J Singh² ¹World Health Organization-Randstad, Shimla, ² International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. Fax: (+91) 177 262 7601. e-mail: ravindermph@gmail.com

Background: Rajasthan, Himachal Pradesh and Goa are three touristy states in India with millions of tourists (both domestic and foreigners) influx each year. Ever since smoke free rules were enacted in 2008 across the country; these states performed well in law enforcement. Since 2008, more than 50 000, 15 000 and 2000 offenders including tourists has been fined for smoking in public places in Himachal Pradesh, Rajasthan and Goa respectively. Compliance surveys carried out in 2012 and 1st quarter of 2013 demonstrated high level of compliance in all public places including hospitality venues in all three states. During the process of smoke free rules implementation in these states, few policy makers and stakeholders from tourism industry showed were apprehensive of losing tourists and overall business. Tobacco industry also tried to fuel these concerns on different platforms.

Design/Methods: To understand whether enforcement of smoke free rules in these states has any negative impact on tourist influx; researchers did a literature search and secondary data analysis by visiting state specific and Government of India tourism website. Researchers revisited the state wise compliance surveys and opinion poll reports and also collated current status of enforcement level.

Results: Compliance among the hospitality venues (accommodation and eateries) in comparatively is at par with other public places. Tourists flow in all the three states was increased. In 2013, total 3.12 million tourist visited Goa as compared to 2.78 million and 2.67 million in 2012 and 2011 respectively. Similarly Himachal Pradesh and Rajasthan witnessed an increase of 7-8% in tourist influx in 2013 (Himachal Pradesh: 16.1 million (2012) and 15.0 million (2011) and Rajasthan: 30.1

million (2012) and 28.6 million (2011). There is consistent increase in foreign tourists in all the three states in last three years. Opinion poll in Himachal Pradesh revealed that tourists are also in favour of smoke free public places.

Conclusion: The apprehension that strict enforcement of smoke free rules in the hospitality venues is not correct; quite the contrary, implementation of these laws is often associated with an increase in the rate of growth of tourism revenues. This study debunks the tobacco industry allegation that smoke-free restaurant laws adversely affect tourism, including international tourism. In fact tourists are motivated to demand smoke free public places back home in their states.

PC-1111-05 #Selasatanparokok (Tuesday without cigarettes)

D Putri Margiani,¹ F Prawirakusumah² ¹National Commission on Tobacco Control, Bandung, ²National Commission on Tobacco Control, Bandung, Indonesia. e-mail: deligiapm@gmail.com

Background and challenges to implementation: The tobacco industries kills about 521 people per day and recruits 10,000 youth per day ages 13 – 14 years in Indonesia¹. Advertisements are one of the tactics used to attract new smokers. * In response to the strong presence of the tobacco industries in our community, we formed an organization Bebas Rokok Bandung (Smoke - Free Bandung) 3 years ago and have held a variety of campaign. One campaign that has been implemented successfully is #SelasaTanpaRokok (Tuesday Without Cigarettes).

Intervention or response: The #SelasaTanpaRokok campaign became a part of our Mayor's weekly schedule, aimed at reaching out to the Bandung community. #SelasaTanpaRokok has reached 2 735.435 tweets with the original tweet representation breakdown being 32.80%, retweets consisting of 65.30%, and replies at 1.90%. The #SelasaTanpaRokok campaign started with the programs targeted at the community. Other days of the week include a culinary night, English language day, local language, and car free day for example. Then Bebas Rokok Bandung advocated to the Mayor to make Tuesday as #SelasaTanpaRokok. The #SelasaTanpaRokok campaign was adopted by the Government of Bandung on 6th January 2014 by the Mayor's of Bandung, Ridwan Kamil through his personal twitter account, according to www.keyhole.co (per 2 month in february - march 2015)

Results and lessons learnt: As a result our advocacy and the Mayor's support, #SelasaTanpaRokok has also been carried out by various agencies in Bandung (Departement of Education, Departement of Health, Departement of youth and Sport, and the City Government) which prohibit the employees from smoking on Tuesday. The program has also inspired other regions like Garut and Tasik to adopt one day without cigarettes

Conclusions and key recommendations: Indonesia is the 5th highest user of social media and the most active in the

world. Other advocates can learn #SelasaTanpaRokok campaign how to engage the power of social media towards tobacco control goals and thereby influence stakeholders on policy decisions regulations in their community.

PC-1112-05 Enforcement of smoke-free laws in public transport terminals in metropolitan Manila, Philippines, after the sin tax law

M L Alzona,¹ L Wood² ¹Metropolitan Manila Development Authority, Makati City, Philippines; ² International Union Against Tuberculosis and Lung Disease, Paris, France. Fax: (+632) 882 0870. e-mail: drlalzona@yahoo.com.ph

Background and challenges to implementation: Raising taxes is the most effective measure for tobacco control. The Philippines passed the Sin Tax Law in December, 2012. A year later, the Department of Health announced a decrease in consumption of cigarettes among the young and poor. To be most effective, tax increases must be supported by other comprehensive tobacco control strategies, including enforcement of smoke free laws. The Metropolitan Manila Development Authority supported by a grant from Bloomberg Philanthropies through The Union, launched enforcement of the Smoke Free Environment policy in public transportation terminals in Metropolitan Manila in July, 2011. From inception until March 31, 2014, a total of 220, 157 violators have been apprehended for smoking.

Intervention or response: To determine if the Sin Tax Law (STL) had an impact on smoking in public transportation terminals, a review of smoking violations from 3 apprehension sites was undertaken. Data was compared from the period prior to STL (July, 2011 to December, 2012) to period following implementation of STL (July, 2013 to December, 2014). Number of enforcers and duration of enforcement periods remained the same.

Results and lessons learnt: There was 112% increase in apprehensions after STL. With its passage, the industry aggressively advertised. "Don't Be a Maybe" signs became prominent at points of sale. Elections inhibited officials from acting appropriately on TAPS violations. While STL increased price of cigarettes, they remained cheap (a premium brand sells for USD 1.34 per pack) and the industry swamped the market with lower price brands. Single cigarettes are widely sold and cost from 2 to 6 US cents only. 70% smoking violators in public transportation terminals are the working class and can still afford cigarettes after the STL.

Conclusions and key recommendations: Despite tax increase, smokers continued by switching to lower price brands. Many found it difficult to quit because of aggressive advertising and uncontrolled sale by the stick. Information on harms must be sustained using mass media for greater reach. Support to quit is needed. SFE and TAPS enforcement can be strengthened with public engagement. Monitoring smoking violations in public places provides valuable insights into the impact of tax increases on smoking behaviour.

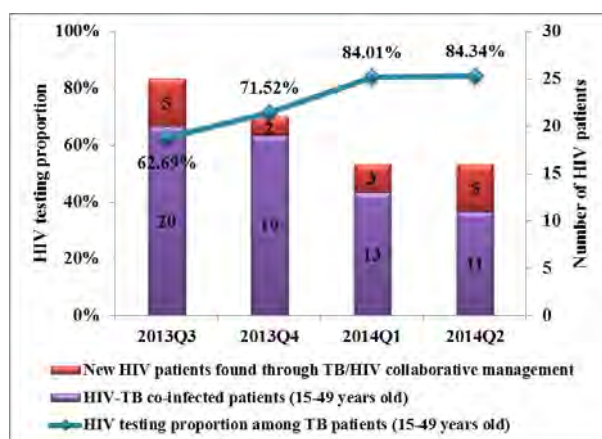
49. Strategies to improve TB-HIV screening and service integration

PC-1113-05 Enhancing integration of HIV testing into the TB control program in Taiwan

W-T Hsieh,¹ M-Y Chiou,¹ P-H Lee,¹ P-C Chan,¹ S-L Yang,¹ C B Hsu,¹ C-H Chen¹ ¹Centers for Disease Control, Taipei, Taiwan. e-mail: bubbles1221toxi@gmail.com

Background: People living with human immunodeficiency virus (PLWH) had 29 times higher risk to develop active tuberculosis (TB) than non-HIV infected persons, and TB was the leading cause of death among PLWH. Collaborative management of TB-HIV had been recommended by WHO that aimed to reduce the burden of TB and HIV in populations affected by both infections. However, a previous study revealed that only 17% of all TB patients received HIV testing in Taiwan. In 2012, the prevalence of HIV among new TB patients with age of 15-49 years old was 2.42%, which was higher than the HIV prevalence of general population of the same age group (0.2%).

Intervention: All newly confirmed TB patients with aged 15-49 years old in TB registry during July 2013 to June 2014 were cross-linked with the national HIV surveillance system by individual identification. If unknown HIV status was found, the public health staff would provide counseling and testing, or encourage TB patients to receive HIV testing in TB care facilities within the target period (3 months after the date of TB reporting). We used descriptive analysis to depict the trend of targeting patients receiving HIV testing, the HIV prevalence and the result of linking-to-care among young HIV-TB co-infected patients in our study.



Results: A total of 3596 TB patients aged 15-49 years old were reported, and 63 HIV co-infected patients had been identified before TB reporting. We found that 2664 TB patients (overall 75.4 %) received HIV testing with the increasing trend of testing proportion during the study period. The majority of TB patients received HIV testing at health care facilities (63.4%), and 15 (0.56%) newly diagnosed HIV- infected patients were identified. The prevalence of HIV infection among TB patients aged 15-

49 years old was 2.17%, and the coverage of initiating highly active anti-retroviral therapy (HAART) among TB-HIV patients was up to 89.7%.

Conclusions: The proportion of HIV testing could be improved among young TB patients by enhancing TB-HIV collaborative management in Taiwan. This intervention identified HIV-positive TB patients who were unaware of their HIV status and linked or referred to appropriate medical care. The HIV prevalence among TB patients was stable after enhancing HIV surveillance. To improve TB-HIV collaborative management, further study about the reasons why TB patients refused HIV testing should be conducted.

PC-1114-05 Progress in TB-HIV collaborative activities in the two regions of Ethiopia

T Anteneh,¹ M Nigussie,² D Habte,¹ D J Dare,¹ I J Abdulahi,³ M Aseresa Melese,¹ Y Haile,⁴ P G Suarez⁵

¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, ²Amhara Regional Health Bureau, Bahar Dar, ³Oromia Regional Health Bureau, Addis Ababa, ⁴United States Agency for International Development (USAID), Addis Ababa, Ethiopia; ⁵Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: tanteneh@msh.org

Background and challenges to implementation: The HIV epidemic presents a major challenge to the control of tuberculosis in Ethiopia. To address this challenge, the Ethiopian Federal Ministry of Health (FMOH) in collaboration with development partners has been implementing the WHO recommended TB-HIV collaborative activities for over a decade now. In this paper, we present progress in key TB-HIV collaborative activities in two regions of the Ethiopia, which were supported by the Help Ethiopia Address the Low Performance of TB (HEAL TB) - five year USAID funded project, led by Management Sciences for Health (MSH) since July 2011. **Intervention or response:** Federal Ministry of Health with support from HEAL TB provided training to health care workers on the comprehensive TB-HIV curriculum, regular mentoring and supportive supervision through the district health system, and job aids and supplies. We also ensured adequate supply of test kits, laboratory supplies and medicines through the government system. Health facilities that did not meet the minimum service quality were placed on a performance improvement plan and closely monitored every quarter to ensure progress. We present the result of the data collected from health facilities.

Results and lessons learnt: By June 30, 2014, the proportion of TB patients tested for HIV increased from 70% in October 2011 to 94% in the first phase supported 10 zones. Similarly, the testing rate increased from 85.5% to 94% in the 11 zones supported during the second phase. Of those tested, 89.0% and 88.4% were linked to ART services in the phase 1 and 2 health facilities respectively by the end of June 30, 2014. The percentage of newly diagnosed TB-HIV co-infected patients started on ART has reached 79%, from as low

as 35% at baseline. Similarly, CPT uptake rate among TB-HIV patients improved from 18% to 87.4%. On the other hand, the proportion of HIV infected TB patients declined from 11% to 7.5% over the last three years (Table). During July 2012-June 2013, HIV testing among TB patients in the project supported zones reached 95.4%.

Conclusions and key recommendations: Capacity-building of health care workers through training and regular mentoring are effective interventions to improve HIV and TB services for TB-HIV co-infected patients.

Table TB-HIV program performance in HEAL TB supported zones, Ethiopia

Project phase	Period	Total new TB cases	% TB patients with HIV result	% HIV positive	% started on CPT	% enrolled on ART
Phase I	Jul 12-Jun 13	22 778	95.4%	10.4%	87.4%	79.0%
	Jul 13-Jun 14	23 437	94.0%	8.0%	86.0%	77.0%
Phase II	Jul 11-Jun 12	20 538	88.0%	11.0%	NA	NA
	Jul 13-Jun 14	17 989	94.0%	7.0%	90.0%	82.0%
Phase I and II (Overall)	Jul 13-Jun 14	41 426	94.0%	7.5%	88.0%	80.0%

PC-1115-05 Road-map to effective community-centric TB-HIV collaboration: contribution of the NGO-consortium of India in GF-supported TB project

S Mukhopadhyay,¹ S Cornelius,¹ B Samuel,¹ M Jose,¹ D Thuralayil Cherian,² G Karapetyan² ¹World Vision India, New Delhi, India; ²World Vision US, Washington DC, USA. e-mail: sugata64@gmail.com

Background and challenges to implementation: TB-HIV collaboration is mostly health-system centric which means the activities aim generally to medical management of co-infected cases without considering much the importance of community sensitization and mobilization. The NGO-consortium led by World Vision India (WV India) made meaningful contribution to bring the TB-HIV collaborative programs at community level. It strengthened key linkages which not only enhanced notification of TB-HIV co-infected cases and TB cases in HIV high-risk groups but also improved their service-utilization.

Intervention or response: Under the GF-supported TB Project (Axshya) WV India and 6 partners established linkages with 1) 65 district level networks of PLHIV and 2) 450 Targeted

Intervention: (TI) HIV projects in 74 districts of 8 states of India. Using specially designed training modules, 1617 PLHIV and 374 Program Managers of the TI projects were sensitized on TB by Project Axshya from Apr'13 to Dec'14. They were also assisted in developing and implementing their organizational TB action plans including creating case-wise line-lists of the referrals to

TB services and their outcomes. These activities enabled PLHIV and HIV high risk groups to gain knowledge and awareness on TB, reduce stigma and myths and subsequently utilize the services under the national TB & AIDS programs.

Results and lessons learnt: Between April 2013 to December 2014 the PLHIV networks identified 986 presumptive TB cases (following WHO's standard symptom selection criteria) through community level TB education and active case search, 953 of them tested in local RNTCP-affiliated laboratories, 83 of them found to be SS+ Pulmonary TB and put on DOT. They were also initiated ART and CPT. The HIV-TI projects referred 504 presumptive TB cases from the high risk groups like FSWs, IDUs, migrants, MSM/TG and truckers, 493 of them tested in RNTCP, 23 detected with SS+ Pulmonary TB and put on DOT. The project spent around 30 USD to help the PLHIV networks and TI-HIV projects to detect one TB case.

Conclusions and key recommendations: The interventions establishing linkages with PLHIV networks and TI projects created the road-map to effective community-based TB-HIV collaborative programs where dual infected, affected and vulnerable community groups and networks are sensitized, de-stigmatized and mobilized to optimally utilize the existing services with the help of a NGO-consortium under the GF-supported TB project.

PC-1116-05 Uptake of partner testing among notified TB cases in Kenya in 2013

D Nyangahu,¹ R Muthee,¹ B Langat² ¹National Tuberculosis, Leprosy and Lung Disease Program, Nairobi, ²The National Treasury, Nairobi, Kenya. e-mail: drunyaboke@gmail.com

Background: Routine HIV testing for people with tuberculosis (TB), their partners' and families, and people with symptoms of TB is one of the priorities of HIV-TB interventions as outlined by PEPFAR. Partner testing and counseling is one of the critical action steps if the mileage on PwP interventions has to be attained. The study sought to describe the uptake of partner testing, its effect on uptake of other TB-HIV interventions and treatment outcomes among TB-HIV co-infected patients.

Design/Methods: A retrospective study based on the Kenya national TB surveillance data of 2013 was conducted to describe the uptake of partner testing among TB patients. Descriptive statistics were used and chi-square tests were applied to establish if there was any association among the paired variables using SPSS.

Results: Partner testing uptake was 37.1 % and 5 % of the partners declined the HIV test. The discordance rate among HIV+/TB patients was 22.3 % while among HIV-/TB patients was 2%. Amongst TB-HIV+ patients whose partners were tested, 89.8 % of them were on ART as compared to 79.7 % of those whose partners had not been tested. There were better outcomes (treatment completion) among those who had their partners tested,

and fewer out of controls were recorded from HIV-positive TB patients whose partners had been tested.

Conclusion: HIV Partner testing among TB patients is an acceptable public health intervention that can roll out in a TB control program. The partner testing uptake is low hence it is paramount to enact practical and plausible measures to mitigate challenges and setbacks to partner testing. Special interventions need to be tailored to hard to reach areas, as in addition to having low uptake, the public sector registered lower performance in comparison to the private sector in these areas. HIV partner testing can contribute to better linkage to ART and CPT services. There is need to undertake further research on provider and client factors that affect uptake of partner testing.

PC-1117-05 The majority of TB cases among PLHIV in Lesotho are clinically diagnosed: START study baseline characteristics

D O'Connor,^{1,2} K Frederix,¹ L Maama-Maime,⁴ S Saito,^{1,3} Y Hirsch-Moverman,^{1,3} B Pitt,¹ A Howard^{1,3} ¹ICAP at Columbia University, New York, NY, ²Columbia University, College of Physicians and Surgeons, New York, NY, ³Columbia University, Mailman School of Public Health, New York, NY, USA; ⁴Lesotho Ministry of Health, Maseru, Lesotho. e-mail: koenfrederix70@gmail.com

Background: The Start TB patients on ART and Retain on Treatment (START) Study is an ongoing cluster-randomized trial evaluating the effectiveness, cost-effectiveness and acceptability of a combination intervention package (CIP) vs. standard of care (SOC) to improve early ART initiation and TB treatment success among adults with TB-HIV in Berea district, Lesotho.

Methods: Twelve health facilities (HF) were randomized to CIP or SOC, with stratification by HF type (hospital or health center). A standardized survey was administered to assess available services prior to CIP implementation. CIP includes nurse training and mentorship; patient education and transport reimbursement for patients and treatment supporters; and village health worker (VHW) and SMS text message adherence support. After CIP implementation, routine clinical data were collected for all new adult TB-HIV patients. Descriptive statistics were used to characterize baseline facility and participant characteristics. Chi-square, Fisher's Exact, and t-tests were used to compare characteristics by study arm.

Results: Of the 12 HF, 4 are managed by Government of Lesotho (GOL), 7 by Christian Health Association of Lesotho (CHAL), and 1 by Red Cross; 10 are rural and 2 semi-urban. Prior to CIP implementation, 6 HF had nurses trained in TB-HIV co-treatment, 12 provided VHW adherence support, 6 provided patient education, and none provided transport reimbursement or SMS adherence support. Among 624 new TB-HIV patients between 4/2013-9/2014, 62% were at CIP HF, mean age was 39, 57% were male, 15% were factory or mineworkers, 85% had category I TB treatment, 85% had pulmonary TB (smear positive 30%, smear negative 54%, no smear 16%) and 21% were on ART at TB treatment initiation. Median (IQR) time from HIV

diagnosis to TB treatment initiation was 14days (1-224) and, among 99 TB-HIV patients with available data, median (IQR) CD4 count was 140cells/mm³ (59-323). A greater proportion of patients at CIP HF had category II TB treatment (19% vs. 10%, $P = 0.002$). Other characteristics did not differ significantly by study arm.

Conclusion: Seventy percent of pulmonary TB patients were clinically diagnosed; 16% were without sputum smear. Improved clinical and laboratory diagnostic capacity for TB among PLHIV in Lesotho is urgently needed.

Facility Characteristics			Participant Characteristics		
	CIP (N=6) n (%)	SOC (N=6) n (%)		CIP (N=387) n (%)	SOC (N=237) n (%)
Type of facility			Mean (SD) age, y	38.8 (10.7)	39.7 (11.4)
Health center	5 (83.3)	5 (83.3)	Male	227 (58.7)	127 (53.6)
Hospital	1 (16.7)	1 (16.7)	Occupation*		
Facility management			Factory worker	19 (5.1)	13 (5.8)
GOL	2 (33.3)	2 (33.3)	Miner/ex-miner	36 (9.8)	21 (9.4)
CHAL	3 (50.0)	4 (66.7)	Other	314 (85.1)	189 (84.8)
Red Cross	1 (16.7)	0 (0)	TB treatment category		
Facility location			Category I	314 (81.1)	214 (90.3)
Semi-urban	2 (33.3)	0 (0)	Category II	73 (18.9)	23 (9.7)
Rural	4 (66.7)	6 (100)	Site of disease		
Patient support			Pulmonary	337 (87.1)	193 (81.4)
Health education	3 (50.0)	3 (50.0)	Smear positive*	93 (28.7)	59 (32.2)
Village health worker	6 (100)	6 (100)	Extra-pulmonary	50 (12.9)	44 (18.6)
Transport reimbursement	0 (0.0)	0 (0.0)	On ART at TB treatment initiation*	89 (23.6)	42 (18.1)
SMS adherence support	0 (0.0)	0 (0.0)	Median (IQR) CD4, cells/mm ³	147 (81-266)	132 (55-368)
Nurses trained in TB/HIV co-treatment	3 (50.0)	3 (50.0)	Median (IQR) time from HIV diagnosis to TB treatment initiation, days*	14 (1.0-252.5)	13 (1.0-138.0)

*n values where less than 624; Occupation, n=592; Smear microscopy, n=601; On ART at TB treatment initiation, n=609; Median CD4, n=99; Median time from HIV diagnosis to TB treatment initiation, n=487

PC-1118-05 Improving antiretroviral therapy uptake for TB-HIV co-infected patients in Nkangala District, Mpumalanga Province

M Sithole,¹ J Zingwari¹ ¹University Research Co LLC, Pretoria, South Africa. e-mail: jebbyzing@gmail.com

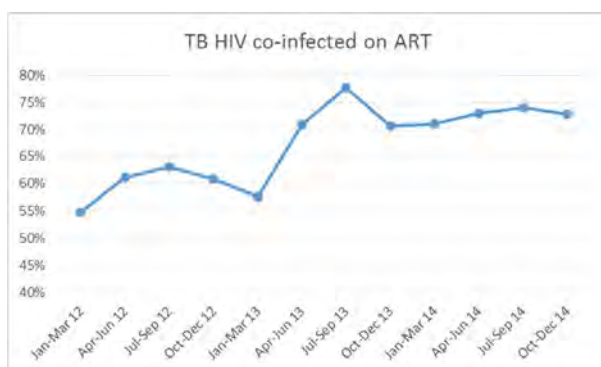
Background: Nkangala District is located in Mpumalanga Province, one of the top four high HIV burden provinces in South Africa. In 2011, the district reported 5742 new TB cases. 61.5% of the TB patients are co-infected with HIV. South African TB guidelines recommend antiretroviral therapy (ART) for all TB HIV co-infected patients. Baseline assessment conducted in January- March 2012 in Nkangala district, revealed low ART uptake among TB-HIV co-infected patients with 54.8% of TB HIV co-infected patients on HAART. Poor TB HIV service integration, poor adherence to guidelines and poor recording and data management were identified as contributors for poor performance.

Interventions: To address these challenges, the USAID TB program collaborated with the district health team and conducted support supervisory visits, focusing on high case load, poorly performing facilities. Activities conducted during these visits included mentoring and coaching, data validation and analysis of paper-based TB registers and patient files and data from the electronic TB register to identify performance gaps related to ART initiation. Training was given to health care workers on

quality improvement. Facilities were supported in developing and implementing quality improvement plans.

Results and lessons learnt: In Nkangala district, ART uptake increased from 54.8% in Jan-March 2012 to 73% in Oct-Dec 2014 as shown in figure below. Integration improved patient management as this encouraged team based approach to TB and HIV services thus improving quality of services.

Conclusion: Integration of TB and HIV services in facilities improves the management of TB HIV co-infected patients. This should be supported by comprehensive and integrated supervision support. As facilities scale up integration of TB and HIV services, there is need to constantly monitor implementation and assess the impact of different models using standardised outcome measures. Data management is critical to the successful integration of TB and HIV services.



PC-1119-05 Performance of TB screening and testing in sub-populations of people living with HIV in Uganda

F Semitala,^{1,2,3} C Yoon,^{3,4} J Katende,^{1,3} A Andama,^{2,3} P Byanyima,³ I Ayakaka,³ M Kanya,^{1,2,3} A Cattamanchi^{3,4}

¹Makerere University Joint AIDS Program, Kampala,

²Makerere University College of Health Sciences, Kampala,

³Infectious Diseases Research Collaboration, Kampala, Uganda; ⁴San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA. e-mail:

semitala@gmail.com

Background: WHO recommends that all PLHIV should be screened for active tuberculosis (TB) using a symptom-based tool, followed by confirmatory testing if symptomatic. However, the utility of symptom screening and confirmatory testing among sub-populations of PLHIV are unknown. We evaluated the diagnostic accuracy of the WHO symptom screen, smear microscopy and Xpert MTB/RIF (Xpert) in two important sub-populations: clients new to and clients already enrolled in HIV/AIDS care.

Design/Methods: We enrolled consecutive PLHIV with CD4 cell-counts ≤ 350 cells/uL presenting to the Mulago Immune Suppression Syndrome Clinic (Kampala, Uganda) from July 2013-April 2015 for antiretroviral therapy (ART) initiation. We administered the WHO symptom screen and collected sputum for smear microscopy, Xpert

and culture. We calculated the diagnostic accuracy of symptom screening in all clients and confirmatory tests (smear and Xpert) among symptomatic clients in reference to culture. We compared clinical characteristics and diagnostic accuracy between clients new to and clients already enrolled in HIV/AIDS care.

Results: Of 665 clients, 232 (35%) were new to HIV/AIDS care. These clients had significantly lower median CD4 cell counts (144 vs. 199 cells/uL, $P = 0.003$) and a higher prevalence of culture-positive TB (24% vs. 9%, $P < 0.001$) than clients already enrolled in HIV/AIDS care. The majority of clients new to (93%) and already enrolled in (85%) HIV/AIDS care screened positive by the WHO symptom screen. In both sub-populations, the WHO symptom screen had high sensitivity (98% [95%CI 90-100%] and 95% [95%CI 82-99%], respectively) but poor specificity (8% [95%CI 5-14] and 16% [95%CI 13-20%], respectively) for active TB. The sensitivity of smear (35%, 95%CI 25-46%) and Xpert (47%, 95%CI 37-58%) was poor but specificity of both tests was high (99%, 95%CI 98-99.9%), with no clinically significant differences between sub-populations.

Conclusion: TB prevalence is high among PLHIV initiating ART in Kampala, especially among clients new to HIV/AIDS care. Symptom-based screening results in nearly all clients requiring confirmatory TB testing. Neither smear nor Xpert were sufficiently sensitive confirmatory tests, missing more than half of all TB cases. Until better screening and rapid confirmatory tests are available, routine culture should be considered prior to ART initiation, particularly for all clients new to HIV/AIDS care

PC-1120-05 Improving antiretroviral therapy uptake among TB-HIV co-infected clients in care: lessons from quality improvement implementation in Kampala, Uganda

A Burua,¹ E Mabumba,² D Lukoye,¹ M Kenneth,¹

M Ruhweza,¹ F Mugabe,² B Woldemariam,³ P G Suarez⁴

¹Management Sciences for Health/Track Tuberculosis Activity Project, Kampala²Uganda National TB and Leprosy Program,

Kampala, Uganda; ³Management Sciences for Health, Addis Ababa, Ethiopia; ⁴Management Sciences for Health,

Arlington VA, USA. e-mail: aburua@msh.org

Background and challenges to implementation: HIV and TB continue to be diseases of public health concern in Uganda. To decrease the burden of HIV among TB patients, the national guidelines recommend early initiation of antiretroviral therapy for TB-HIV co-infected patients. At the end of 2012, ART uptake among TB-HIV co-infected patients in Kampala was only 56% far below the national targets of 100%.

Intervention or response: The USAID funded TRACK TB project provides technical support to Kampala Capital City Authority in TB control including implementation of continuous quality improvement approaches in TB care among other things. An assessment of TB HIV collaborative activities indicated gaps in provision of ART to TB-HIV co-infected patients, inadequate pro-

vider capacity to provide ART and incomplete recording. Five out of the 20 high volume health facilities in Kampala piloted the Quality Improvement (QI) interventions which includes problem identification, analysis, team problem solving, implementation of solutions and monitoring. The Health care providers in these five facilities were trained and received monthly coaching in QI methods which included onsite training and mentorship on management of ART and allocation of clinic staff to harmonize TB and ART registers regularly. The other facilities received routine mentorships in TB care. The facilities performance was then measured by tracking indicator on proportion of TB-HIV co-infected patients that received ART.

Results and lessons learnt: ART provision for TB-HIV co infected patients at the 5 pilot facilities improved from 71.4% in February to 100% in December 2014. In contrast, 8 health facilities comparable with the pilot facilities that had no QI interventions improved from 67.6% in February to 82.4% in July but later declined to 66.7% in December 2014. Challenges of poor involvement of the facility leadership in QI activities affected performance and a lesson learnt is that on-site mentorships and QI coaching should target the facility leadership as well to achieve sustainable improvements.

Conclusions and key recommendations: Mentorship combined with application of QI methods and engagement of health facility leadership were found to be feasible for improvement of TB care and yields more improvement compared to provision of only clinical mentorship support.

PC-1121-05 Factors related to sub-standard offer and documentation of HIV testing for persons with tuberculosis in a low-incidence, high-resource setting

R Bhavaraju,^{1,2} M Passannante,² C Delnevo,³ E Pevzner,⁴ M J Lewis³ ¹International Union Against Tuberculosis and Lung Disease, New York, NY, ²Rutgers University, Newark, NJ, ³Rutgers University, New Brunswick, NJ, ⁴US Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: rbhavaraju@theunion.org

Background: The recommended offer of HIV testing to persons with TB in the United States is lower than national standards and is less than in many resource-poor countries. US patients have high access to testing and the ability to manage co-infected patients. This study explored factors related to offer and documentation of HIV testing in the State of New Jersey.

Design/Methods: Surveillance data (2000-2013) for 9502 persons with TB were analysed looking at age, sex, substance use, correctional/long term care facility residence, birthplace, race/ethnicity and year. Using outcomes of offer and documentation of testing, χ^2 tests were done and 2 logistic regression models created, stratifying by provider type. The latter was based on a qualitative study by these authors that indicated a difference in HIV testing exists in patients seeing private and public health providers.

Results: Less than 60% of patients had a documented HIV test status. Fifty percent of patients were seen by public health providers and this increased yearly as did the offer and documentation of HIV testing ($P < 0.0001$). In the 3 strata models, females were less likely to be offered testing but documentation of HIV testing status was 17-25% more likely to be available. Birthplace was not a significant predictor in all strata, however, in the public sector, non-US-born persons were ~30% less likely to be offered HIV testing (OR=.70; 95%CI =.58-85), but with greater odds of documented testing status (OR =1.34; 95%CI =1.13-1.60). By age, persons 65+ were most likely to have HIV testing offered compared to other age groups but presence of documented results were 1.7-3.5 times the odds (95%CI = 1.46-4.16) in other age groups. Substance users had double the odds of HIV testing offered in all strata (OR = 2.289-2.61; 95%CI = 1.77-4.37). Persons of Black race also had 2-3 higher odds of HIV testing offered and documentation compared to White persons in all strata (OR = 2.45-3.06; 95%CI =1.81-3.83); other races (with the exception of Hispanics under private care) were less likely to be offered or have documented HIV testing.

Conclusion: Despite access, universal HIV testing rates in TB patients is low, and varies by provider type and demographic characteristics. The lack of documented testing status in a system with advanced disease surveillance provides an incomplete picture and lost opportunities for the appropriate care of co-infected persons. Educational outreach to TB providers is needed.

ABSTRACT PRESENTATIONS SUNDAY 6 DECEMBER 2015

e-POSTER SESSIONS

11. m-health solutions

EP-185-06 WelTel LTBI: participant experiences with a text-messaging intervention to improve latent tuberculous infection treatment adherence in Canada

K Smillie,^{1,2} D Mahal,² M Van Der Kop,^{2,3} J Johnston,^{1,2} R Lester² ¹British Columbia Centre for Disease Control, Vancouver, BC, ²University of British Columbia, Vancouver, BC, Canada; ³Karolinska Institutet, Stockholm, Sweden. e-mail: kirsten.smillie@bccdc.ca

Background: Successful treatment of latent tuberculosis infection (LTBI) is critical to reduce the impact of TB; however, in North America, fewer than half of individuals starting LTBI treatment complete therapy. A multi-site, randomized controlled trial is testing the effectiveness of a text-messaging intervention to improve LTBI treatment completion in British Columbia, Canada. We conducted a qualitative study to understand participants' experiences with the intervention.

Objectives: 1) acceptability of the intervention; 2) if the intervention mitigated barriers to care; and 3) whether it affects clients' perceptions of the healthcare system.

Design/Methods: Participants were recruited from two urban TB clinics in British Columbia. Individuals were eligible to participate if they were ≥ 19 years of age; starting LTBI treatment; able to send text messages in English or have assistance text-messaging; access to a mobile phone. Interviews were conducted either in-person or over the telephone and were recorded and transcribed verbatim. Interview data were analyzed using inductive thematic analysis. Transcripts were read numerous times by two researchers who then coded important concepts, events, and experiences using NVivo 9 software.

Results: To date, we have conducted 12 interviews with participants, eight of whom were women. Recruitment will continue until data saturation is reached. The median age of participants was 37 years (range: 23–56). Of the 12 participants, nine had completed LTBI treatment, while four stopped treatment early due to side effects. All interviews were conducted in English except for one, which was conducted in Punjabi. Participants found the intervention easy to use. The intervention was appreciated for its simplicity, as it only required basic English to respond to the open-ended question (Are you OK?) with a yes/no answer, and the use of any type of mobile phone. Nearly all participants reported the weekly text-message helped them engage in treatment,

whether by being reminded of their health, or having timely access to clinician support. Many participants felt cared for as a result of the weekly message. Some participants found the message to be monotonous and recommended varying or personalizing the outgoing message.

Conclusion: The weekly SMS intervention was accepted by a diverse group of participants who found it easy to use, and appreciated the increased communication and provision of support from clinicians.

EP-186-06 Real-time monitoring of drug-resistant TB cases for better programme management: e-Smarts in Andhra Pradesh, India

J Jaju,¹ S Achanta,¹ J P Carel,¹ M Parmar,¹ A Sreenivas¹ ¹World Health Organization Country Office for India, New Delhi, India. e-mail: achantas@rntcp.org

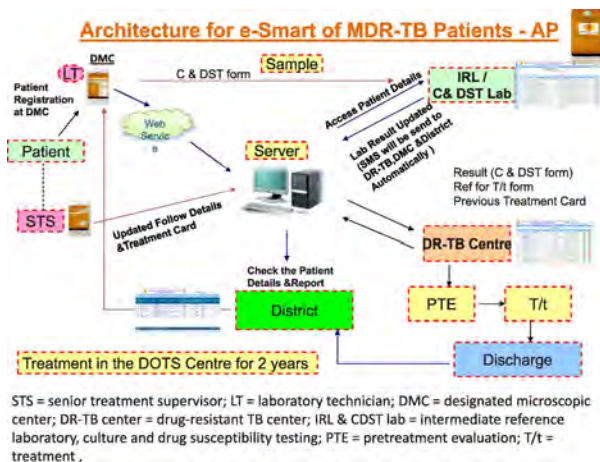
Background: Programmatic management of Drug Resistant TB in India faced large scale recording and reporting challenges. There was no real time data exchange between centralized Culture & Drug Susceptibility Testing (C&DST) Labs, Drug Resistant TB (DR TB) centres where treatment is initiated and Districts where ambulatory treatment is continued. The aggregate reporting system though electronic was not suitable for efficient patient wise management or for data analysis. A set of five treatment cards at various levels were maintained for each patient to update treatment status for the two years of MDR-TB treatment. Paper based system of communication at multiple levels caused delay in transmission of information, transcription errors and involved tedious processes to update records and prepare programme reports

Intervention: In 2012, an electronic web based surveillance system 'e-Smarts' was customized in AP, linking Labs, DR TB centres and districts for real time data exchange. Patient wise information of drug resistant TB suspects, test results, treatment initiation details, ambulatory DOT is entered electronically. Auto generated e-mails and messages of test results to programme staff, off line data entry mode, automatic treatment card updation and technical platform which is compatible with National e-recording system, Nikshay, are some of its unique features

Results: e-Smarts is being used by 6 C&DST Labs, 19 DR-TB centres and 24 Districts in erstwhile AP (Telangana and AP) since 2013. Currently, 45546 details of samples have been entered at C&DST Labs, 32053(70%) test results declared, 3739 started on treatment and 2286 (61%) treatment cards updated. Programme staff received 50691 e-mails and 56859 messages. This tool is used for monitoring time to declare results, time to treatment initiation and regular updating of treatment cards. It is also used in identifying regional level gaps in programme implementation. Time taken to prepare routine programme quarterly reports has decreased from 3 days to a few minutes. Compliance in reports generated by e-Smarts and by manual prepara-

tion has increased to 95 % in 4th quarter 2014 versus 2nd quarter 2014 when it was 70%.

Conclusions: Data quality and use of data for analysis has improved. Programme is gradually transitioning from a paper based system to a paperless electronic system. Advantages are real-time data sharing at all levels, reduction of paperwork and decreased errors due to data transcription



EP-187-06 Government commitment in GxAlert mobile technology solution enhanced DR-TB management in Nigeria

K Jimoh Agbaiyero,^{1,2,3} L Ekblad,^{1,3} M Benezet,³ G Akang,² J Takle,⁴ C Macek⁴ ¹Abt-HFG Project, Abuja, ²National TB and Leprosy Control Program, Abuja, Nigeria; ³Abt Associates, Bethesda, MD, ⁴SystemOne, Boston, MA, USA. e-mail: kehindeagbaiyero@yahoo.com

Background and challenges to intervention: The World Health Organization rank Nigeria among high DR-TB burden countries in the world. The country relies on GeneXpert machine to often diagnosis DR-TB. However, testing for TB and reporting results is a lengthy process partly due to a reliance on paper records, overburdened labs, and slow data transit systems making it difficult for the Nigeria Tuberculosis Program to account for patients diagnosed for DR-TB, enroll them for care and management decisions are not timely or focused on priority needs.

Intervention: GxAlert is configured on GeneXpert systems by installing a modem from a telecom that gives access to internet and encrypting the data sent to the GxAlert database. The system sends GeneXpert MTB/RIF diagnostic results in real time to a secure web-based database, shortening a reporting period from months to mere seconds and enabling better data quality and faster recruitment of patients into appropriate care. Due to its success in improving data system and patient management, the government decided to scale up to all facilities in the country.

Results and Lesson Learnt: GxAlert eliminated the need for human error in data entry, reduced the lag time, and helped pinpoint patients that should be place on care.

More patients have been enrolled for DR-TB care. GxAlert strengthened surveillance of DR-TB, TB in children and TB in the HIV infected, speeding response and improving programmatic decision making for enrollment and placement of DR-TB patient on treatment, GxAlert also Prevent cartridge stock-outs and track usage for accurate ordering. GxAlert has received adequate government commitment.

Conclusions and key recommendations: Networking all the rapid GeneXpert diagnostic machines in Nigeria to GeneXpert, the National TB and Leprosy control program and private health systems are now able to report rapid TB and HIV indicators automatically and send targeted action messages ("alerts") by SMS/text and/or email to health system decision makers, deliver real-time disease surveillance data to the GxAlert database. There's ownership and sustainability from the government of Nigeria as the NTP is scaling up to all the genexpert facilities nationwide.

EP-188-06 Patient incentives, mobile health and electronic medical records for community-based DR-TB treatment at Indus Hospital, Pakistan

H Hussain,^{1,2} A Malik,^{1,2} N Salahuddin,¹ S Khowaja,² S Butt,¹ M Basir,¹ U Khan,² A Khan² ¹Indus Hospital, Karachi, ²Interactive research and Development, Karachi, Pakistan. e-mail: hamidah.hussain@irdresearch.org

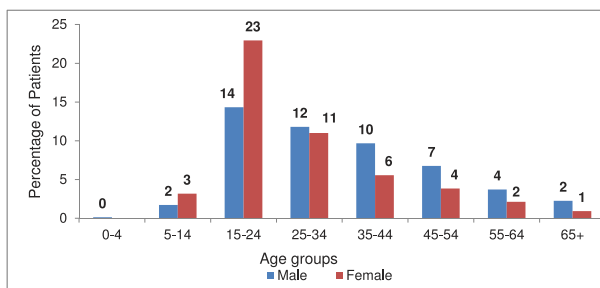
Background and challenges to implementation: The Indus Hospital in Karachi started treating DR-TB patients in an ambulatory setting in 2008 with the objective of providing free, comprehensive, community based management for drug-resistant tuberculosis. In 2010 The Indus Hospital became a Sub-Recipient for GF and was one of three initial PMDT sites in Pakistan.

Intervention or response: We conducted a cohort based retrospective review of the DR-TB patient enrolled from Q4 2008 till Q1 2015. All patients are provided with consultations, diagnostics; monthly follow-up; psychological counseling; and quality assured second line drugs. A treatment supporter provides daily DOT at patients home. Patients are also provided with monthly enablers in the form of food basket for family and travel cost. The treatment supporter also receives the same food basket. Nutritional supplements are provided to patients with low BMI. Data are collected and maintained in open source electronic recording and reporting system.

Results and lessons learnt: Of the 754 patients enrolled with a median age of 30 years (IQR 22-40 years). 50% were females; 37% of all patient and 23% of all female were between 15-24 years of age. Majority 653 (87%) had history of first or second line drugs where as 101 (13%) were new cases. 547 (72%) patients were confirmed MDR while 119 (16%) patients were MTB R resistant through Xpert; 12% were XDR, PDR and mono DR patients. The DST for second line drugs showed 11.5% of patients resistant to Ethionamide; 23.5% resistance to Fluoroquinolones (FQ); 2.3% were resistant to any injectable and 3.7% of patients were

resistant to both FQ and any of the injectable. Treatment outcomes are available for 456 (60%) patients. The overall treatment success rate for MDR patients was 75% and 61% for XDR where as yearly cohort wise treatment success in 2009 was 100 %, 78% in 2010, 74% in 2011 and 79% in 2012. Over all mortality rate was 12%, default rate of 4% and 6% patients failed treatment.

Conclusions and key recommendations: Ambulatory care model with patient enablers and efficient tracing through electronic data management is highly successful in high burden and low resource setting like Pakistan and should be scaled up.



EP-189-06 Satellite technologies use for MDR-TB treatment support

A Ismayilov,¹ A Trusov,² M Sianozova,³ F. Rahimov,¹ S. Odinaeva,¹ D. Ismatov⁴ ¹Project HOPE, Dushanbe, Tajikistan; ²Project HOPE, Millwood, VA, USA; ³Project HOPE, Yerevan, Armenia; ⁴Sarfaro LLC, Dushanbe, Tajikistan. Fax: (+992) 227 3646. e-mail: aismayilov@projecthope.org

Background and challenges to implementation: Tajikistan is among the 27 high burden multidrug-resistant tuberculosis (MDR-TB) countries in the world. It has one of the highest estimated TB cases (all forms) 142 (range 70-239) per 100 000 population incident number in the WHO European Region. According to the latest drug resistance survey in 2011, the prevalence of MDR is 13% among new and 54% among previously treated TB cases (WHO report, 2013). Sustainable provision of DOT during the long course of MDR-TB treatment in civilian populations living in remote and impenetrable districts remains a challenge.

Intervention or response: In order to pilot opportunities to strengthen and guarantee DOT for MDR-TB patients, two visiting social workers from different NGOs were equipped with and trained to use small donated GPS tracker devices. The trackers have been used to monitor DOT of 10 patients in two different districts for three months. A special geozone (R50m) was appointed for each patient on the map, as well as a DOT medical unit where the social worker is collecting Second Line Drugs. The tracker sends data via GMS and reports to the server on GPS positioning, which is easily reached by NGO coordinators and Project HOPE managers. Reports contain data on the amount of time spent and shows travel on a map among geozones (Pic 1). The system allows recording the dialog between patient and social

worker. The GPS system and audio recording is used only upon mutual agreement.

Results and lessons learnt: Project managers, and all interested parties can supervise social workers online with data on current location, attendance, health message delivery, and etc. User friendly setup and functional ease have already attracted NTP and other TB implementers interest in the country.

Conclusions and key recommendations: Such simplified accessories may improve managerial issues and highly increase the probability of properly delivered DOT at the community level, thus increase the likelihood of treatment success for MDR-TB patients. It is an exemplary Community and Private business involvement mixture into Tajik TB control measures. Now Satellite technology for MDR-TB treatment is being intensively discussed and planned for use under the New Funding Mechanism of the GFATM grant.



EP-190-06 Using mobile health to strengthen community-based management for MDR-TB in Myanmar

S Aung,^{1,2} A Innes,² P Tun,¹ N Naung,¹ KZ Aye,¹ KS Win³ ¹FHI 360 Myanmar, Yangon, Myanmar; ²FHI 360 Asia Pacific Regional Office, Bangkok, Thailand; ³Myanmar Medical Association, Yangon, Myanmar. e-mail: ainnies@fhi360.org

Background: An estimated 9000 MDR-TB cases arise each year in Myanmar. One key limitation for scaling up MDR-TB treatment is the low capacity and availability of directly observed therapy (DOT) providers. The USAID Control and Prevention-Tuberculosis (CAP-TB) project pilot-tested Myanmar's first community DOT providers for MDR-TB, filling a critical gap for patient support. To ensure quality care by community DOT provision, CAP-TB developed DOTsync, a mobile health application to train and track community volunteers in their daily work.

Intervention: DOTsync was created using Dimagi's open source CommCare software. The mobile app goes through simple steps to guide the activity workflow in the home, providing checklists to review DOT, health education messages, and audio visual aids for patient communication. Forty-two community DOT providers were trained to use DOTsync in Yangon and Mandalay. Utilization was tracked by monitoring the frequency and timing of data upload to the cloud. Data are presented for six months of implementation.

Results: We found that 76% (32/42) of the trained community DOT providers consistently used CommCare during their activities, which included direct observation of MDR-TB therapy, health education, infection control and side effect checklists, and referrals for treatment complications or presumptive TB cases among contacts. After launching DOTsync in select townships, the number of people reached for health education increased by 40% (from 324 to 452). At the start of DOTsync, 29 presumptive TB/MDR-TB cases had sputum tested, of which 28% were smear positive. After DOTsync, 39 of 65 (60%) presumptive cases had sputum tested with a smear positivity rate of 33%. Users and beneficiaries had positive feedback from their experience with DOTsync's integration into their daily lives.

Conclusions: DOTsync was successfully used to strengthen community-based MDR-TB prevention and patient support. Compared to pre-DOTsync, the identification of presumptive TB/MDR-TB cases was more efficient, with a higher sputum positivity rate. DOT provision was monitored by tracking the daily data upload to the cloud, enabling timely follow-up for missed doses and quality control for community volunteers. The Myanmar NTP is now using DOTsync in Yangon townships with the highest MDR-TB prevalence. DOTsync's longer term impact on TB/MDR-TB case detection and MDR-TB treatment success will be evaluated with this scale-up.

EP-191-06 Using mHealth techniques, onsite coaching and incentives to motivate rural pharmacies to screen and refer individuals with TB symptoms in Viet Nam

H Ngo,¹ Dat Tran,¹ Tuan Nguyen,¹ J Neukom,¹ M Theuss¹
¹Population Services International (PSI/Viet Nam), Hanoi, Viet Nam. e-mail: nh.ytcc@gmail.com

Background and challenges to implementation: In Viet Nam, while most investments in TB programming have focused on public sector channels, a significant proportion of TB care is provided by pharmacies and private clinics. Data collected in 2013 reflects 80% of individuals with TB symptoms first seek care from pharmacies or private clinics. In this context, PSI implemented a program designed to motivate rural pharmacies to screen and refer individuals with TB symptoms.

Intervention or response: During the first 9 months of project, PSI signed agreements outlining commitment from 1,305 rural pharmacies in 3 provinces to screen and refer customers with TB symptoms. Based on insights about rural operators, PSI designed onsite coaching and mHealth tools, print materials and non-monetary incentive packages to encourage and reward them. Face-to-face, print and SMS messages consistently emphasized how TB screening and referral practices could help improve pharmacies as businesses committed to serving their communities. A mobile screening app, print screening guide and a referral card with list of TB care sites, were designed to motivate pharmacies to comply with national guidelines. Pharmacy referrals were 1 of 4 channels used to increase TB case detection.

Results and lessons learnt: Between Jul 2014 and Mar 2015, the project screened 4382 individuals in rural districts of 3 provinces. Among these, 3,882 were successfully referred for diagnosis at the nearest referral site and 692 cases of smear positive (SS+) TB were detected. Pharmacies generated 11.3% of the total, clinics (81.1%), outreach (0.1%) and camps (7.5%). Results through the pharmacy channel increased steadily over time, as repeat coverage of signed rural pharmacy operators increased. Monitoring data highlights the deeply engrained patterns of TB customer care which need further efforts to address—including sale of antibiotics prior to screening or referral for TB diagnosis—as well as the limitations of some mHealth techniques in cases where individuals have limited text messaging capacity.

Conclusions and key recommendations: Multiple points of contact are required to change pharmacy operator behaviors related to care for TB suspected customers—including repeat face-to-face coaching, simple prints and tools, and non-monetary incentives valued by rural pharmacies. SMS or call-back messaging may be more effective than mobile screening apps for individuals with limited text messaging capacity.

EP-192-06 Does the use of electronic health records improve data capture of TB screening in an HIV setting? The Maina Soko Military Hospital case study

J Nikisi,¹ G Muyunda,¹ T Sajisa,² K Asiedu¹ Jhpiego-An
 affiliate of Johns Hopkins University, Lusaka, ²Ministry of Defense, Lusaka, Zambia. Fax: (+260) 211 253314. e-mail: Joseph.Nikisi@jhpiego.org

Zambia has an HIV of 13.3% prevalence and faces a high burden of TB. Approximately 65% of patients with TB are co-infected with HIV. As a part of integrating TB and HIV activities, almost 100% of TB patients undergo HIV testing and counseling and this is well documented. However, there has been a challenge in documenting TB screening occurring in HIV settings. As a result, it is difficult to ascertain the coverage of TB screening among HIV patients. Zambia has implemented SmartCare, an Electronic Health Record (EHR), since 2005. The system is rolled out in 832 of 1800 health facilities. The EHR covers most clinical areas including HIV care and treatment and TB services; data is captured during each patient interaction. Jhpiego supports Maina Soko Military Hospital (MSMH) one of the first sites with SmartCare. The expectation was the introduction of EHR would improve data capture and documentation of TB screening in the HIV setting leading to improved patient care. HIV care and treatment SmartCare data from January 2012 to December 2014 was reviewed. Data was analyzed using the number of patients commencing ART as the proxy for patients in care and treatment and compared to the total number of patients screened for TB during the same period from the same pool of patients. A total of 1283 patients were commenced on ART but only 69 patients were documented

in SmartCare as having received a TB screen (5.7 %). However, a review of the physical register during the same time period showed 437 patients were screened for TB (34%). Implementation of SmartCare did not improve data capture of TB screening among HIV patients. In fact, paper documentation had a better data recording. Challenges exist around staff attitude, acceptance of new technology systems and appreciation of the importance of timely, accurate, complete and up to date data for clinical and program decision-making. While technology can support improved data collection and quality, if not accompanied by provider orientation and training, appropriate change in behavior, attitude and practices the same documentation challenges remain. It is recommended that the actual coverage of TB screening among HIV patients be explored. Furthermore the EHR system should be reviewed to require key data entry by providers during patient interaction and prompt to screen for TB. This should include appropriate provider orientation and training in SmartCare with emphasis on data quality and use for decision making.

12. Pneumonia and indoor air pollution

EP-194-06 High prevalence of byssinosis among powerloom workers in Burhanpur, India

A Das,¹ B Thapa,¹ S Chadha,¹ V Lal² ¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ²All India Institute of Medical Sciences, Jodhpur, India. e-mail: adas@theunion.org

Background: In India, the Power-loom sector provides employment to 5.74 million persons, accounting for 62 % of the country's cloth production. The prevalence of byssinosis is not known amongst the power-loom workers. The objective of the study was to determine the prevalence of byssinosis amongst the power-loom workers and assess the relationship of duration of exposure with other co-variables.

Design/Methods: This was a cross sectional study conducted in Mominpura, a muslim-dominated, power-loom dependent administrative ward of Burhanpur in Madhya Pradesh, India having 2818 adult population. Semi-structured questionnaire was administered to gather data on patient demographics, duration of exposure to cotton dust, smoking, and presence of symptoms of byssinosis in 291 power-loom workers in 2014. Peak Expiratory Flow Rate (PEFR) was measured and chest X-rays was taken. The outcome measures were, prevalence of byssinosis, grades (Hunter's classification), relationship of duration of exposure-2-10 years (short exposure) and more than 10 years (prolong exposure) with other co-variables (age, sex, smoking, grades of byssinosis, reduction in PEFR, and chest X-ray abnormalities).

Results: The mean age of the participants was 40±12.6 years (range 16-75 years). The male to female ratio was 3.5:1 (Male, 225; Female 65), and 77% were married. The prevalence of byssinosis, based on Hunter's classification, was 98% ($n = 284$). Of those, 239 (84%) were

in Grade 0.5, 32 (11%) in Grade 1, 8 (3%) in Grade 2 and 5 (2%) in Grade 3. PEFR was reduced in 44% ($n = 124$). Of those having byssinosis in whom PEFR was reduced, 81 (29%) had PEFR reduced by more than 50%, and of these, 69 (82%) were in early stage of byssinosis (Grade 0.5). Among 124 participants in whom chest X-rays was done, 102 had byssinosis (Grade 0.5) and only 19% (19) had abnormal chest X-rays. Of 284 who had byssinosis, 44 (15%) and 240 (85%) had short and prolong exposure to cotton dust, respectively. Older age group (>35 years), smokers and those who smoked more than 10 sticks/day, grade 1 byssinosis, and more than 30% reduction in PEFR had prolonged exposure ($P < 0.05$).

Conclusion: Byssinosis was common among powerloom-workers in Burhanpur. Work place safety rules and regulations need to be enforced in order to tackle this problem in the study setting. This study could not be generalized and further study in a nationally representative sample is required to determine the epidemiological situation of byssinosis in the country.

EP-195-06 Microbiological characteristics and predictive factors for mortality in pleural infection: a single-center cohort study in South Korea

YS Kwon,¹ C.K. Park,¹ H.J. Shin,¹ YI Kim,¹ SC Lim¹

¹Chonnam National University Hospital, Gwangju, Republic of Korea. Fax: (+82) 622 258 578. e-mail: yongsu3@gmail.com

Background: Identification and understanding of the pathogens responsible for pleural infection is critical for treatment with the proper antibiotics. This study sought to determine microbiological characteristics of pleural infection and to identify potential predictive factors associated with mortality.

Design/Methods: In this retrospective study, we analyzed patient information from 114 cases of parapneumonic effusion with a total of 134 microorganisms that were isolated using two culture systems (standard method and pairs of aerobic and anaerobic blood culture).

Results: Of all isolated microorganisms, the most frequently found pathogen was streptococci (35.8%), followed by staphylococci (19.4%), anaerobes (15.7%), and gram-negative bacteria (9.0%). Streptococci were the main microorganisms found in standard culture (48.1%) and community-acquired infections (58.7%) and were susceptible to all antimicrobial agents in drug sensitivity testing, whereas staphylococci were the most frequently isolated pathogens found in blood culture (26.8%) and hospital-acquired infections (33.8%), and were primarily multidrug-resistant (69.2%). Patient history of smoking, no use of intrapleural fibrinolytics, surgery, and severity score (CURB-65 ≥ 2) were significantly associated with 30-day mortality in univariate analysis. In multivariate analysis, smoking (OR = 4.051, 95%CI = 1.21-13.61, $P = 0.024$), CURB-65 ≥ 2 (OR = 3.42, 95%CI = 1.15-10.14, $P = 0.027$), and no use of intrapleural fibrinolytics (OR = 8.19, 95%CI = 1.02–

66.14, $P = 0.048$) were significant predictive factors for 30-day mortality.

Conclusion: Common pathogens of pleural infection in this study were similar to other studies, which consist of streptococci, staphylococci, and anaerobes. Patient history of smoking, CURB-65 ≥ 2 , and no use of intrapleural fibrinolytics as a medical intervention could be predictive factors for death in pleural infection.

EP-196-06 Study of the clinical characteristics and putcomes of patients admitted with exudative pleural effusion: improving clinical decision making in resource-limited countries

D R Mishra¹ ¹B P Koirala Institute of Health Sciences, Dharan, Nepal. e-mail: deebyaraj@hotmail.com

Background: Pleural effusion complicates various diseases. In resource limited setting like Nepal, where Tuberculosis is so prevalent, it is almost obligatory to rely on clinical and only basic lab parameters to differentiate causes of exudative pleural effusion and specially Tuberculous from Non-tuberculous causes. In this background, we set out to identify if specific clinical characteristics and basic lab parameters would guide differentiation of Tuberculous from other causes of exudative pleural effusion and their effects on the treatment outcome.

Design/Methods: A retrospective study was performed on consecutive patients with exudative pleural effusion admitted in our hospital from April 2013 till July 2014. Complete medical charts were reviewed and only the initial pleural fluid examination was recorded. Statistical data was analysed using SPSS 17 and $P < 0.05$ considered significant.

Results: Among 109 patients, 45(41.3%) of the cases were Tuberculous. Among Non-tuberculous causes, there were 29(26.6%) with Parapneumonic effusions and 23(21.1%) with Malignant Pleural effusions. 60% of Non-tubercular effusions were Right sided. 82.4% of the Parapneumonic effusions were small, whereas 39.1% of the Malignant pleural effusions were large. Compared to Tubercular pleural effusions, increased age, increased duration of symptom, history of smoking and increased pack years statistically favoured a diagnosis of Malignant pleural effusion, whereas presence of fever, cough and increased pleural ADA levels favoured Tubercular pleural effusions. With regards to Parapneumonic effusions, a shorter duration of symptom, smaller effusions, higher pleural Neutrophils, lower pleural lymphocyte neutrophil ratio and lower ADA favoured the 'diagnosis as compared to Tubercular pleural effusions.

Conclusion: There exists important clinical and pleural biochemical differences between Tubercular and other major causes of exudative pleural effusions, the appreciation of which aids in improved clinical decision making with minimal resources and thus has great economic implications in resource limited settings like ours.

EP-197-06 Effect of health education on caregivers' knowledge, attitude and practice of home management of childhood acute respiratory infections in Issele-Aza

S Olarewaju,¹ T Idaboh,² K Odeyemi² ¹Ladoke Akintola University Teaching Hospital, Ogbomoso, ²College of Health Sciences, Lagos, Nigeria. e-mail: oolarewaju7@gmail.com

Background and challenges to implementation: Acute Respiratory Infections (ARIs) among under-five year old children when managed inappropriately by their caregivers' results in preventable mortality and morbidity. Treatment failure, unnecessary adverse effects of antibiotics used, waste of health-care and family resources, and an increased emergence of bacterial resistance are some of the negative consequences of ARI mismanagement. The assessment of the Knowledge, Attitude and Practices (KAP) of caregivers of under-fives on childhood ARIs is important in enabling policy makers plan and provide specific interventions to reduce mismanagement of ARIs. This study assesses the effect of health education on caregivers' KAP regarding home management of ARIs in Issele-Azagba community, Nigeria.

Intervention or response: A quasi-experimental study carried out among 139 caregivers of children aged 0-59 months in Issele-Azagba community in Nigeria, using 139 caregivers of children also aged 0-59 months in Ekwuoma community as controls. Multistage random sampling procedure was used to select the respondents in both groups. The instrument of the study was semi-structured, pre-tested interviewer administered questionnaires adapted from UNICEF (IMCI tool). The intervention was health education based on the "Health Belief Model". Baseline and post intervention data entry and analysis were carried out using SPSS version 16.

Results and lessons learnt: A total of 278 respondents participated in the study. The mean age of the respondents was 33.3 ± 10.0 years and most of them were mothers (81.3%). At baseline, all the respondents in the intervention group and majority (98.6 %) in the control group had heard of ARIs but their comprehensive knowledge on its causative agent, mode of prevention and transmission was low. Likewise, 97.1% and 86.3% in the intervention and control groups respectively had negative attitude regarding appropriate management of ARIs. Inappropriate use of antibiotics was practiced by 75.9% in the intervention group and 56.8% in the control group. Other inappropriate practices including rubbing menthol/balm on the nostrils, neck, chest and sometimes dissolving the menthol/balm in water for the under-fives to ingest as concoctions were observed in both groups. Post-intervention, statistically significant increases were observed from baseline in the proportion of respondents with a better level of knowledge by 41% ($P < 0.05$), positive attitudes by 77%, ($P < 0.05$) and better level of practice by 30.9% ($P < 0.05$) in the intervention group. There were no statistically significant positive changes observed in the KAP of the respondents in the control group

Conclusions and key recommendations: The health education program was effective at improving the

knowledge and practice, and modifying the attitudes of caregivers regarding appropriate home management of childhood ARIs in the intervention group. Strengthening community health education interventions on appropriate management of ARIs especially targeted at young mothers are recommended.

EP-198-06 Barriers in adoption of improved stoves: inquiry among users, non-users and program managers in Sindh and Punjab provinces in Pakistan

T Jamali,¹ A Shahid,¹ Z Fatmi,¹ A Khoso,¹ M M Kadir¹
¹Aga Khan University, Karachi, Pakistan. e-mail: tanzil.jamali@aku.edu

Background: Improved stoves are considered as the mainstay intervention to reduce household air pollution due to biomass use. Several small scales stove intervention initiatives have been undertaken in Pakistan. However, no intervention has seen to sustain. This article inquires about the barriers of adoption of improved stoves in two programs in the provinces of Sindh and Punjab, Pakistan.

Design/Methods: This qualitative study was conducted, to evaluate two stove intervention programs: one in Kasur district in Punjab province and the other in Dhabeji in Sindh province, during May-August, 2014. Two key-informants, in-depth interviews were carried out with program managers and six focus group discussions (3 each from improved and traditional stoves users) were conducted using semi-structured questionnaire. The study explored the factors facilitating or inhibiting the adoption of improved stoves.

Results: Of total 48 women participated in the study who were main cook in the household, 18 were using improved and 30 were using traditional stoves. Women used improved stoves perceived that it decreases respiratory symptoms and illnesses, eye discomfort and prevent blackening of utensils and kitchen. Women were more satisfied with the traditional stoves, owing to the decreased amount of fuel and time consumed. Repairing or constructing a new stove was found easier with those using traditional stoves. Improved stoves once damaged or destroyed, women perceive it difficulty in repairing. Also the chimney is costly and not easily available for replacement.

Conclusion: Women perceive the health and social benefits of improved stoves. However, the main barrier in adoption for improved stoves were time for cooking and fuel consumption. Fuel-efficient stoves need to be designed to improve adoption along with strengthening of the program credit and supply-chain strengthening for provision of continuous training and material such as chimney.

EP-199-06 Detecting pneumonia in resource-poor settings: searching for new devices for frontline health workers

K Baker,¹ A Mucunguzi,² L Matata,³ M Posada,⁴ T Memera,⁵ K Kallander¹ ¹Malaria Consortium, London, UK; ²Malaria Consortium, Kampala, Uganda; ³Malaria Consortium, Juba, South Sudan, Republic of; ⁴Malaria Consortium, Phnom Penh, Cambodia; ⁵Malaria Consortium, Addis Ababa, Ethiopia. e-mail: k.baker@malariaconsortium.org

Background: Globally, pneumonia remains the leading infectious cause of death in children under five years. Diagnosis can be challenging given the current available tools for frontline health workers in resource-poor settings. Community health workers (CHWs) and first-level health facility workers (FLHFWs) diagnose pneumonia primarily through counting the respiratory rate of children who have cough or difficulty breathing. However, counting respiratory rate is often challenging and misclassification is common. Malaria Consortium's Pneumonia Diagnostics project is identifying the most accurate and acceptable respiratory rate timers and pulse oximeters to support CHWs and FLHFWs in the detection of pneumonia symptoms in children. The research project is based in four low-income countries – Cambodia, Ethiopia, South Sudan and Uganda.

Design/Methods: The project combines qualitative and quantitative methodologies in three phases: device selection; accuracy evaluation; and field testing. The device selection phase was based on the following stages: landscape review; CHW focus group discussions; device scoring; pile sorting with CHWs and key Ministry of Health personnel to assess acceptability and scalability; and laboratory testing for accuracy and robustness.

Results: The landscape review identified 190 respiratory rate and pulse oximetry devices. Focus group discussions with CHWs identified 20 product attributes that were used to score and rank these devices. CHWs in all countries expressed a 'felt' need for new pneumonia diagnostic devices. Issues with current devices included suitability, usability and durability. CHWs most frequently highlighted the need for automation in their ideal device. Pile sorting of the twelve highest scoring devices (8 pulse oximeters and 4 respiratory rate counters), by CHWs and government stakeholders, favoured the fingertip pulse oximeters due to their ease of use. All laboratory tested devices passed, except one fingertip pulse oximeter, which failed to switch on after the tests were completed. Based on the laboratory test results and pile sorting exercise, 9 devices proceeded to the accuracy evaluation phase.

Conclusion: Phase one of the research project indicates that frontline health workers in resource poor settings seek new devices to support the detection of pneumonia in children. For these devices to be acceptable to CHWs and FLHFWs, manufacturers need to ensure devices are automated, accurate and easy to use.

EP-200-06 Diagnosis of chronic pulmonary aspergillosis: conventional and newer tools

M Richardson¹ ¹Mycology Reference Centre Manchester, Manchester, UK. e-mail: Malcolm.Richardson@manchester.ac.uk

Chronic pulmonary aspergillosis (CPA) is a slowly progressive inflammatory destruction of lung tissue due to *Aspergillus* infection. It is estimated that the global burden of CPA is in excess of 3 million individuals. These patients require special attention because of the possibility of developing subsequent invasive pulmonary aspergillosis, given their poor health and worsening immune state. Conventional diagnostic modalities include culture of respiratory secretions, serology (precipitin tests and indirect haemagglutination) and imaging. The main radiographic features are chronic pulmonary infiltrates, progressive cavitation, and subsequent aspergilloma formation. Chronic cavitary pulmonary aspergillosis (CCPA), which is synonymous with complex aspergilloma, shows one or more pre-existing and / or newly formed pulmonary cavities that may or may not contain an aspergilloma, and cavity expansion and / or increasing pericavitary infiltrates. Newer diagnostic tools include various ELISA formats for detecting *Aspergillus*-specific IgG, detection of *Aspergillus* biomarkers such as galactomannan in serum, sputum and bronchoalveolar lavage fluid. Other methods that are being developed include biomarker detection in exhaled breath condensate, and monitoring of exhaled volatile organic compounds (extrolites) specific for *Aspergillus*. The performance of the *Aspergillus* Western blot (Asp-WB) IgG kit (LDBio Diagnostics, Lyon, France), a recently commercialized immunoblot assay for the diagnosis of various clinical presentations of chronic aspergillosis, has recently been reported (Oliva et al., J Clin Microbiol 2015; 53: 248-254). Serum samples ($n = 267$) were derived from patients with *Aspergillus* disease, including 89 cases of chronic pulmonary aspergillosis. The Asp-WB kit performed well for the diagnosis of CPA in nonimmunocompromised patients, with an enhanced standardization and a higher sensitivity than precipitin tests. In summary, the diagnostic criteria for CPA also need to exclude infectious (TB, non-TB mycobacterial infection, histoplasmosis and coccidiomycosis) or non-infectious (lung cancer, rheumatoid arthritis and sarcoidosis) pulmonary disease that can mimic or promote the occurrence of CPA.

13. Case finding and contact tracing**EP-201-06 Effectiveness of active tuberculosis screening program for Aboriginal students living in urban area, 2011-2012**

Y-T Liao,¹ C B Hsu,¹ C-H Yang,¹ C-H Chen¹ ¹Centers for Disease Control, Taipei, Taiwan. Fax: (+886) 233 936 149. e-mail: yuntsan@cdc.gov.tw

Background and challenges to implementation: In Taiwan, people residing in mountainous areas have much higher incidence of tuberculosis (TB) than general population. Chest X-ray (CXR) screening program had been conducted by Taiwan CDC for decades in mountainous area. Yet most young students originated in these areas might leave their hometown and study in urban areas, and became a substantial gap for CXR screening program. Therefore, CDC coordinates with educational sector to implement new active screening strategy aiming at this group.

Intervention or response: The program used free CXR screening voucher and X-ray patrol truck to provide service to aboriginal students. In 2011, we first focused on senior high school and technical college students, and further expanded to college and university students in 2012.

Results and lessons learnt: There were 2969 and 4741 students received the X-ray screening in 2011 and 2012, and the participating rates among eligible population was 34% and 57% respectively. TB detection rate were 134.7/ 100 000 and 105.5/ 100 000 in 2011 and 2012, which were 6.6 and 6.1 times higher than general population of the same age in Taiwan. Especially, the detection rate was highest among senior high school students participating screening in 2012 (179.2/ 100 000).

Conclusions and key recommendations: Through coordinating with educational sector, CDC provides screening service for 7710 aboriginal students in urban areas during 2011-2012. We found that, although not living in mountainous areas, the target population in this program still provided a TB detection rate as high as people staying in mountainous areas. According to this, we modified our policy since 2013 to include this people as one of target populations in active case finding (ACF) program performed by local health authorities.

EP-202-06 Contribution of chemists to TB control in semi-urban areas of West Bengal, India

B Sengupta,¹ A Chakraborty,¹ S Sarkar,² S Halder³ ¹Care India, Kolkata, ²Revised National TB Control Programme, Kolkata, ³Department of Health and Family Welfare, Kolkata, India. e-mail: bsengupta@careindia.org

Background and challenges to implementation: Involvement of chemists in TB Control programme in West Bengal is a pilot initiative by CARE India and supported by Lilly MDR-TB partnership. The implementation started during October 2012 in consultation with Bengal

Chemists & Druggist Association (BCDA) and RNTCP in two districts.

Intervention or response: Based on the lists shared by BCDA, CARE Field Officer (FO) visited each and every chemist shop to understand their willingness to participate in the program. The training module for the community pharmacists which is acknowledged by CTD was translated into local language and used for the training. Referral slips and necessary formats were developed as per need. Till June 2014 a total of 278 chemists have been trained using the module. Project monitoring data shows that out of these 278 trained chemists 70 are regularly participating in the program.

Results and lessons learnt: 96% of the chemists have the correct knowledge on the commonest form of TB and are aware of how disease spreads. 83 % of the chemists were able to answer correctly what they mean by DOTS. 63% chemists have correct knowledge on duration of treatment of newly diagnosed TB patient while the rest gave incorrect answer. 100% chemist are remains that TB is curable if the drug taken in regular basis and follow the regimen. 25% chemists have referred patients suspected of TB during the last one month. 4% of them have provided sputum containers 28% of them have used RNTCP referral slip during referral and 47 % mentioned that they have referred verbally. 25% chemists got feedback from the RNTCP officials on the result of sputum test. 53% chemists shared the information on TB patients who are taking medicine from private sector. 48% chemists have recorded the information of private TB patients regularly while 5% of them have kept the records inconsistently. 20% chemists have stopped to stock anti TB drug in their shop.

Conclusions and key recommendations: Majority of the chemists have very good understanding on TB and the mode of disease transmission. Use of referral slip for documentation at the DMC and feedback from the system is a challenge. Sharing information on TB patients on treatment from private sector is increasing as 53% of them are sharing the information with RNTCP. Scaling up of the intervention through other CSOs to improve the notification of TB cases from private sector is recommended.

EP-203-06 Study of active case finding for tuberculosis in prisons in Gujarat, India

P Dave,¹ S Bharaswadkar,² A Amar Shah,² B Vadera,² H Thanki,² K Rade,² S Khaparde,³ A Sreenivas²

¹Commissionerate of Health, Gandhinagar, ²World Health Organization, Country Office for India, New Delhi, ³Central TB Division, Ministry of Health & Family Welfare, New Delhi, India. e-mail: bharaswadkars@tbcindia.nic.in

Background and challenges to implementation: Overcrowding in prisons poses a risk for increased TB transmission. India's National Strategic Plan articulates active case finding in vulnerable and high risk groups like Prisoners. However no clear guidelines have been issued to implement this. We conducted systematic screening and active case finding amongst prisoners under pro-

grammatic settings with objective to assess feasibility and effectiveness of this strategy.

Intervention or response: Out of 27 jails in 21 districts in Gujarat, cross sectional study was undertaken in 23 jails in 2014. Team of 1 doctor and 3 paramedical workers with the help of local jail staff screened all prisoners and presumptive TB cases were subjected to sputum smear microscopy and X-ray. The results were entered and analyzed in MS Excel.

Results and lessons learnt: Total 92% (10 306) prisoners were screened. 601 (6%) presumptive TB cases were identified. Of them, 559 (93%) of presumptive TB cases were subjected to sputum smear microscopy. 6% (36) cases were screened with X-ray chest. 19(3%) smear positive TB cases were diagnosed. 1(3%) probable TB case was identified. All diagnosed patients were put on treatment.

Conclusions and key recommendations: It is feasible to organize active case finding session in prisons with formal communication and established coordination between Health officials and jail authorities. Sizable i.e. 601 (6%) of the prisoners were identified as presumptive TB cases. It indicates that case finding efforts may get an impetus if such sessions are organized in high risk settings like Prison. Only 6% of the presumptive TB cases underwent X-ray examination because prisoners who are presumptive TB cases had to be shifted to facility where X-ray machine is available. If portable X-ray machine are made available for such activities it can be made more effective. 3% (20) TB cases were diagnosed which indicates that organizing such activities may be effective in improving case notification under programme. Such initiatives are important for reaching out missing cases. Moreover newer molecular diagnostic techniques like Xpert MTB/RIF may be utilized for such activities which may further improve yield of these case finding activities. Programme may undertake such initiatives systematically at periodic intervals in all prisons to ensure early and prompt diagnosis of TB and prevent further infection in these congested settings.

EP-204-06 TB Reach project in Odisha, India: intervention to find 'missed' TB cases from migrant slum dwellers and industrial laborers

S Pattanaik,¹ A Dutta¹ ¹Asian Institute of Public Health, Bhubaneswar, India. e-mail: dr.sarthakpattanaik@gmail.com

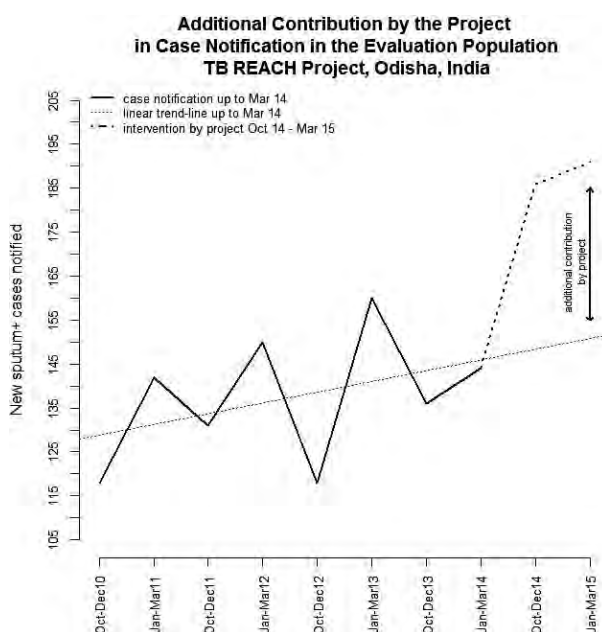
Background: As per WHO estimates, 3 million TB cases remain undetected annually; who fail to receive standardized TB care, suffer severely and continue to spread infection in the community. Mostly, "missed" cases come from vulnerable migrant populations of slum-dwellers and industrial labours, who often fail to access local National TB Programme (NTP) services, due to unfamiliarity with it or for prohibitive opportunity costs of accessing these often patient-unfriendly services. Consequently, the presumptive TB patients (PTP) from these vulnerable communities often present to "neighbourhood" non-formal healthcare providers (NFHP) for symptomatic relief, who fail to channelize them to

appropriate diagnosis and treatment. Our project funded by TB REACH was planned to detect such “missed” cases. We aim to assess the early effects of the intervention, so that positive learning can be scaled-up.

Intervention: The project operates in urban slums of Bhubaneswar, the rapidly-growing capital city and the mining and ferro-alloy-related industrial labour settlements in Jajpur, in Odisha, India. The project targets 0.55 million migrant slum dwellers and industrial labours, nested within 1.55 million evaluation population, spread across four basic NTP management units. The project uses a network of sensitized and incentivized NFHPs for identifying PTPs early; collection and transportation of sputum by community health workers; and examining specimens using two modern Xpert MTB/RIF machines; one installed at public hospital, Bhubaneswar, other at an industry-owned clinic at Jajpur. Bac+ve cases are referred promptly to NTP for treatment. The present assessment study has collected sputum examination and new smear/Bac+ve positive case notification data from local NTP for October 2014 to March 2015; and also for corresponding quarters of four previous years.

Results: The project, starting in November 2014, has tested 824 specimens using Xpert MTB/RIF of which 173 were Bac+ positive (4 were Rif resistant). Despite working for 5 months, in comparison to 280 new smear/Bac+ve cases diagnosed between October 2013 and March 2014; the project helped to increase case detection to 388 between October 2014 and March 2015, in the evaluation population; an “additional” contribution of 98 cases.

Conclusions: Projects targeting vulnerable populations through their “neighbourhood” providers using convenient patient-friendly diagnostic strategies can detect “missed” cases substantially.



EP-205-06 ‘Seeking the lost’: Intensified tuberculosis case finding amongst vulnerable communities in southern India

C K K Gali,¹ T Thomas,¹ S Gadala,¹ R Ananthakrishnan,² A Jacob,³ M Das,⁴ V Sameer,¹ P Isaakidis⁴ ¹Catholic Health Association of India, Secunderabad, ²Resource Group for Education and Advocacy for Community Health, Chennai, ³International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, ⁴Médecins Sans Frontières, Mumbai, India. e-mail: gkkr109@gmail.com

Background: India’s Revised National Tuberculosis Control Programme (RNTCP) primarily relies on passive case finding to detect new cases of TB. The new sputum case detection rate in Karnataka, a state in southern India was 58% in 2013. One Designated Microscopic Centers (DMC) exists for every 100 000 population in the plains, and in hilly areas, the state government establishes 1 DMC for a population of 50 000. About 24% of Karnataka’s population is specifically classified by the Census of India as belonging to lower (scheduled) castes; 7%, to the tribal groups. Low socio-economic status and marginalization is correlated with TB, requiring interventions to increase TB case detection rates.

Intervention: Project Axshya (through Round 9 of the Global Fund to Fight AIDS, Tuberculosis and Malaria) helps expand the reach and effectiveness of RNTCP, engaging communities to improve TB services for vulnerable populations. An Intensified Case Finding (ICF) intervention was initiated under Project Axshya in 16 districts, covering 56% of Karnataka’s population (34 million), including 54% of its lower caste and 45% of its tribal population. This study focuses on ICF activities in two districts (Kolar and Bidar) – wherein areas mapped to have a predominant vulnerable population (20 DMCs, intervention area) received the ICF intervention whereas the remaining (11 DMCs, non-intervention area) did not. To evaluate the effect of ICF on TB case detection, we reviewed the routine programme data and compared the change in a) number of presumptive TB patients examined b) smear-positive patients detected and treated in the intervention and non-intervention areas before (July-December 2012) and after (July-December 2013) implementing the intervention.

Results: The number of smear-positive cases detected increased by 8.8% relative to the pre-intervention period (July-December 2012) in intervention communities as compared to an 8.6% decrease in communities without the ICF intervention. This study showed that an innovative, community-based, education-cum-case finding intervention increased the number of TB cases detected and treated and brought TB diagnostic and treatment services closer to vulnerable communities, boosting awareness about RNTCP services.

Conclusions: In conclusion, ICF using family counseling mechanisms and community-based TB screening led to a modest increase in the number of smear positive TB cases diagnosed among vulnerable communities in India.

EP-206-06 Model-based evaluation of contact investigations for tuberculosis in low-burden settings

G Guzzetta,^{1,2} M Ajelli,¹ Z Yang,³ L Mukasa,^{4,5} N Patil,^{4,5} J Bates,^{4,5} D Kirschner,⁶ S Merler¹ ¹Fondazione Bruno Kessler, Trento, ²TrentoRise, Trento, Italy; ³University of Michigan, Ann Arbor, MI, ⁴Arkansas Department of Health, Little Rock, AR, ⁵University of Arkansas for Medical Sciences, Little Rock, AR, ⁶University of Michigan, Ann Arbor, MI, USA. e-mail: guzzetta@fbk.eu

Background: Active screening of contacts of tuberculosis (TB) patients is one of the main TB control strategies in low-burden countries. To date, evidence from epidemiological studies is insufficient to prove and quantify the effectiveness of such programs in reducing incidence in the general community.

Design/Methods: We propose an individual based model of TB transmission dynamics occurring in a time-evolving network of contacts, realistically reproducing socio-demographic characteristics of the resident population of Arkansas, USA in the absence of migration. The model incorporates TB control interventions implemented by the local Department of Health, which include contact tracing activities. TB incidence over time and by age from the period 2001-2011 are used to calibrate the model, and its predictions are validated against several independent data sets from Arkansas and the US.

Results: The model predicts that contact tracing prevented about 30% of TB cases and deaths that would have occurred in the U.S.-born Arkansas population in 2001-2014 if only passive diagnosis were in place. Inclusion of contacts of sputum smear-negative patients in the program accounted for about half of avoided cases. According to the model, only about 5% of all TB cases from endogenous reactivation occurring over the next 60 years will be prevented by contact tracing; of these, about half are prevented by successful treatment of latent infections, and the other half by avoided transmission due to the early diagnosis afforded of actively found cases. The model also predicts that improving the performance of contact investigations to meet targets set for 2015 by the U.S. Centers for Disease Control has large potential for further reducing the TB burden.

Conclusion: This work demonstrates the significant impact of contact tracing to reduce TB burden in high resource settings and identifies critical aspects (e.g. extensive inclusion of contacts of smear-negative patients) that may be leveraged to improve program effectiveness. We also show that the limiting factor for TB control in the next decades will be endogenous reactivation due to prevalent latent infections, especially from older cohorts who experienced epochs of higher TB transmission. Therefore, in absence of additional interventions, the decline of TB in low burden countries will be driven mainly by demographic forces.

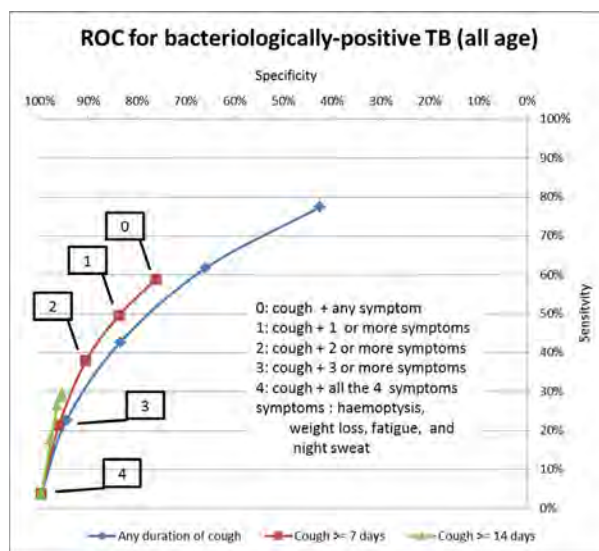
EP-207-06 Study of symptom screening for active case detection in the community using prevalence survey data

K Okada,¹ N Yamada,¹ S Saint,² T E Mao² ¹Research Institute of Tuberculosis / Japan Anti-tuberculosis association (RIT/JATA), Tokyo, Japan; ²National Center for Tuberculosis and Leprosy Control (CENAT), Phnom Penh, Cambodia. e-mail: okadak@jata.or.jp

Background: "End TB Strategy" aims at a 10% reduction rate per year between 2016 and 2025 and more efforts need to be made to accelerate a current decline rate of 1.5%/ year in incidence by optimizing current tools including active case finding (ACF) especially in high risk groups of TB. However, one of the drawbacks in ACF is more prohibitive and resource-consuming than passive case finding (PCF). Although many countries adopt prolonged cough (lasting 2-3 weeks) as presumptive TB, only 30% of bacteriologically positive TB in the community meet the definition.

Objective: To examine what symptom screening method is effective in terms of sensitivity and specificity by using national prevalence survey data obtained from Cambodia, 2011.

Methods: First, we identified TB-related symptoms by examining the association of seven TB-related symptoms (sputum, haemoptysis, chest pain, weight loss, fatigue, fever and night sweat) with being smear-positive or bacteriologically positive TB by logistic regression models. Next, we compared sensitivities and specificities among symptom screening methods which include the duration of cough (any duration, 7 days or longer, and 14 days or longer) and the number of symptoms selected by the multivariate logistic regression model, by using receiver operating characteristic (ROC) curves.



Results: All the seven symptoms were significantly associated with being TB case by univariate analysis with $P < 0.05$. By multivariate analysis, four symptoms (haemoptysis (OR = 1.87 (95%CI: 1.09-3.20), weight loss (OR = 1.42 (95%CI: 1.08-1.85), fatigue (OR = 1.29

(95%CI: 0.96-1.72), and night sweat (OR = 1.34 (95%CI: 1.02-1.77)) were selected to examine the sensitivities and the specificities. As a result of comparison in ROC curve, 7-day or longer cough only, or 7-day or longer cough with one of the four symptoms was suboptimum for symptom screening to detect bacteriologically positive TB.

Conclusion: The suboptimum symptom screening with 17% of the community people screen-positive provides 50% sensitivity and 84% specificity for bacteriologically positive TB. For those with screening positive, other tests, for example, chest radiography examination followed by Xpert test can be proposed. Further studies including operational researches are required to examine the efficiency and the cost effectiveness.

EP-208-06 Prevalence of positive tuberculosis skin test among health care workers in San Juan de Lurigancho district, Lima, Peru

J Sedamano,¹ C Ugarte-Gil,¹ C Zamudio,¹ G Soto,² C Munayco,³ C Seas^{1,4} ¹Instituto de Medicina Tropical Alexander von Humboldt, Lima, ²Dirección General de Epidemiología - Ministerio de Salud, Lima, Peru; ³Uniformed Services University of Health Sciences, Bethesda, MD, USA; ⁴Hospital Nacional Cayetano Heredia, Lima, Peru. e-mail: juana.sedamano@upch.pe

Background: Identification and treatment of individuals with Latent Tuberculosis Infection (LTBI) is one of the biggest challenges for Tuberculosis (TB) control. Health Care Workers (HCWs) are under high risk of *M. tuberculosis* transmission, which varies depending on the type of facility where HCW work, community TB prevalence, area of the facility in which HCW work and effectiveness of preventive measures. In 2012 Peru had an incidence of 119 TB cases per 100 000 habitants, that concentrates in urban areas, 54% of TB cases, 82% of MDR-TB cases, and 89% of XDR-TB cases in Peru were reported in Lima and Callao. San Juan de Lurigancho (SJL) district on its own represents 17.1% of cases of TB in Peru, and presents an incidence above the national estimate.

Objectives: To estimate the prevalence of positive Tuberculosis Skin Test (TST) in HCW in SJL and to investigate factors associated with a positive value of TST.

Methods: An observational cross-sectional study was conducted between September 2014 and March 2015 among HCWs working at least 3 months at their primary care health centers. TST was performed and the result was read after 48-72 hours. In addition, all participants completed a questionnaire regarding demographics and use of TB prevention strategies. We considered ≥ 10 mm of induration as a positive TST.

Results: 248 HCW were enrolled. TST was administered to 198 participants, of which 9 did not return for the reading appointment. Of the 50 workers, who did not undergo the TST, 26 had a previous positive TST, 14 had a history of active TB and 10 refused the application of the TST. Among the 248 HCWs, 81.1% were women; the mean age was 42 years (SD: 11.2). The mean period

of work was 153.2 months (SD: 127.3). The prevalence of a positive test in 198 participants who received the TST was 56.6% (95%CI: 49.5%-63.7%). When considering those who had a previous positive TST result and those with a history of active TB ($n=238$), the prevalence was 64.1% (95%CI: 58.0%-74.4%). TST positive HCWs have longer mean periods of work compared with TST negative (116.2 months vs. 72.5 months; $P < 0.05$). Only being 40 years old or older (adjusted PR: 1.4 95%CI: 1.1-1.7) remained significantly associated with an increased risk of a positive TST after multivariate analysis.

Conclusions: The prevalence of positive TST is high in HCWs in SJL. Our results indicate the need for greater implementation of preventive measures to avoid TB acquisition among HCW.

EP-209-06 Contribution of the private sector to TB treatment outcomes: experiences from Kampala city, Uganda

D Muhwezi,¹ D Lukoye,¹ M Ruhweza,¹ A Etwom,¹ D Okello,² P G Suarez,¹ E Birabwa,³ D Sama¹ ¹TRACK TB Project, Management Sciences for Health, Kampala, ²Kampala Capital City Authority, Kampala, ³United States Agency for International Development (USAID), Kampala, Uganda. e-mail: dmuhwezi@msh.org

Background and challenges to implementation: Evidence suggests that failure to engage all health providers in identification of presumed TB cases hampers case detection, delays diagnosis, leads to inappropriate or incomplete treatment leading to increasing drug resistance. Public-Private Mix (PPM) in various countries has demonstrated improved Tuberculosis case detection and treatment results. By January 2013, Kampala city had 49 Tuberculosis (TB) diagnostic and treatment Units (DTUs) which were very few in relation to the population served limiting access to services. Our aim is to describe the PPM approach that was adopted in Kampala city to engage the private sector and the results achieved so far. **Intervention or response:** KCCA with support from the USAID funded Track TB project engaged private health-care facilities in Kampala that did not previously provide TB care services. These were selected based on the disease burden as per patient records in the unit registers for 2013. Key medical staffs from these facilities were then trained in TB case detection, diagnosis, treatment, patient follow up and reporting using standard NTLP tools. The Union/TB Reach project also supported enrollment of some private facilities to provide services. Facilities that provided TB care at the time received mentorship to improve their quality of TB service delivery. The facilities then initiated the process of systematic screening of patients at entry points of each facility especially the outpatient department using the intensified case finding form. Facilities with laboratory services went on to analyze sputum while facilities without sufficient laboratory capacity referred the presumed TB cases to the nearest established TB diagnostic units.

Results and lessons learnt: Overall, the number of DTUs has increased from 49 to 72 by engaging 23 private health facilities while the number of health workers trained in TB diagnosis and treatment has increased from 147 to 216 over the same period. TSR improved from 63.1% in the fourth quarter of 2013 to 75.7% in the fourth quarter of 2014. The loss to follow up has reduced from 30% to fewer than 5% over the same time period. **Conclusions and key recommendations:** The implementation of the PPM for TB control in Kampala improved case holding as reflected by the improved TSR and reduced patient losses to follow up. More work is required to overcome the barriers to implementation and to make gains in case notification using PPM.

Time Period	TSR by facility type (%)			Lost to follow up by facility type (%)		
	Government	NGO	Private	Government	NGO	Private
Oct - Dec '13	64.9	74.8	63.1	30	15	30
Jan - Mar '14	68.1	72.8	63.7	20.20	10.10	2.80
Apr - Jun '14	75.2	81.7	87.5	20.40	6.30	27.60
Jul - Sep '14	80.5	83.8	85.3	9.40	9.40	5.60
Oct - Dec '14	81.2	79.6	75.7	9.70	1.60	6.90
Average TSR	73.98	78.54	75.06	7.20	5.20	3

14. Sniffing out TB: from nose to immunochemistry

EP-210-06 prepIT©•MAX: a chemical lysis method to optimize the performance of molecular TB assays

J Niles,¹ B Ray,¹ O De Bruin,¹ G Robideau,¹ C Kelly-Cirino¹
¹DNA Genotek, Ottawa, ON, Canada. e-mail: cassandra.kelly-cirino@dnagenotek.com

Background: Molecular technologies have great potential to increase the sensitivity and accuracy of tuberculosis diagnosis, but their performance hinges on the quality and quantity of TB DNA obtained from primary samples. prepIT•MAX (PT•MAX), a simple chemical lysis method, improves the performance of molecular assays by increasing the recovery of high-quality TB DNA from sputum samples and simplifies laboratory workflows by eliminating the need for bead beating and complex extraction methods.

Design/Methods: TB-positive sputum, or TB-negative sputum spiked with attenuated *Mycobacterium tuberculosis* (aMTB) were processed with NaOH/NALC, or OMNIgene©•SPUTUM reagent. DNA from NaOH/NALC treated sediments was extracted by bead-beating whereas DNA from OMNIgene©•SPUTUM treated sediments was extracted with PT•MAX. Performance was compared in real-time qPCR targeting the TB RD4 region, pyrosequencing for rifampicin and isoniazid antibiotic resistance markers, and the Hain Lifesciences GenoType MTBC line probe assay. PT•MAX DNA was

also used for whole genome sequencing from aMTB culture.

Results: TB DNA extraction with PT•MAX resulted in significantly improved detection of mid- and low-positive samples. qPCR detection from low-positive samples was 25% with the SOC compared to 87% with PT•MAX. Detection from mid-positive samples was 70% with the SOC versus 100% with PT•MAX. Detection of antibiotic resistance markers was much improved by the use of PT•MAX. PT•MAX enabled 100% detection of the rpoB and inhA markers, while the SOC only achieved 50% and 90% detection respectively. The SOC method required an average of 20 days culture growth whereas PT•MAX enabled same-day results without culturing. The PT•MAX and SOC extraction methods both demonstrated 100% detection of aMTB by the GenoType MTBC line probe assay and the RD4 qPCR assay. The line probe bands obtained from PT•MAX were of equal or greater intensity than those obtained from the SOC method in 93% of the samples. Similarly, in the RD4 qPCR assay, PT•MAX Ct values were equivalent or better than SOC Ct values in 87% of the samples. Whole genome sequencing from a pure culture of aMTB yielded an assembled genome of high-quality reads, which was over 99% match to the reference *M. tuberculosis* genome.

Conclusion: prepIT•MAX significantly improves the performance of established molecular methods for TB diagnosis and can shorten the time required to deliver a clinically relevant result back to the patient.

EP-211-06 OMNIgene® SPUTUM: a novel transport chemistry that liquefies and decontaminates sputum while maintaining viability of *Mycobacterium tuberculosis*

B Ray,¹ O De Bruin,¹ J Niles,¹ G Robideau,¹ C Kelly-Cirino¹
¹DNA Genotek, Ottawa, ON, Canada. e-mail: cassandra.kelly-cirino@dnagenotek.com

Background: Putrefaction of sputum during transport and loss of viable *Mycobacterium tuberculosis* by NaOH-NALC standard of care (SOC) method are factors contributing to delay in diagnosis and treatment of TB. A novel transport chemistry, OMNIgene•SPUTUM (OM•SPD), decontaminates sputum while maintaining viable MTB for testing by smear, culture and molecular diagnostic methods. The long shelf-life of OM•SPD eliminates the need for daily NaOH-NALC preparation.

Design/Methods: Functional assessment of OM•SPD was performed for (i) long-term sputum transport from remote sites in Nepal (ii) reduction of culture contamination in Lowenstein-Jenson slants (LJ) and Mycobacterium Growth Indicator Tubes (MGIT) in two countries and (iii) compatibility with smear microscopy, Cepheid GeneXpert MTB/RIF, pyrosequencing and line probe assay (LPA).

Results: In Nepal, *M. tuberculosis* was detected in 100% of sputum samples held in OM•SPD, compared to 81% of SOC samples after 2-6 days in transport. In addition,

OM•SPD decreased average time-to-positive (TTP) by 5 days on LJ. OM•SPD transported sputum showed no culture contamination compared to 13% for raw transported sputum. Samples transported in OM•SPD allowed immediate processing upon arrival, while samples transported according to SOC required NaOH-NALC processing by the laboratory. Furthermore, OM•SPD transported sputum was compatible with smear microscopy. In a second study, sputum was treated with either OM•SPD or NaOH-NALC for 15 min. Samples treated with OM•SPD showed concordance with the SOC in TTP by LJ and MGIT. OM•SPD treated sputum was found to be compatible with pyrosequencing for antibiotic resistance profiles, LPA, and GeneXpert MTB/RIF. After treatment with OM•SPD, MTB was detected in 88-93% of samples using standard GeneXpert protocols, comparable to the *M. tuberculosis* detection rate of 90-93% of samples using SOC.

Conclusion: Our results show that OM•SPD enables long-term transport of sputum without the need for cold chain stabilization, while maintaining viable *M. tuberculosis* for smear, culture, and molecular tests. Field use of OM•SPD obviates the need for processing with NaOH-NALC in the laboratory. OM•SPD eliminates contamination and decreases time required to call TB samples positive, which will enable quicker initiation of treatment regimens and improvements in TB diagnostics to assist high-burden countries to meet the WHO End TB Strategy goals by 2035.

EP-212-06 A new tuberculosis screening tool: a hand-held electronic nose. A cross-sectional field study in Indonesia

A M Saktiawati,^{1,2} Y Stienstra,² Y W Subronto,¹ S Sumardi,¹ M Bruins,³ J Gerritsen,³ O Akkerman,² T Van Der Werf² ¹Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia; ²University Medical Center Groningen, Groningen, ⁴eNose B.V. (The eNose Company), Zutphen, Netherlands. e-mail: a.morita_iswari@yahoo.com

Background: Early diagnosis of tuberculosis (TB) is challenging in low-resourced, highly burdened settings. An accurate, easy-to-use, point-of-care diagnostic tool is needed. An earlier release of a neuronal network-based multi-detector system showed promise but it needed gas collection in a bag (Bruins M, et al. Tuberculosis (Edinb) 2013; 93: 232–238). A next-generation, mass produced robust electronic nose (eNose) may detect TB with adequate sensitivity and specificity by analyzing exhaled breath.

Design/Methods: This study was carried out in three governmental chest clinics and Sardjito Hospital, Yogyakarta, Indonesia. For this development phase, we recruited different diagnostic groups of subjects in order to build pattern recognition techniques. We enrolled 20 TB patients, 20 TB suspects that were later diagnosed with disease other than TB, 20 patients with a variety of other pulmonary diseases than TB, 20 healthy matched-controls, and 7 patients with Multi Drug Resistant TB. Subjects had to breathe gently through the eNose

without using sampling bags, prior to any treatment. TB was diagnosed by sputum smear microscopy as well as by culture and clinical follow-up. After collecting the data in the field, data were loaded on a laptop and later transferred by internet for statistical analysis in the Netherlands. After data compression using a PARAFAC/TUCKER3 algorithm, an artificial neural network was used to distinguish between sick and healthy individuals. χ^2 and Fisher's exact test were used to analyse the association between different parameters and breath test outcome. Ethics approval from the Gadjah Mada University Ethics Committee was obtained, and participants gave informed consent.

Results: All (87) subjects completed the study protocol without significant difficulty. Median age was 45; range: 20-70 years; and median BMI was 20; range: 14.7-32.9 kg/m². The eNose device had sensitivity of 0.92 (95%CI=0.74-0.99), and specificity of 0.88 (95%CI=0.76-0.95), positive likelihood ratio of 7.36 (CI: 3.7-14.9), and negative likelihood ratio of 0.09 (CI: 0.02-0.35). Comorbidities, use of antibiotics not active against TB, prior food intake, and smoking did not have significant association with the breath test outcome ($P > 0.05$).

Conclusion: In this development phase, the eNose had high sensitivity, specificity, and likelihood ratios. It is also an easy-to-use device. It needs to be further developed in a validation study that is currently in progress.



EP-213-06 CD27 expression as a new tool to distinguish active tuberculosis from LTBI

D Goletti,¹ E Petruccioli,¹ L Petrone,¹ V Vanini,¹ G Cuzzi,¹ F Palmieri,¹ E Girardi¹ ¹Istituto Nazionale per le Malattie Infettive, Rome, Italy. Fax: (+39) 6558 2825. e-mail: delia.goletti@inmi.it

Background: Control and elimination of the global tuberculosis (TB) may be enhanced by identifying and treating latent tuberculosis infection (LTBI). LTBI is identified by a normal chest X-ray in a healthy subject with a positive response to immune tests as QuantiFERON TB Gold (QFT) which, unfortunately, does not distinguish between LTBI and active TB. Recently in studies from high TB endemic countries the cytometry evaluation of the down-modulation of the surface molecule CD27 on TB-specific CD4 T-cells producing IFN γ in peripheral blood mononuclear cells (PBMC) has been associated to active TB, providing evidence of being

a potential tool to distinguish active TB from LTBI. No studies have been conducted in Europe and using whole blood which is an easier sample to obtain compared to PBMC.

Design/Methods: To validate in a low TB endemic country as Italy if the down modulation of CD27 evaluated by cytometry in whole blood is a tool to discriminate, among QFT-IT-positive patients, active TB from LTBI. 62 HIV-uninfected QFT-positive subjects were enrolled: 15 active TB; 17 cured TB; 30 LTBI. Whole blood cells were stimulated with "RD1" proteins (ESAT-6 and CFP-10), and as recall antigen with Cytomegalovirus lysate (CMV). Antigen-specific response was evaluated by cytometry calculating IFN γ production. The data were presented as a RATIO of the Median Fluorescence Intensity (MFI) of CD27 in the CD4 $^{+}$ T-cells gate over the MFI of CD27 in the gate of CD4 $^{+}$ IFN γ^{+} T-cells responding to the stimulus.

Results: A higher RATIO to RD1 antigens was found in active TB compared to cured TB and LTBI ($P = 0.01$ and $P = 0.0013$ respectively) due to a down modulation of CD27 specific T-cell in active TB. Conversely no differences of MFI RATIO were observed in response to CMV stimulation among the different groups. Based on the significant difference found in the quantitative analysis in response to RD1, we performed a ROC analysis to evaluate the potential of CD27 MFI RATIO for TB diagnostics. By ROC analysis a significant area under the curve (AUC) was found when comparing TB versus LTBI (AUC, 0.86; 95%CI, 0.69-1, $P = 0.001$). For scoring purposes we found that a cut-off of 3.19 predicted active TB with 75% sensitivity (95%CI, 42.81% to 94.51%) and 100% specificity (95%CI, 79.41% to 100.0%).

Conclusion: This study proposes a new cytometric tool in whole blood based on the modulation of TB-specific CD27 $^{+}$ CD4 $^{+}$ T-cells to distinguish, among QFT-positive subjects, TB disease from LTBI.

EP-214-06 Rapid detection of viable *Mycobacterium tuberculosis* using qPCR with propidium/ethidium monoazide

A Takaki,¹ K Chikamatsu,¹ A Aono,¹ H Yamada,^{1,2} K Sakashita,³ L Yi,³ T Matsumaru,¹ S Mitarai^{1,2} ¹The Research Institute of Tuberculosis (RIT), Japan
²Anti-Tuberculosis Association (JATA), Kiyose, Tokyo,
³Graduate school of Biomedical Science, Nagasaki University, Kiyose, Tokyo, Japan. Fax: (+81) 42 492 4600. e-mail: takaki@jata.or.jp

Background: Recently, nucleic acid amplification techniques (NATs) including Xpert[®]MTB/RIF are used widely for the rapid diagnosis pulmonary tuberculosis (TB). However, NATs detect all bacterial DNA regardless of the viability, and cannot be used to monitor the treatment outcome. Given the long time for TB culture, to develop rapid methods for quick distinction of viable *M. tuberculosis* from dead one is very important for accurate treatment plans. The qPCR methods with Propidium/ Ethidium monoazide (PMA/EMA) are widely used for the evaluation of viable microorganisms like

Escherichia coli and *Cronobacter sakazakii*, but not for *Mycobacterium*. To date, no method is available for clear distinction and accurate quantification of viable *M. tuberculosis*. In this study, we try to develop the qPCR system for accurate quantification of viable *M. tuberculosis* in clinical specimen.

Design/Methods: PMA/EMA can cross-link to double stranded DNA of dead/injured bacteria through the impaired membrane. The cross-linked DNA cannot be denatured, thus, only live bacteria can be detected using PMA/EMA-qPCR system. *M. tuberculosis* H37Rv in the logarithmic growth phase was killed by boiling 10 min or 10N formalin. The numbers of live cell (with PMA/EMA) and total cell (no treatment) were quantified by TaqMan PCR system. To confirm the result, we counted the bacterial number under microscopy with Ziehl-Neelsen staining (total cell count), Auramin O-CTC double staining and culture (CFU count).

Results: The proportion of viable *M. tuberculosis* in the logarithmic growth phase using microscopy and culture were 67–100%. Those of TaqMan PCR with PMA (100–200 μ M) and EMA (100–200 μ g/ml) were 41–54% and 61–90%, respectively. The viability measured by AO-CTC double staining was low (15–48%) compared with conventional methods. With killed bacteria, PMA/EMA-qPCR indicated 10–20% and 1–11% of viability, respectively. Therefore, EMA treated specimens were considered indicating the cell viability correctly.

Conclusion: We considered that EMA-qPCR system could quantify viable *M. tuberculosis* more accurately than PMA-qPCR in our setting. This method could be applied to evaluate clinical specimens.

EP-215-06 Improved diagnosis of extra-pulmonary tuberculosis by antigen detection in extra-pulmonary samples by immunochemistry-based assay

M Jørstad,^{1,2,3} M Marijani,³ M Ali,³ L Sviland,^{1,2} T Mustafa^{1,2} ¹Haukeland University Hospital, Bergen,
²University of Bergen, Bergen, Norway; ³Mnazi Mmoja Hospital, Zanzibar, Tanzania. e-mail: melissa.jorstad@gmail.com

Background: Extrapulmonary tuberculosis (EPTB) constitutes 20-40 % of all tuberculosis (TB) cases and poses diagnostic challenges due to the paucibacillary nature of disease, leading to lower sensitivity of routine acid-fast microscopy and culture methods. Immunochemistry with an antibody against the *Mycobacterium tuberculosis* complex specific antigen MPT64 is a robust and easily applicable method, which has shown higher sensitivity and specificity in the diagnosis of EPTB. However, the feasibility of implementation of the assay in the routine diagnostics and the cost-effectiveness remains to be evaluated. The aim of this study was to improve the diagnosis of EPTB by implementation and validation of the sensitive and specific immunochemistry-based assay in the routine diagnostics in a resource-constrained setting.

Design/Methods: The study was conducted at Mnazi Mmoja Hospital, Zanzibar, from August 2014 till April 2015. Patients suspected of having EPTB as identified by using standardized clinical diagnostic algorithms were included. The samples were collected from the respective sites; by tapping of abdominal-, pleural-, and CSF fluid, fine needle aspiration (FNA) of lymph nodes and biopsy of lymph nodes where FNA was inconclusive, and drainage of abscess material. Samples were subjected to routine diagnostic work-up; Ziehl-Neelsen (ZN) staining, cytology, histology, culture and immunochemistry assay and Xpert MTB/RIF. Positive ZN staining, and/or positive culture, and/or positive Xpert MTB/RIF and/or response to treatment were used to define a TB case.

Results: There were 83 patients enrolled in the study, 46 males and 37 females, median age 30 years. The sites of infection were 37 lymph nodes, 24 pleura, 11 abdominal, 9 meninges, 1 spine and 1 osteomyelitis. Based on clinical criteria and initial investigations, 48 patients were started on antituberculous therapy. Among these, 7 were positive with ZN staining, 4 with culture (24 unfinished results), and 29 were positive with immunochemistry assay. 28 of these samples were examined with Xpert MTB/RIF, and *M. tuberculosis* was detected in 5 samples. All samples positive with ZN staining, culture, and Xpert MTB/RIF were also positive with the immunochemistry assay.

Conclusion: The immunochemistry assay for identification of the antigen MPT64, is implementable in resource-constrained settings, and may prove a valuable and cost-effective test for correct and earlier diagnosis of EPTB.

EP-216-06 Molecular detection of *M. tuberculosis* from sputum in a novel transport medium is not affected by laboratory delay and ambient temperature

S Omar,^{1,2} R Peters,^{2,3} N Ismail,^{1,2} A W Dreyer,¹ P B Fourie²
¹National Institute for Communicable Diseases, Johannesburg, ²University of Pretoria, Pretoria, ³Anova Health Institute, Johannesburg, South Africa. e-mail: shaheedvo@nicd.ac.za

Background: Modern molecular-based approaches to detection of *M. tuberculosis* in sputum samples promise quicker and more accurate detection of cases. However, processing sputum samples at central diagnostic facilities provides a diagnostic approach, but requires a safe and efficient system that is not affected by transport delays and ambient temperature to be feasible. We evaluated the technical properties of PrimeStore® Molecular Transport Medium (PS-MTM) for its ability to inactivate mycobacteria and ensuring stability of DNA over time at ambient temperatures, and to assess the compatibility of the transport medium with DNA extraction systems.

Design/Methods: For assessing inactivation ability, a matrix of high-concentration *M. tuberculosis* spiked to proteinacious sputum was inoculated into PS-MTM and regularly sampled for culturing over time. Compatibility tests employed QiaAMP DNA, MagNAPure 96 and Nuclisens EasyMag. Spiked sputum directly to Xpert

MTB/RIF served as control. To show DNA stability, changes in Ct-values were recorded at 5 time-points over 28 days of positive samples bench-stored in PS-MTM. For detection of *M. tuberculosis* in clinical samples, 256 specimens were investigated.

Results: Complete inactivation of *M. tuberculosis* occurred within 30 minute of exposure at ratio of 1:2 for sputum to PS-MTM. PS-MTM in automated bead-based extraction systems produced the highest DNA (estimated lower limits of detection: 169 and 173 CFU/mL respectively). The Xpert MTB/RIF control was less sensitive at concentrations below 2500 CFU/mL. No significant change occurred over time in Ct-values (< 5% on a mean starting value of 22.47) for PS-MTM samples over 28 days at ambient temperature. Of 256 clinical sputum specimens, 10.2% were culture positive and 11.0% positive by real-time PCR (PS-MTM samples). Against culture, detection of *M. tuberculosis* from sputum in PS-MTM had a sensitivity of 77% (CI 95%: 56-91%) and specificity of 96% (CI 95%: 93-98%).

Conclusion: Collecting and transporting sputum from TB suspects in PS-MTM offer safe transport at ambient temperature, DNA stability for extended periods without cooling, specimens directly suitable for molecular testing and sequencing, and on-shelf long-term molecular biobanking that could save on storage costs. Detection of *M. tuberculosis* positive samples from clinical specimens with low CFU/mL concentrations is improved when sputum is collected in PS-MTM.

EP-217-06 Cough sample collection and processing for the diagnosis of pulmonary TB

W Elmaraachli,¹ P Sislian,² S Chapman,²
 R Laniado-Laborin,³ D Martinez-Oceguera,³
 N Areli Avila,³ A Catanzaro¹ ¹University of California, San Diego, San Diego, ²Deton Corp, Pasadena, CA, USA; ³Clinica y Laboratorio de Tuberculosis, Hospital General Tijuana, Tijuana, Mexico. e-mail: welmaraachli@ucsd.edu

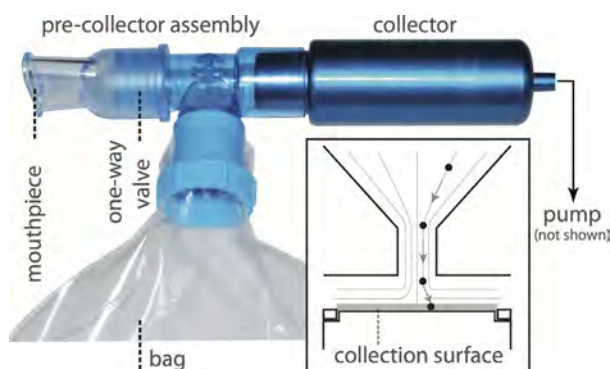
Background: We propose that the infectious droplets in cough can be collected and used as a means to diagnose active TB. Deton's patent-pending Cough Collector (Figure) replaces sputum samples by capturing airborne bacteria directly from cough for subsequent diagnosis. The Cough Collector improves TB diagnosis by collecting samples from all patients, including those who cannot expectorate sputum, thus potentially avoiding invasive procedures such as bronchoscopy. It is simple, non-invasive, and can be use in low-resource facilities with minimal training. Aerosolized *M. tuberculosis* captured by Deton's Cough Collector can be eluted directly from the collection surface for diagnostic analysis. No liquefaction or decontamination of the sample is necessary thus allowing direct transfer of the cough sample to an automated diagnostic platform, eliminating manual steps, and possibly avoiding the decreased yield associated with the decontamination procedures that sputum samples are subjected to. .

Design/Methods: Patients suspected of having TB presenting to Tijuana General Hospital were recruited. Sputum was collected for acid fast bacillus smear and

culture (BBL MGIT). Cough samples were collected from each patient on the same day as the sputum sample using the Cough Collector by having them cough into the mouthpiece every 10 seconds for 10 minutes. The collection surface was removed and placed in a micro-fuge tube; DNA extraction was then performed. TB DNA was detected by real-time polymerase chain reaction (rt-PCR) using the AnDiaTec *Mycobacterium tuberculosis* Complex kit.

Results: 13 patients were recruited, 9 of whom were smear positive (and culture-positive) for *M. tuberculosis*. The Cough Collector successfully detected *M. tuberculosis* in 8 of these patients.

Conclusion: The Cough Collector may present a potentially simpler and more reliable method of sample collection for the diagnosis of TB through the collection of cough droplets. More studies with larger numbers of patients are required.



15. From TB diagnosis to outcomes, and everything in between

EP-218-06 TB treatment outcome in TB-HIV co-infected cases stratified by ART, Brazil, 2011

P Bartholomay Oliveira,¹ A Torrens,¹ F Dockhorn,¹ D Barreira¹ ¹Ministry of Health, Brasília, Distrito Federal, Brazil. Fax: (+556) 132 138 215. e-mail: patricia.bartholomay@saude.gov.br

Background: Tuberculosis (TB) and human immunodeficiency virus (HIV) present a huge challenge to health, social, economic and developmental welfare. In the context of TB-HIV collaborative activities, World Health Organization (WHO), recommends that all TB patients should be screened for HIV and the antiretroviral therapy (ART) should be offered to HIV-infected TB individuals irrespective of their CD4 count. This is crucial for reducing mortality among TB patients living with HIV. The aim of the current study is to assess TB treatment successes in TB-HIV co infected cases stratified by ART. **Design/Methods:** The study has a retrospective cohort design using routine program data. It was included in the study all new TB cases diagnosed and registered in 2011. Study variables were extracted from a linkage database of the Aids and TB reporting systems. Percentages were calculated to report treatment outcomes. Potential

confounders were assessed in the predictive model and variables with completeness above 80% and statistical significance in the bivariate analysis ($P < 0.05$) were included in the final model. The association measure relative risk and confidence interval between exposure to ART and TB treatment successes in TB-HIV co infected cases was estimated by Poisson regression with robust variance model. Data was analyzed in Stata v.12 software.

Results: In 2011, 63.6% (46 865) of TB new cases were screened to HIV and 7628 (10.3%) had a positive result. Among TB-HIV coinfectd cases only 49.5% (3,502) were under ART. The cure rate was 63.1% among those exposed to ART, 27.7 percentage points higher than among those not exposed. Multivariate analysis found a relative risk of 1.72 (1.63 – 1.81) of the PBF benefit in tuberculosis treatment success when adjusted for the covariates age group, race, TB type, diabetes mellitus, alcoholism, directly observed treatment.

Conclusion: The present study using record linkage of TB and HIV/ aids datasets – unprecedented in the country – shows the effectiveness of ART in TB cure rate in TB-HIV coinfectd cases. The integration between both TB and HIV programs improve care and support for individuals affected by both diseases. Although progress is being made, gaps in the implementation of collaborative interventions remain far from expected targets.

EP-219-06 Effect of a daily 15 mg/kg dose of rifapentine on steady state pharmacokinetics of efavirenz, emtricitabine and tenofovir in HIV-positive patients

C Farenc,¹ S Doroumian,¹ V Esposito,² L Perrin,¹ C Rauch,¹ X Boulenc,¹ I Cieren-Puiseux,³ M Maroni³ ¹Sanofi, Montpellier, ²Sanofi, Chilly-mazarin, ³Sanofi, Gentilly, France. e-mail: isabelle.cieren-puiseux@sanofi.com

Background: Late 2014, the FDA granted the indication for the treatment of Latent TB infection for rifapentine (RPT). This approval was based on the results of the CDC-TBTC S26 which showed that weekly RPT+isoniazid (900mg each) for 3 months is effective and well tolerated in active TB prevention. RPT is an inducer of CYP3A4 and 2B6, isoforms involved in the metabolism of the anti-retroviral drug, efavirenz (EFV). A study showed that concomitant use of weekly RPT and daily EFV is possible with no dose adjustment (EFV AUC0-24 decrease <15%). The TBTC, with the aim of shortening TB treatment duration, is setting up a phase 3 study (S31), including HIV+ patients, to determine the efficacy of 17-week regimens containing daily RPT (1200mg) vs.the standard 26-week regimen. A preliminary study was conducted to assess interactions between daily RPT and Atripla®, a combination of EFV 600mg, emtricitabine (FTC) 200mg, and tenofovir disoproxil fumarate 300mg. FTC and tenofovir are not metabolized by CYP450 but are substrates of transporters which may be up-regulated in presence of RPT.

Design/Methods: 13 HIV+/TB-free patients with CD4 Tcell count >350 cells/mm³ and viral load<LOQ,

receiving Atripla® as background therapy, were enrolled in an open-label, single sequence, 2-period, non-randomized study. PK interactions were assessed after single and 21 days of daily 15mg/kg RPT dosing. Blood samples were collected over 24 hours post Atripla® dose, before, after the first and last dosings of RPT. Plasma concentrations were quantified by LC/MS, PK parameters calculated by a non-compartmental analysis. Estimates of C_{min}, C_{max}, and AUC₀₋₂₄, geometric mean ratios with 90% CIs for EFV, FTC and tenofovir co-administered with RPT vs. alone were obtained using linear mixed effects model.

Results: GEOMETRIC MEAN RATIOS (with/without repeated doses of RPT) efavirenz (EFV) emtricitabine (FTC) tenofovir Parameter estimate 90% CI estimate 90% CI estimate 90% CI C_{max} 0.83 (0.72-0.94) 1.11 (0.99-1.24) 1.20 (1.02-1.40) C_{min} 0.63 (0.52-0.76) 1.14 (0.99-1.31) 1.05 (0.92-1.20) AUC₀₋₂₄ 0.67 (0.59-0.78) 1.01 (0.97-1.06) 1.04 (0.97-1.11). The co-administration of Atripla® and RPT was well tolerated and no clinically significant changes of CD4 cell counts or viral loads were observed.

Conclusion: After 21 daily administrations of 15mg/kg RPT, FTC and tenofovir steady state exposures were comparable to Atripla® administered alone whereas EFV steady state exposure was decreased by 17% for C_{max}, 37% for C_{min} and 33% for AUC₀₋₂₄. The magnitude of the EFV-RPT interactions is modest considering the observed high inter-subject variability of EFV exposure (AUC₀₋₂₄ CV%: 77 to 85%). Some patients had C_{min} and mid dosing interval concentrations of EFV <1000 ng/ml. Further investigations of EFV PK and HIV treatment response when RPT is given at 1200mg daily to TB-HIV + patients will be done in S31.

EP-220-06 Effect of yoga on lung function and exercise tolerance in pulmonary impairment after tuberculosis

R Singla,¹ M Mallick,¹ S Sharma,¹ N Singla,¹ S Gupta,¹ S Munjal,¹ U K Khalid,¹ I V Basavaraddi² ¹National Institute of Tuberculosis & Respiratory Diseases, New Delhi, ²Morariji Desai National Institute of Yoga, New Delhi, India. Fax: (+91) 1 126 517 834. e-mail: drrupaksingla@yahoo.com

Background: Yoga includes relaxation, balanced diet, shatkarma (cleansing practices), yogasana (yogic postures), positive thinking and mediation. Yoga is suited for promoting relaxation, psycho-emotional stability and exercise tolerance. After treatment of tuberculosis significant number of patients are left with sequelae. Yoga may be helpful in such patients. However, studies showing the effect of yoga in pulmonary impairment after tuberculosis are not available. The study was aimed to see the effects of yoga on lung functions and exercise tolerance in patients with pulmonary impairment after tuberculosis.

Design/Methods: A randomized case control study in which 74 smear positive pulmonary tuberculosis patients, with symptoms or Forced Expiratory Volume in 1st second (FEV1) less than the lower limit of predicted

normal, were enrolled within 3 months after their treatment completion and randomized in two groups of 37 each: Study group and Control group. Patients in study group practiced yoga for three months along with pharmacotherapy whereas patients in control group continued pharmacotherapy only. Lung function tests including spirometry, lung volumes and diffusion study (DLCO), and 6-minute walk test were done at the baseline and end of 3 months.

Results: 32 patients in study group and 31 patients in control group completed the study. Patients in study group showed significant improvement in mean % improvement in various lung function parameters compared to control group [FEV1 (13.37% vs. -6.69%, $P < 0.001$); TLC (8.16% vs. 0.26%, $P = 0.002$); DLCO (16.23% vs. -10.47, $P < 0.001$); (6-minute walk distance (11.95% vs. -1.22%, $P < 0.001$)). The study group showed improvement in lung functions after 3 months of Yoga practice whereas the control group without addition of Yoga showed deterioration of lung functions.

Conclusion: Yoga improves pulmonary functions and exercise tolerance in patients with pulmonary impairment after tuberculosis. It could be a useful adjunct in the management of pulmonary impairment after tuberculosis.

EP-221-06 Factors associated with high mortality Among TB-HIV co-infected patients in Kenya

B Ulo,¹ F Ngari,² D Mobegi,¹ J Ong'ang'o,³ E Masini,² M Mungai,¹ H K Kipruto,⁴ S Muhula¹ ¹AMREF Health Africa Kenya, Nairobi, ²Ministry of Health, Nairobi, ³Kenya Medical Research Foundation, Nairobi, ⁴World Health Organization Kenya Country Office, Nairobi, Kenya. e-mail: ulobenson@yahoo.co.uk

Background and challenges to implementation: In Kenya, despite decline in TB mortality between 2012 and 2013, mortality among TB-HIV co-infected patients increased by 23.4 % from 7,700 to 9,500 and accounts for 60% of TB deaths annually. Kenya has a policy of immediate start of anti retroviral therapy (ART) to TB and HIV co-infected patients but ART uptake is 86%. We sought to understand factors associated with high mortality among these patients from TB data that is captured in a case based electronic reporting system called TIBU.

Intervention or response: Data for all TB and HIV co-infected patients notified in TIBU from January 2013 to December 2014 from all TB treatment sites countrywide was extracted. Descriptive statistics used to quantify proportions of patients who died against various independent variables. We ran logistic regressions to determine predictors to mortality using SPSS version 21. Proportions of key variables were determined against outcome of died or alive as the dependent variable. Using Binary logistic regression we determined individually significant variable that were then analyzed together.

Results and lessons learnt: In total of 179 881 TB patients were registered in 3,320 facilities between 1st

January 2013 and 31st December 2014. Of these, 34.5% [62,023 (30 659 female and 31 364 male)] patients were co-infected. Mean age in years was 37 and 35 for died and alive respectively. Of all 7886 deaths, 59% (4644) were among TB-HIV co-infected patients. For those with ART initiation date recorded, 67.5% (1,129) of deaths occurred within two months before and after start of TB treatment. Death rate was 10% and 7% for those within two months before and after TB treatment start respectively. Only 39.9% of those on ART were referred from HCC. After adjusting for other factors, death in TB-HIV co-infected patients were significantly associated with being male, [OR] = .785, 95% confidence interval [CI]: .734-.840), BMI < 18.5, [OR] = .711, 95% [CI]: .868-.737), not receiving ART [OR] = 1.354, 95%CI: 1.237-1.482), and patient types: Retreatment smear negative [OR] = 1.694, 95%CI: 1.04-4.02), Return after default [OR] = 1.926, 95%CI: 1.224-3.031 and Retreatment extra pulmonary [OR] = 1.751, 95%CI: 1.105-2.776.

Conclusions and key recommendations: TB-HIV co-infected patients had a high case mortality rate during intensive phase of TB treatment. Close monitoring and documentation is required especially in the HIV care clinic.

EP-222-06 Outcomes of HIV-TB co-infected patients on rifabutin and antiretroviral therapy in Kenya, 2012

H Weyenga,¹ A Katana,¹ J Kioko,² E Masini,² C Munguti,¹ E Ngugi,¹ M Schmitz,¹ L Ng'ang'a¹ ¹Center for Disease Control, Nairobi, ²Ministry of Health, Nairobi, Kenya. e-mail: howeyenga@gmail.com

Background: Tuberculosis (TB) is a leading cause of morbidity and mortality in HIV-infected patients. Optimal TB treatment and HIV viral suppression are critical predictors of patient outcomes. Unfortunately, drug-drug interactions between the current first-line (rifampicin-based) TB regimen and commonly used antiretroviral (ARV) drugs complicate treatment for TB-HIV co-infected patients. Rifampicin significantly reduces the plasma level of lopinavir/ritonavir (LPV/r). The Kenya ARV guidelines recommend substitution of rifampicin with rifabutin for TB-HIV co-infected patients on LPV/r. Although 83.7% of Pulmonary TB (PTB) and 81.2% of extra pulmonary TB (EPTB) HIV-infected patients on rifampicin are successfully treated, outcomes for patients on rifabutin are unknown. We analyzed national TB data to describe treatment outcomes for co-infected patients on rifabutin and LPV/r-based ARV regimen

Design/Methods: We used national TB data to identify all TB-HIV co-infected patients who had been placed on rifabutin from January to December 2012. We abstracted demographic and clinical data and computed point estimates, for TB treatment outcomes Cured, Failed, Completed treatment, Died, Defaulted and Successfully treated which were defined using the WHO definition and reporting framework

Results: Overall, 57 patients had been placed on rifabutin and LPV/r regimens; 36 (63.2%) were female. The median age was 38 years (IQR 30.5-45.0), median body mass index (BMI) was 18.7Kg/m² (IQR16.5-20.8) and median CD4 count was 105 cells/mm³, (IQR 14-188). Of these, 42 (73.7%) had PTB, with 14 (33.3%) having positive sputum smears, whereas 15 had EPTB. Of the sputum smear positive cases, 9 (64.3%) were cured, 2 (14.3 %) completed treatment, and 3 (21.4 %) failed. Among smear negative cases, 23 (82.1%) completed treatment and 5 (17.9 %) died. Of the EPTB cases, 12 (80.0%) completed treatment, 2 (13.3%) died and 1 (6.7%) defaulted. Sex, [OR 0.42; 95%CI (0.09-2.00)], PTB, [OR 0.63; 95%CI (0.11-2.60)], CD4 count <50/mm³, [OR 0.55; 95%CI (0.13-2.39)], and BMI <16Kg/m², [OR 0.55; 95%CI (0.13-2.39)], were not significantly associated with treatment outcomes

Conclusion: TB treatment success for HIV infected patients on rifabutin was similar to the average treatment success for all HIV-TB patients on rifampicin. Rifabutin should be encouraged in programmatic settings in Kenya to treat TB-HIV co-infected patients on LPV/r based ART regimens. A larger sample size is required to determine factors significantly associated with outcomes

EP-223-06 Predictors of tuberculosis treatment outcomes in a primary care setting in South Africa

G Louwagie,¹ L Ayo-Yusuf,^{1,2} I Chaparanga¹

¹University of Pretoria, Pretoria, ²Sefako Makgatho Health Sciences University, Tshwane, South Africa. e-mail: goedele.louwagie@up.ac.za

Background: There is limited information on the effects of socio-economic status, substance use and psycho-social factors on tuberculosis (TB) treatment outcomes in TB patients with high HIV co-infection rates.

Methods: This was prospective cohort study of 1926 newly diagnosed TB patients at six large clinics in a South African township. Current tobacco smokers in this cohort were enrolled in a tobacco cessation trial, but all participants were followed up for TB treatment outcomes. We collected information on socio-economic status, substance use (tobacco smoking, alcohol problem and illicit drug use) and psycho-social variables (social support, perceived stress and recent depressive symptoms) using structured interviewer-administered questionnaires. HIV- and TB-related information was obtained from clinical records and TB outcomes from the TB register. Data analysis entailed univariable and multivariable multilevel logistic regression with facility as random effect.

Results: TB treatment was successful (cured or completed) in 77.8% (1258/1618) of the participants. Sixteen percent of the participants were excluded from the analysis because of missing outcomes or transfer out. TB treatment was independently more likely to be successful in women (Odds Ratio [OR] 1.56, 95% Confidence Interval [CI] 1.21; 2.02), in married participants (OR 1.52, 95%CI 1.14; 2.03) and in participants who

completed high school versus primary school only (OR 2.14 [95%CI 1.49; 3.09]). HIV-positive participants (whether on antiretroviral treatment [ART] or not) were less likely have a successful outcome (OR 0.55 [95%CI 0.34; 0.89], OR 0.50 [95%CI 0.31; 0.80], OR 0.49 [95%CI 0.31; 0.79] for HIV positive on ART, unknown ART and not on ART respectively, versus HIV negative). The same variables were predictors for TB treatment "default". Psycho-social variables, tobacco smoking, alcohol problem or illicit drug use did not influence TB treatment outcomes.

Conclusions: TB treatment outcomes were worse in participants who were male, unmarried, uneducated or HIV-positive. Ever tobacco smoking or social support at baseline did not predict outcomes. We recommend tailoring TB adherence programmes to the often neglected high risk groups, in particular unmarried men with low education. Better monitoring of outcomes is necessary to differentiate TB treatment interruption ("default") from loss to follow-up due to death.

EP-224-06 Limitations of chest radiography for TB screening in healthy HIV-infected adults revealed by comparison with CT

H Esmail,^{1,2} D Chhiba,³ Q Said-Hartley,³ P Scholtz,³ H Goodman,³ R Wilkinson^{1,2,4} ¹University of Cape Town, Cape Town, South Africa; ²Imperial College London, London, UK; ³Groote Schuur Hospital, Cape Town, South Africa; ⁴The Francis Crick Institute Mill Hill Laboratory, London, UK. e-mail: hanifesmail@gmail.com

Background: Chest radiographs (CXR) have been widely used to screen at risk populations for active and inactive tuberculosis (TB) for over 75 years. Although certain limitations of TB screening CXR are recognised, it has never been evaluated in comparison to a gold standard of computed tomography (CT).

Design/Methods: As part of a study 35 asymptomatic, HIV-1 infected, antiretroviral therapy naïve adults (median CD4 count 517/mm³), living in Cape Town, South Africa with evidence of latent TB by QuantiFERON Gold In-tube and no previous history of TB treatment underwent digital CXR followed by [18F]-fluoro-2-deoxy-D-glucose combined positron emission and computed tomography (FDG-PET/CT). Using the CT component (Kv = 120, mA = 100, slice thickness 3mm), participants were classified as having changes consistent with active TB, inactive TB or no evidence of TB, with allowances made for the lower spatial resolution of CXR. 7 consultant radiologists, blinded to clinical details and CT findings, then reported the CXR. A structured reporting form was used to ensure all sections of the CXR were reported, with a final classification made as for CT. All readers reported CXR independently in a different random order on diagnostic monitors in low ambient light.

Results: Agreement between the seven readers by kappa (k) statistic was slight, k = 0.10. Agreement of each CXR reader with CT varied between slight, k = 0.05 and fair, k = 0.32. Using a binary classification of TB related changes (active or inactive TB) or no TB related changes,

the sensitivity of CXR readers varied from 33.3%-100% (median 86.7%) and specificity 25%-94.7% (median 45%). A reciprocal relationship for these parameters was apparent for each reader, with 5 readers having high sensitivity and low specificity (over-reading) and 2 readers having low sensitivity and high specificity (under-reading). The positive and negative predictive value of CXR readers varied from 50%-83.3% and 66.7%-100% respectively.

Conclusions: This is the first time TB screening CXR have been evaluated against CT. Agreement between CXR readers and CT was slight to fair. Some radiologists had a tendency to over-read and others to under-read screening CXR. We have provided novel insight into the limitations of TB screening CXR. CT is not a viable screening test but is a useful research tool in this setting and could inform strategies to improve the reporting of TB screening CXR.

EP-225-06 Genetic polymorphisms of N-Acetyltransferase 2 in TB-HIV cotreated patients in Durban, South Africa

T Mthiyane,¹ C Connolly,² Y Balakrishna,² T Reddy,² H Mcilleron,³ A Pym,⁴ R Rustonjee¹ ¹Medical Research Council, Cape Town, ²Medical Research Council, Durban, ³University of Cape Town, Cape Town, ⁴KwaZuluNatal-Research Institute for Tuberculosis and HIV, Durban, South Africa. e-mail: thulimthiyane24@gmail.com

Background: Drug induced hepatitis in tuberculosis patients taking anti-tuberculosis treatment is the most common adverse event often associated with isoniazid. Polymorphisms of N-acetyl transferase 2 (NAT2) vary considerably among different ethnic groups and are said to affect drug metabolism. We investigated NAT2 single nucleotide polymorphisms in Durban black South African population as there is limited information available.

Design/Methods: One hundred and twenty two HIV-infected participants were enrolled, 102 with culture-confirmed pulmonary-TB and 20 without TB, whole blood was drawn and processed genotyped for NAT2 190C>T, 282C>T, 341T>C, 403C>G, 411T>A, 481C>T, 857G>A, 590G>A and 803A>G using Life Technologies pre-validated Taqman assays (Life Technologies, Paisley, UK). All TB patients received standard anti-TB treatment. Fisher's exact test was used to compare AE acquisition between the three groups.

Results: 100 out of 102 TB-HIV participants had genotype results and were evaluated. 61% (61/100) were found to be slow metabolisers (NAT2*5/*5 and NAT2*5/*6), 25% (25/100) were intermediate (NAT2*4/*5 and NAT2*5/12), and 14% (14/100) were rapid metabolisers (NAT2*4/*11, NAT2*11/12 and NAT2*12/12). Twenty HIV non-TB participants were also analysed, 12(60%) were slow 8 (40%) intermediate metabolisers and none were rapid. NAT2*5 was the most common haplotype among the TB-HIV and HIV non-TB groups. The proportion of patients falling into the slow, intermediate and rapid category did not differ significantly in the TB and non-TB groups (P 0.122). Of the 60

patients who experienced adverse events among the slow, intermediate and rapid groups, 29(47.5%), 19 (76%) and 12(86%) respectively, experienced at least one adverse event, 55% had at least one hepatic adverse event. There was a significant difference in the prevalence of AE between the three groups (P 0.005). The proportion who experienced an AE did not significantly differ between the intermediate and rapid group.

Conclusion: There was a high prevalence of slow followed by intermediate metabolisers. Results are consistent with what has been reported in previous literature among the African population in South Africa, except for the absence of NAT2*5B and NAT2*6A. In this study, the number of adverse events, including hepatic, were highest among the intermediate and rapid metabolisers. This is contrary to most research results in this area. We need more trials to validate these results

EP-226-06 Implementation of intensified case finding and Xpert® MTB/RIF as initial TB diagnostic in HIV-positive individuals with presumed TB in 21 health facilities in Kampala, Uganda

J Lemaire,¹ R Nyinoburyo,¹ M Muttamba,¹ D Asimwe,¹ G Lukyamuzi,¹ A Nakanwagi-Mukwaya,² M Joloba,³ F Mugabe⁴ ¹Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland; ²International Union Against Tuberculosis and Lung Disease, Kampala, ³Makerere University, Kampala, ⁴Ministry of Health, Kampala, Uganda. e-mail: jeff.lemaire@finddx.org

Background: Kampala district in Uganda accounted for 3808 notified new bacteriologically confirmed (SM+/bac+) TB cases from Q3 2012 to Q2 2013 (baseline). Supported by a TB-REACH Wave 3 grant from the StopTB Partnership for the period of July 15th 2013 to June 30th 2015, FIND and partners have rolled-out Xpert MTB/RIF (Xpert) as an initial test for diagnosis of TB among HIV positive patients in 21 HIV-TB care facilities (6 testing and 15 referral sites) in Kampala coupled with intensified case finding (ICF) activities both in outpatient departments (OPD) and HIV clinics.

Methods: Four GeneXpert-IV platforms were installed in Kampala in July 2013 followed by 2 additional instruments in July 2014. Xpert testing is available to 8 public and 13 private clinics through a motorbike referral system. Two approaches were newly implemented to increase TB case finding; 1) ICF activities are carried out in 12 OPD and 16 HIV clinics by actively screening clinic attendees for TB symptoms through a small questionnaire. 2) HIV positive (+) TB suspects are directly tested by Xpert (compared to following an initial smear negative (-) result), while HIV- TB suspects undergo smear microscopy (SM) as per national guidelines.

Results: ICF: From Q3 2013 to Q4 2014, 43'094 OPD and 4'774 HIV patients were actively screened for TB symptoms from which 9'465 (22%) and 1'732 (36%) suspects were identified respectively, and referred to clinicians for further evaluation, after which only 4'854 (51%) from OPD (of which 853 HIV+) and 894 (52%)

from HIV clinics were referred for laboratory testing. A total of 727 SM/Xpert+ were identified through ICF at OPD (566) and HIV clinics (161). Xpert as initial test: during the same period, an additional 11'077 HIV+ TB suspects (passive findings) were tested with Xpert as an initial diagnostic test. From the resulting 2'057 (19%) confirmed TB cases, 118 (6%) were resistant to rifampicin. During these 18 months, the NTLP reported 6'221 new SM+/bac+ notified cases in Kampala district, representing 509 additional TB cases (9% relative increase) as compared to the baseline, to which both project interventions contributed to.

Conclusion: After 18 months of implementation of this 24 month project, innovative approaches of ICF and frontloading Xpert for HIV+ TB suspects have led to the identification of 2'784 new TB cases in 21 health facilities in Kampala district, and contributing to a 9% relative increase in case notifications as compared to baseline.

ORAL ABSTRACT SESSIONS

21. TB epidemiology: post and future insights into case finding, drug resistance and mortality

OA-459-06 Tuberculosis case finding through active screening using mobile phone application in Jakarta: implementation of a TB Reach project

Y Permata,¹ D Purba,¹ R Tjiong,¹ A Loebis,¹ E Burhan,² D A Asri,¹ I Kurniawati,³ A Shankar⁴ ¹Inovasi Sehat Indonesia, Jakarta, ²Faculty of Medicine Universitas Indonesia, Jakarta, ³Provincial Health Office, Jakarta, Indonesia; ⁴Harvard School of Public Health, Boston, MA, USA. e-mail: yusie.permata@gmail.com

Background and challenges to implementation: Indonesia is one of the high burden countries for tuberculosis (TB). The prevalence of TB in Indonesia was 680 000 in 2013, with 64 000 deaths. Worldwide, Indonesia ranks four for TB incidence number. National TB program in Indonesia has not included active case finding as one of the strategies to find TB cases as recommended by WHO. As part of TB Reach project, we did active screening to intensify TB case finding in several settings in Jakarta, Indonesia.

Intervention or response: We have conducted active screening in out-patient departements (obstetric, diabetes, and HIV clinic) of hospitals, private clinics, factories, prisons, and social shelters during the period of November 2013 to mid April 2015. Trained screeners interviewed respondents in the study settings using mobile application developed by Inovasi Sehat Indonesi. Demographic data, body weight, height, TB-related symptoms and risk factors were collected. Based on the questionnaire scoring, respondents were categorized as high TB suspects, medium TB suspects, or not a supsect. High and medium TB suspects were requested to give

their sputum for GeneXpert MTB/RIF assay in our diagnostic centers. SPSS program were used for univariate and multivariate data analysis. We excluded incomplete data from the analysis

Results and lessons learnt: In 15 months period, we have screened 41 546 people, with 7059 people were suspected to have TB, but only 5,934 who were willing to give out their sputum. Of all tested, 714 were *Mycobacterium tuberculosis* positive (around 10% of suspects). Among *M. tuberculosis* positive, 60 were rifampicin resistance TB cases (8.4%). The prevalence of diabetes mellitus (DM) in tested were 13%. Among tested, 21.7% were malnourished, 53.7% normal BMI, and 24.6% overweight. We found that TB is associated with malnutrition (RR 2.67; *P* 0.001) and DM (RR 1.41; *P* 0.001). The main challenge we faced was around 15.9% TB suspects screened refused to collect their sputum. The number of TB cases found could be higher if all suspects' sputum are tested.

Conclusions and key recommendations: The significant number of TB cases detected in our study shows that active screening is a crucial strategy to find TB cases. Active screening should be included as a part of national TB program in Indonesia, especially in high-risk population such as malnourished people and DM patients, so that active TB cases can be diagnosed and put in treatment earlier to halt the transmission.

OA-460-06 Mortality and pre-treatment loss to follow-up in patients being investigated for TB in a pilot case manager intervention

N Maraba,¹ K McCarthy,¹ G Churchyard,^{1,2} A Grant,² V Chihota¹ ¹RESEARCH, The Aurum Institute, Johannesburg, South Africa; ²London School of Hygiene & Tropical Medicine, London, UK. e-mail: nmatatabane@auruminstitute.org

Introduction: South Africa has replaced microscopy with Xpert MTB/RIF, in a centralised laboratory network, as the first test for TB. Pre-treatment loss to follow-up, defined as failure to start TB treatment within 28 days among people with a positive test result, remains high. We investigated a case manager strategy to improve linkage to TB and HIV care: we describe mortality and pre-treatment loss to follow-up.

Methods: Prospective cohort design. Consecutive consenting adults who provided sputum for TB investigations using Xpert MTB/RIF in 5 primary care clinics in Gauteng and Mpumalanga provinces, South Africa were enrolled and completed a baseline questionnaire. All participants were assigned a trained lay "case manager" facilitating their linkage into HIV and/or TB care and were followed up for three months. At 3 months, mortality was determined by telephonic calls to next of kin /friends or home visits if the participant could not be contacted.

Results: We report on preliminary results from the study. 761 persons were screened, 412 (54%) participants were enrolled with median age 36 years (interquartile range: 30-44), 274 (67%) HIV positive and 228 (55%) being

females. Thirty eight (9%) participants had a positive TB test result at enrolment. By 28 days after enrollment, 34 (90%) had started TB treatment, 2 (5%) had died and 2 (5%) had not started treatment, giving a total of 4 (11%) classified as pre-treatment loss to follow-up. At end of 3 months follow-up, 11/412 (3%) participants had died. Of those who died, 9 (82%) were HIV positive, 1 (9%) negative and 1 (9%) declined HIV testing.

Conclusion: Despite support from a case manager, early mortality was high among people being tested for TB. Additional strategies to reduce mortality among this group need to be explored.

OA-461-06 Predictors of mortality in patients diagnosed with preXDR- and XDR-TB: results from the South African National TB Programme, 2009-2010

D Evans,¹ K Schnippel,² E Budgell,¹ K Kate,¹ K Shearer,¹ R Berhanu,^{1,2} L Long,¹ S Rosen^{1,3} ¹Health Economics and Epidemiology Research Office, Johannesburg, ²Right to Care, Johannesburg, South Africa; ³Boston University School of Public Health, Boston, MA, USA. e-mail: devans@heroza.org

Background: Extensively drug resistant (XDR) TB has been associated with poor outcomes and high mortality in multiple cohort studies. South Africa was one of the first countries to report XDR-TB and annually reports nearly 1000 XDR-TB diagnoses.

Methods: Retrospective, de-identified descriptive analysis of patients reported in the EDRweb, the electronic national case register for all DR TB, who initiated treatment between January 2009 and September 2010. We used the WHO standard definition of XDR-TB; preXDR-TB was defined as resistance to either a fluoroquinolone (FLQ) or a second line injectable (SLI) in addition to rifampicin and isoniazid (MDR-TB). Treatment outcomes included success (cured or completed), failed, lost to follow-up, and died. Person-time accrued from treatment initiation until the earliest of outcome date recorded or 36 months on treatment. Cox hazard models were used to identify predictors of all-cause mortality.

Results: 10 600 patients initiated DR TB treatment and were reported in EDRweb. Of these, patients with MDR-TB (8611; 81.2%) or rifampicin mono-resistant TB (211, 2.0%) were excluded from the analysis. Of the 1778 (16.8%) analyzed, 936 had XDR TB, 422 had preXDR FLQ, and 420 had preXDR SLI. 77% (1375/1778) had an HIV status recorded; of which 62% were co-infected with HIV, and 76% were receiving ART. Outcomes were reported for 1231 (69%) patients: 526 (43%) died, 171 (14%) had a successful outcome, 175 (14%) were lost to follow up and 359 (29%) failed treatment. Median time to death after starting treatment was 4.4 months. Mortality was higher among those with XDR-TB (47%; 1.56/100 pyrs) than those with preXDR FLQ (38%; 1.11/100 pyrs) or preXDR SLI (38%; 1.12/100 pyrs). Predictors of mortality included history of TB treatment in patients with preXDR SLI (hazard ratio 2.35 95%CI [1.13-4.87]) and XDR-TB (HR 1.83 [1.07-

3.13]; baseline smear positivity in patients with preXDR FLQ (HR 2.34 [1.46-3.74]) and XDR-TB (HR 1.84 [1.37-2.47]); and older age (≥ 45) (HR 2.18 [1.35-3.52]) in preXDR FLQ patients.

Conclusion: This analysis of South Africa's national database confirms that mortality in preXDR and XDR-TB patients remains very high. XDR-TB and preXDR was defined using laboratory results alone which may result in exposure misclassification and underestimate mortality rates. The likelihood of additional high mortality among those without an outcome reported or lost to follow up further increases the urgency of improving XDR-TB treatment.

Table 1. Predictors of mortality by 36 months among patients with XDR TB or preXDR TB (n = 1778).

	Mortality by 36 months - Adjusted HR* and 95% CI		
	preXDR TB FLQ N = 113/298	preXDR TB SLI N = 106/280	XDR TB N = 307/653
Total with outcome			
Male gender	0.77 (0.50 - 1.19)	0.59 (0.37 - 0.93)	0.86 (0.65 - 1.14)
HIV status (Reference HIV negative)	1.0	1.0	1.0
Positive not on ART	1.82 (0.93 - 3.56)	1.09 (0.49 - 2.42)	0.88 (0.53 - 1.44)
Positive on ART	1.38 (0.82 - 2.32)	0.91 (0.54 - 1.54)	1.32 (0.95 - 1.82)
Unknown	0.60 (0.29 - 1.27)	0.93 (0.49 - 1.74)	0.66 (0.43 - 1.00)
Age at registration (Reference 18-45 yrs)	1.0	1.0	1.0
<18	0.80 (0.28 - 2.30)	0.23 (0.03 - 1.69)	0.40 (0.16 - 0.97)
≥ 45	2.18 (1.35 - 3.52)	1.42 (0.88 - 2.29)	1.19 (0.85 - 1.66)
Previous history (Reference New)	1.0	1.0	1.0
Retreatment after default	0.19 (0.04 - 0.83)	2.35 (1.13 - 4.87)	1.83 (1.07 - 3.13)
Retreatment after cure	0.61 (0.27 - 1.36)	1.02 (0.50 - 2.10)	0.68 (0.39 - 1.18)
Treatment Failure	0.59 (0.38 - 1.02)	0.97 (0.53 - 1.77)	0.88 (0.60 - 1.30)
Other	0.61 (0.20 - 1.87)	0.64 (0.14 - 2.85)	0.93 (0.56 - 1.54)
Year registration (Reference 2009)	1.0	1.0	1.0
≥ 2010	1.15 (0.75 - 1.76)	1.22 (0.77 - 1.92)	0.96 (0.73 - 1.25)
Baseline smear (Reference Negative)	1.0	1.0	1.0
Positive	2.34 (1.46 - 3.74)	1.47 (0.93 - 2.34)	1.84 (1.37 - 2.47)

*Hazard ratio calculated using Cox proportional hazards method. HR: hazard ratio; CI: confidence interval; XDR TB: extensively drug resistant TB; FLQ: fluoroquinolone; SLI: second-line injectable drug; ART: antiretroviral therapy.

OA-462-06 Trends of rifampicin-resistant pulmonary TB in South Africa: data from the national laboratory-based TB surveillance system

A Nanoo,¹ C Ihekweazu,² S Candy,³ N Ismail¹ ¹Centre for Tuberculosis, National Institute for Communicable Diseases, Johannesburg, ²Division of Public Health Surveillance and Outbreak Response, National Institute for Communicable Diseases, Johannesburg, ³Corporate Data Warehouse, National Health Laboratory Service, Johannesburg, South Africa. e-mail: anantan@nicd.ac.za

Background: South Africa has the third highest burden of pulmonary tuberculosis (TB) globally and while rates of multidrug resistant TB (MDR) are low, absolute case numbers are high. Rifampicin resistance (RR) is regarded as a proxy for MDR and new diagnostics are primarily targeting this drug for testing. We describe the trends in RR and MDR-TB over a 9 year period.

Design/Methods: Data on microbiologically-confirmed TB cases diagnosed between 2004 and 2012 was extracted from a routine laboratory-based surveillance system using the National Health Laboratory Service's Corporate Data Warehouse. Basic descriptive statistics was used to describe the time trends of rifampicin resistant tuberculosis (RR TB) in South Africa. The prevalence of MDR-TB relative to RR TB was determined. Data are reported unadjusted for testing rates.

Results: Between 2004 and 2012, 115 129 cases of RR TB were diagnosed, 93 426 (81.1%) of which were also confirmed MDR-TB cases (Table 1). The proportion of

microbiologically-confirmed TB cases that were RR increased from 1.8% in 2004 to 5.1% in 2012 (χ^2 $P = 0.000$). A similar trend was also observed for MDR proportions. The proportion of RIFR cases that were confirmed as MDR cases ranged between 90.9% and 63.0% over the study period.

Conclusion: The prevalence of rifampicin resistant TB in South Africa increased steadily between 2004 and 2012 and has almost tripled from the 2004 baseline. However, the proportions remain below 10%. The use of RR as predictor for MDR is not absolute with at least 10% being mono-resistant rather than MDR. However, the decline in the predictive value of RR for MDR in later years may be attributable to the introduction of the Line Probe Assay that is known to miss a small proportion of cases with phenotypic isoniazid resistance or to testing patterns. Our findings of increases in RR prevalence needs to be further investigated to correct for testing patterns and further evaluation of this data in the Xpert MTB/RIF era is also required

Year	TB cases diagnosed	MDR	
		RR n (% RR OF TB)	n (% MDR OF TB; % MDR of RR TB)
2004	241 411	4 294 (1.8)	3 852 (1.6; 89.7)
2005	270 496	3 443 (1.3)	3 164 (1.2; 91.9)
2006	312 507	9 775 (3.1)	8 885 (2.8; 90.0)
2007	318 191	12 500 (3.9)	11 045 (3.5; 88.4)
2008	343 935	12 793 (3.7)	11 201 (3.3; 87.6)
2009	339 956	15 030 (4.4)	12 932 (3.8; 86.0)
2010	400 237	16 898 (4.2)	14 368 (3.6; 85.0)
2011	433 003	19 744 (4.6)	14 974 (3.5; 75.8)
2012	405 836	20 652 (5.1)	13 005 (3.2; 63.0)

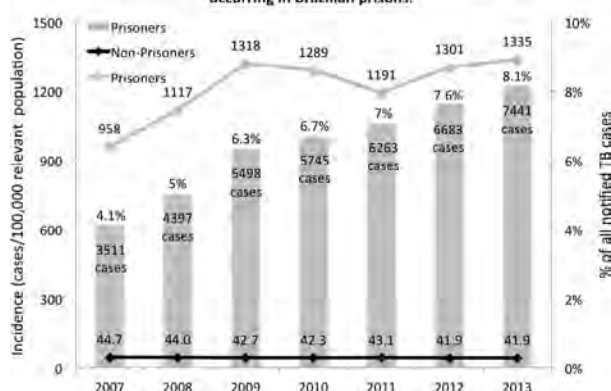
OA-464-06 Rapidly increasing tuberculosis burden in Brazilian prisons offsets gains in general population

P Bourdillon,¹ J Croda,^{2,3} A Ko,^{1,4} J Andrews⁵ ¹Yale School of Medicine, New Haven, CT, USA; ²Federal University of Grande Dourados, Dourados, Mato Grosso do Sul, ³Oswaldo Cruz Foundation, Campo Grande, Mato Grosso do Sul, Brazil; ⁴Yale School of Public Health, New Haven, CT, ⁵Stanford University, Stanford, CA, USA. e-mail: paul.bourdillon@yale.edu

Background: Brazil has the world's 4th largest prison population, which increased from 335 410 to 557 285 from 2007-2013. Although TB rates are high in this risk group, the population contribution of prison transmission on the Brazilian TB burden has not been evaluated.

Design/Methods: We obtained data on reported tuberculosis cases from 2007 to 2013 in the national surveillance database (Sistema de Informação de Agravos de Notificação; SINAN). Data was extracted according to demographics including incarceration status, sex, race, age, education, and state as well as clinical factors including disease site, HIV status, and sputum smear. We used population estimates for Brazil and inmate census reports to calculate annual TB incidences.

Figure 1. Increasing cases, incidence and proportion of tuberculosis occurring in Brazilian prisons.



Results: From 2007-2013, the number of cases doubled from 3511 to 7411 per year, and the proportion of cases notified from prisons increased from 4.1% to 8.1% of all cases reported in Brazil. The average incidence among prisoners was 28.3 times that of the general population, 1216 and 42.9 per 100 000 respectively. The incidence among prisoners rose by 39% (958 to 1335 per 100 000; $P < 0.0001$) compared to a 6% decrease among non-prisoners (44.7 to 41.9 per 100 000; $P < 0.0001$); the net effect was just 2% decline in the combined population. There was significant variability between states, with average 2007-2012 incidences in prisons ranging from 224 (Amapá State) to 3066 (Rio de Janeiro State) per 100 000. Men comprise 94% of the prison population and 91% prison TB cases, of which 79.3% are aged 20-39. Although there were fewer female prisoners, they had a higher average incidence of TB than males (1812 vs. 1179 per 100 000), more extrapulmonary cases (13% vs. 5.8% of cases), and higher risk of documented HIV co-infection than males (15.6% vs. 10.2% of cases).

Conclusions: The growing TB epidemic in prisons now accounts for 8% of Brazil's disease burden. Given the high inmate throughput, prisons may serve as reservoirs for transmission to the general population and present an increasing obstacle to broader tuberculosis control efforts. Young men comprise the majority of cases in prisons, but female prisoners are at higher risk of TB and HIV co-infection, which may warrant targeted screening. Effective interventions must be implemented to address the alarming incidence of tuberculosis in Brazilian prisons and make an impact on the national disease burden.

OA-465-06 Under-reporting of sputum smear-positive tuberculosis cases in Kenya

D Tollefson,¹ F Ngari,² M Mwakala,² D Gethi,³

H K Kipruto,⁴ K Cain,⁵ E Bloss¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²National Leprosy, Tuberculosis and Lung Disease Unit, Nairobi, ³Kenya Medical Research Institute (KEMRI), Kisumu, ⁴World Health Organization Country Office Kenya, Nairobi, Kenya. ⁵U.S. Centers for Disease Control and Prevention (CDC), Kisumu, Kenya. e-mail: vtu3@cdc.gov

Background: The World Health Organization (WHO) has declared finding missed tuberculosis (TB) cases a top priority to reach global TB targets, yet the level of under-reporting of TB cases is largely unknown in high TB burden countries. This study was conducted to quantify the level of under-reporting of sputum smear-positive TB cases to the national TB surveillance system in Kenya.

Design/Methods: Kenya's National TB Program (NTLD-Unit) and the U.S. Centers for Disease Control and Prevention conducted a national, retrospective TB inventory study in Kenya, following WHO guidelines. All sputum acid-fast bacilli smear-positive TB cases recorded by laboratories (public or private) from April 1 to June 30, 2013 were extracted from paper TB laboratory registers in 73 sub-counties, which were selected by stratified random sampling based on TB burden. These laboratory cases were matched to TB cases reported within the national, electronic TB surveillance system (TIBU) in 2013 using name, age, and combinations of sex, geography, and time from diagnosis to treatment initiation. Lab-diagnosed smear-positive cases not found in TIBU were defined as unreported to the NTLD-Unit. A national estimate for under-reporting was calculated in R software, adjusting for study design.

Results: In sampled sub-counties, 822 of 3,425 (24%) of smear-positive TB cases found in lab registers during the study period were not reported in TIBU. The average proportion of laboratory cases not reported in TIBU was greatest in high TB burden sub-counties (25%) and lowest in low TB burden sub-counties (17%). Under-reporting in sub-counties ranged from 0% to 44%. The highest average level of under-reporting occurred in sub-counties in Nairobi (34%) and Nyanza region (30%), while the lowest occurred in sub-counties in Central (16%) and Eastern (17%) regions. The estimated level of under-reporting of smear-positive TB cases in Kenya was 23.8% (95%CI: 21.2–26.4%).

Conclusions: In Kenya, almost one-quarter of smear-positive TB cases diagnosed during the study period were unreported to the NTLD-Unit. Findings suggest the real burden of TB is higher than what is currently reported in Kenya. TB surveillance should be strengthened to ensure all TB cases are recorded and reported. Additional research is needed to identify risk factors and reasons for under-reporting.

OA-466-06 Isoniazid mono-resistance is associated with increased mortality in a large cohort of tuberculosis patients in Durban, South Africa

Y Van Der Heijden,¹ F Maruri,¹ F Karim,² G Parker,² Y Moosa,³ T Sterling,¹ T Chinappa,⁴ P Alexander²

¹Vanderbilt University School of Medicine, Nashville, TN, USA; ²KwaZulu-Natal Research Institute for TB and HIV, Durban, ³Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, ⁴Ethekewini Municipality, Durban, South Africa. Fax: (+1) 615 343 6160. e-mail: yuri.vanderheijden@vanderbilt.edu

Background: Isoniazid (INH) mono-resistant tuberculosis (TB) is often considered to be of little clinical significance, though some studies suggest an association with poor patient outcomes. We hypothesized that patients with INH mono-resistance had worse clinical outcomes than patients with drug-susceptible TB.

Design/Methods: We identified patients with INH mono-resistant TB in a retrospective cohort of TB patients seen at a single, large, urban TB clinic in Durban, South Africa (Prince Cyril Zulu Communicable Disease Centre) from January 2000 through December 2013. For comparison, we identified all patients with drug-susceptible TB, defined as any patient with *Mycobacterium tuberculosis* isolates susceptible to INH and rifampin and all other anti-TB drugs tested. Patients in both groups received six months of standard four-drug TB treatment. TB outcomes included all-cause mortality and poor outcome (defined as death plus treatment failure).

Results: There were 79 527 TB patients seen at the clinic during the study period, of whom 19 094 had pulmonary TB and available drug susceptibility test results. Of these, 488 (2.6%) had INH mono-resistance and 15 374 (80.5%) had drug-susceptible TB. Patients with INH mono-resistance were more likely to have died (3.3% vs. 1.7%, $P=0.01$) and treatment failure (3.3% vs. 0.6%, $P<0.001$), and less likely to have had treatment success (42% vs. 50.1%, $P<0.001$) compared to patients with drug-susceptible TB. Patients did not significantly differ with regard to loss to follow-up or transfer out of care. Also, patients did not differ with regard to being HIV seropositive (79% vs. 76%, $P=0.34$), though only 41% had known HIV serostatus. In a multivariable logistic regression model adjusting for age, sex, and race, patients with INH mono-resistance were more likely to have died than patients with drug-susceptible TB (odds ratio [OR] 1.94; 95% confidence interval [CI] 1.16, 3.24; $P=0.01$; see Table). In a similar model, patients with INH mono-resistance were more likely to have a poor outcome than patients with drug-susceptible TB (OR 3.01; 95%CI 2.07, 4.38; $P<0.001$).

Conclusion: Patients with INH mono-resistance had worse clinical outcomes than patients with drug-susceptible TB. Despite the limitations of a retrospective study, our findings from this large TB cohort support the need for further studies investigating appropriate rapid diagnostic and treatment approaches for patients with INH mono-resistant TB. Table. Multivariate logistic

regression model of predictors of death. Odds Ratio 95% Confidence Interval P INH mono-resistant TB 1.94 1.16, 3.24 0.01 Age (per 1-year increase) 1.03 1.02, 1.04 <0.001 Female sex 1.07 0.82, 1.38 0.63 Race Asian vs. Black 1.15 0.65, 2.03 0.64 Coloured vs. Black 0.96 0.49, 1.88 0.91 White vs. Black 0.41 0.06, 2.94 0.37

22. The nature of the beast: emerging molecular information about mycobacteria

OA-467-06 Selective reconstitution of interferon-gamma gene function in T cells suffices to restore protection against mycobacterial lung infection

P Blank,¹ K Borst,¹ E Grabski,¹ T Frenz,¹ U Kalinke¹

¹Twincore Institut for Experimental Infection Research, Hannover, Germany. e-mail: Patrick.blank@twincore.de

Background: In the lung the control of mycobacterial infection is dependent on an inter-cellular crosstalk of infected and uninfected cells as well as recruitment of inflammatory cells. Activation and recruitment of cells is mediated by chemokines and cytokines. Amongst cytokines, IFN-gamma has previously been shown to be crucial to mount protective responses against mycobacterial infection in mice and men. IFN-gamma has been reported to facilitate activation of infected macrophages, to induce apoptosis as well as to initiate inflammatory cell recruitment. A combination of these mechanisms is essential to ensure protection against mycobacterial infection. Various cells of the innate and adaptive immune system are able to express IFN-gamma. However, it remained unclear what effect the IFN-gamma expression of the different cell-types has on anti-mycobacterial immunity.

Conclusion: To analyze the function of cell-type specific IFN-gamma we developed a novel mouse model in which the IFN-gamma gene is conditionally inactivated and can be reconstituted by Cre-dependent recombination (IFN-gammaST/ST). For this study we intercrossed mice expressing Cre specifically in T cells (CD4-Cre) with IFN-gammaST/ST. Indeed, CD4-Cre+IFN-gammaST/ST mice showed selective reconstitution of IFN-gamma gene function only in T cells. Intra-tracheal infection of such mice with *Bacillus Calmette-Guérin* (BCG) revealed that unlike IFN-gammaST/ST and conventional IFN-gammako mice, in mice with reconstituted IFN-gamma gene function in T cells protection was restored. Interestingly, the cellular infiltration into the lung of BCG infected CD4-Cre+IFN-gammaST/ST mice resembled that of IFN-gammako and IFN-gammaST/ST mice with elevated numbers of eosinophils and neutrophils. These data indicated that IFN-gammaexpression of T cells alone was not sufficient to promote normal inflammatory cell recruitment. These results have implications for the development of new tuberculosis vaccines.

22. The nature of the beast: emerging molecular information about mycobacteria

OA-468-06 Genomic and proteomic analysis of *Mycobacterium tuberculosis* lineage 7 strains from Ethiopia

S Yimer,¹ A Namouchi,¹ T Riaz,¹ E D Zegeye,²

C Holm-Hansen,³ G Norheim,³ A Aseffa,^{4,5} T Tønjum¹

¹Oslo University Hospital, Oslo, ²University of Bergen, Oslo,

³Norwegian Institute of Public Health, Oslo, Norway;

⁴Armauer Hansen Research Institute, Addis Ababa, Ethiopia;

⁵Armauer Hansen Research Institute, Oslo, Norway. e-mail: yimsolo@yahoo.com

Background: Understanding the various factors driving the tuberculosis (TB) pandemic is essential to achieve the Global Plan for TB control and elimination. Recently, a new phylogenetic *M. tuberculosis* (Mtb) lineage (lineage 7) has been identified in Ethiopia, which is associated with prolonged delay among patients and grows slowly in vitro compared to other lineages. Given the potential implications for pathogenesis and virulence of the bacteria, genomic and proteomic studies on *M. tuberculosis* are warranted. The aim of this study was to delineate the molecular characteristics of *M. tuberculosis* lineage 7 strains by analysing genomic and proteomic profiles.

Design/Methods: The BACTEC MGIT 960 culture system was used to cultivate 30 *M. tuberculosis* lineage 7 isolates. DNA was extracted and whole genome sequencing was performed using the Illumina Hi-seq2000. Overall, after aligning the generated reads for each strain to the genome sequence of the *M. tuberculosis* H37Rv strain, the coverage rate was above 300 times. High resolution Q-Exactive mass spectrometer was used to achieve proteome characterization. MaxQuant software was used to define the amounts of the various proteins present, while post-translational modifications (PTMs) were identified by Proteome Discoverer and manual inspection.

Results: More than 800 mutations or single nucleotide polymorphisms (SNPs) specific to *M. tuberculosis* lineage 7 strains were identified. Compared to other lineages, *M. tuberculosis* lineage 7 strains exhibited a high number of mutations in genes involved in carbohydrate transport and metabolism, transcription, energy production and conversion. Notably, low frequencies of mutations were observed in genes involved in amino acid, lipid and coenzyme transport and metabolism, post translational modification, protein turnover and chaperone. Several interesting proteins, such as transcription factors, membrane proteins and proteins involved in pathogenesis of the bacteria were identified in lineage 7 strains. We also identified novel site-specific PTMs.

Conclusion: This study generated novel knowledge regarding the genomic and proteomic profile of *M. tuberculosis* lineage 7 strains. Further research is essential to understand the consequences of the differential frequencies of mutations observed in the main gene

groups of lineage 7 strains. Taken together, these studies have generated significant novel knowledge on a new lineage of *M. tuberculosis*, which can elucidate how these strains can have fitness for survival despite their relatively slow growth.

OA-469-06 Single cell elucidation of mycobacterial replication dynamics

S Sampson,^{1,2} J Mouton,¹ S Helaine,² D W Holden²

¹Stellenbosch University, Cape Town, South Africa; ²Imperial College of London, London, UK. Fax: (+27) 21 938 9863.

e-mail: jomien@sun.ac.za

Background: In most *Mycobacterium tuberculosis* (*M. tuberculosis*)-infected individuals, the infection persists in a latent, asymptomatic state. Therapies that aim to eliminate tuberculosis (TB) should target these dormant organisms, since these could resume replication to cause active disease. It is thought that persistent mycobacteria exist as a small, viable, but non-replicating (VBNR) population. Currently the majority of drug therapies target actively replicating (AR) bacteria, however “persister” bacteria comprise a subpopulation of bacteria that is recalcitrant to antibiotic treatment. Little is known about persistent mycobacteria, since they are very difficult to isolate. However, recent work has developed and exploited a technique termed Fluorescence Dilution (FD), which showed for the first time that the internalization of Salmonella by macrophages induced the formation of VBNR populations. This approach exploits 2 fluorescent reporters; a constitutive reporter allows the tracking of viable bacteria, while an inducible reporter enables the measurement of bacterial replication. Importantly, we have successfully adapted and optimized this system for use in mycobacteria. The aim of the proposed work was to exploit the FD technology to assess whether host exposure induced the formation of VBNR “persister” bacteria in the model organism *M. smegmatis* as well as *M. tuberculosis*, to broaden the currently limited knowledge of the biology of these bacteria.

Methods: We applied the dual reporter system to interrogate replication dynamics of *M. smegmatis* or *M. tuberculosis* during macrophage infection. RAW264.7 macrophages were infected with *M. smegmatis* or *M. tuberculosis* reporter strains and samples were analysed using flow cytometry and confocal microscopy.

Results: Characterization of intracellular *M. smegmatis* revealed that while the majority of bacteria were non-or slowly replicating, an unexpected sub-population of apparently dividing *M. smegmatis* could be detected. For *M. tuberculosis*, FD technology identified a distinct subpopulation of non-growing mycobacteria. Furthermore, the presence of VBNR and AR mycobacteria within the same macrophage after 72 hours of infection were observed.

Conclusion: These results demonstrate the successful application of the novel dual fluorescent reporter system both in vitro and in macrophage infection models to

provide a window into mycobacterial population heterogeneity.

OA-470-06 Next generation sequencing reveals hidden ethionamide resistance as a likely driver towards resistance beyond XDR-TB in a high-burden population

M Kloppe,¹ G Hill-Cawthorne,² R Van Der Merwe,¹ S Sampson,¹ E Streicher,¹ A Abdallah,³ R M Warren,^{1,3} P Arnab³ ¹Biomedical Sciences, Stellenbosch University, Cape Town, South Africa; ²University of Sydney, Sydney, NSW, Australia; ³King Abdullah University of Science and Technology, Thuwal, Saudi Arabia. Fax: (+27) 21 938 9863. e-mail: marisat@sun.ac.za

Background: In the Eastern Cape Province, South Africa, 90% of XDR-TB strains are of the Atypical Beijing genotype and are resistant to 10 or more anti-TB drugs. This wide-spread hyper-resistance prompted next generation sequencing investigation of molecular features which may predispose these strains to acquire drug resistance while retaining virulence.

Design/Methods: Atypical Beijing genotype isolates ($n = 29$), ranging from “pan-susceptible” to beyond-XDR (known resistance to 11 drugs), were selected for whole genome sequencing (WGS) on an Illumina platform. In addition, RNA sequencing was done at mid-log growth in order to relate chromosomal mutation to gene expression.

Results: Phylogenetic analyses predicted independent evolution of Atypical Beijing genotype strains from MDR-TB to hyper-resistance. Two independent lineages were identified, each with unique genetic features including but not limited to drug-resistance causing mutations. Variant analysis showed an unexpectedly large number of differences in isolates from the same patient, vs. instances of low variation between epidemiologically unlinked isolates. RNA-Seq confirmed up-regulation of the *inhA* operon in isolates with an *inhA* promoter mutation. Furthermore, we identified up-regulation of the toxin-antitoxin (TA) *vapBC22* (implicated in persistence), associated with a frameshift mutation in *vapC22*. Interestingly, *ethA* mutations causing ethionamide (ETH) resistance were found in all Atypical Beijing genotype isolates, including those diagnosed as pan-susceptible based on isoniazid (INH) and rifampicin (RIF) susceptibility.

Conclusion: XDR continues to evolve from an endemic MDR strain, implying failure to effectively treat MDR-TB patients. The deeply rooted mutations conferring resistance to INH and streptomycin suggest initial evolution of resistance prior to the introduction of RIF in the 1970's. Our findings of variable rates of change challenge the definition of recent transmission by WGS. Using a combination of WGS and RNA-Seq we demonstrate the relationship between DNA mutation and gene expression relating to INH resistance, as well as in a TA system implicated in persistence. Identification of an *ethA* mutation in all Atypical Beijing isolates irrespective of their 1st line drug susceptibility phenotype suggest that this lineage is intrinsically resistant to ETH,

which may contribute to increased acquisition of resistance in patients treated with an MDR regimen.

OA-471-06 ASAP, an automated sequence analysis pipeline for whole genome sequencing data, initial applications in *Mycobacterium tuberculosis*

R Van Der Merwe,¹ R M Warren,¹ A Dippenaar,¹ M De Vos,¹ P Van Helden,¹ A Abdallah,² P Arnab,² S Sampson¹ ¹Stellenbosch University, Cape Town, South Africa; ²King Abdullah University of Science and Technology, Thuwal-jeddah, Saudi Arabia. e-mail: rvdms@sun.ac.za

Background: The utility of whole genome sequencing (WGS) in molecular diagnostics is increasing as sequencing costs diminish. Access to a pathogen's genome sequence can help guide clinical intervention through molecular genotyping and subsequent phenotype prediction bases on existing genotype:phenotype models. However, processing whole genome sequence data is a highly complex process with no existing standardized protocols. As such, there is a need for a simple and standardized pipeline for WGS data analysis and variant detection to enable users of all skill levels to reliably extract pertinent information from WGS data to answer biologically and clinically relevant questions. Here we describe ASAP, an automated sequence analysis pipeline for whole genome sequencing data, and show its applications toward *Mycobacterium tuberculosis* WGS analysis and drug resistance prediction.

Design/Methods: ASAP makes use of open source tools for automated quality control, reference alignment and variant calling, followed by novel tools for variant annotation and phenotype prediction using compiled databases. Variant detecting accuracy was validated by comparing it to targeted amplification and Sanger sequencing. The resistance prediction model of ASAP for *M. tuberculosis* was compared to that of culture based DST as well to other resistance prediction software based on WGS data.

Results: The accuracy of ASAP matches that of targeted amplification and Sanger sequencing for regions which are not exceptionally repetitive. ASAP shows superior variant detection accuracy and resistance profiling to existing software. The resistance prediction model used in ASAP for *M. tuberculosis* resistance prediction has a high agreement with DST for first line drugs but with diminished performance for 2nd line drug resistance prediction.

Conclusion: ASAP is the first fully automated pipeline for accurate variant detection in WGS data. Its performance in *M. tuberculosis* resistance profiling closely matches that of DST for resistances with well characterised molecular markers. The utility of WGS in combination with tools such as ASAP is set to expand as genotype:phenotype models are continually improved.

OA-472-06 Host targeted therapy for tuberculosis via aerosol administration of siRNA targeting IL-10 and STAT3

R Upadhyay,¹ A Sanchez-Hidalgo,¹ J Arab,¹ C Wilusz,¹ A Lenaerts,¹ M Gonzalez-Juarrero¹ ¹Colorado State University, Fort Collins, CO, USA. e-mail: mercedes.gonzalez-juarrero@colostate.edu

Background: Eradication of tuberculosis (TB) depends on the development of shorter and more effective treatment regimens, including novel treatment alternatives combined with classical TB therapies. Host targeted therapies [HDT] in combination with current therapies for TB has emerged as one approach towards this goal. In this study we show that it is possible to modulate the lung immune environment of the *Mycobacterium tuberculosis* chronically infected host and increase its own antimicrobial capacity against drug tolerant bacilli. The end result of this therapy is increased capacity by the host to eliminate the drug tolerant bacilli remaining in the lungs during or after standard chemotherapy. Thus, the study presented below aims at identifying HDT for TB via aerosol administration of siRNAs.

Design/Methods: Persistent expression of the cytokine IL-10 and the signal transducer and activator of transcription (STAT) 3 during a chronic infection with Mtb impairs the antimicrobial capacity of the host. Mice were treated during two weeks with isoniazid and rifampin. Then chemotherapy was stopped and mice received aerosols of siRNA targeting il-10 and/or stat3. After siRNA therapy we monitored the pulmonary drug tolerant bacterial load and expression of antimicrobial effector products (NO, NADPH, NOS-2 and Arg-1). In addition, we also monitored changes in the inflammatory course caused by the therapy by recording the histological outcome after chemo- siRNA therapy.

Results: When chronically infected mice received a combined therapy regimen consisting of two weeks of anti-TB chemotherapy followed by intrapulmonary aerosol delivery of siRNAs targeting il-10 and/or stat3 the pulmonary drug tolerant bacterial load was significantly reduced when compared to control mice receiving the same chemotherapy but not siRNA/or siRNA sham treatment (Figure). Furthermore, the pulmonary antimicrobial capacity in these mice was further enhanced as evidenced by higher expression of antimicrobial effector molecules and decreased arginase activity when compared to control groups.

Conclusion: As a proof of concept, here, it is shown that a successful targeting of the host IL-10-STAT3 pathway via siRNAs aerosol delivery can modulate the lung immunity to enhance its own antimicrobial capacity and eliminate more than 90% of the pulmonary drug tolerant bacterial burden.

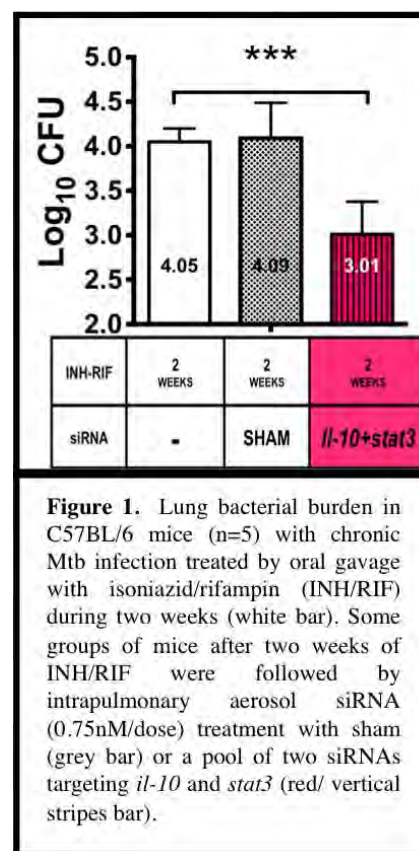


Figure 1. Lung bacterial burden in C57BL/6 mice (n=5) with chronic Mtb infection treated by oral gavage with isoniazid/rifampin (INH/RIF) during two weeks (white bar). Some groups of mice after two weeks of INH/RIF were followed by intrapulmonary aerosol siRNA (0.75nM/dose) treatment with sham (grey bar) or a pool of two siRNAs targeting *il-10* and *stat3* (red/ vertical stripes bar).

OA-473-06 Use of plasma metabolomics at diagnosis to identify metabolic pathways associated with pulmonary tuberculosis clearance: a pilot study

J Frediani,¹ E Chong,¹ J Alvarez,¹ T Yu,¹ D Jones,¹ N Tukvadze,² H Blumberg,¹ T Ziegler¹ ¹Emory University, Atlanta, GA, USA; ²National Center for Tuberculosis and Lung Disease, Tbilisi, Georgia. e-mail: tzieg01@emory.edu

Background: Knowledge of metabolic pathways associated with clearance of *Mycobacterium tuberculosis* in TB disease may provide pathophysiologic insight and identify potential biomarkers. We used plasma metabolomics to identify metabolic pathways associated with pulmonary TB clearance.

Design/Methods: We studied 61 adults with pulmonary TB disease (18 with multidrug-resistant TB [MDR-TB]) enrolled in a double blind, controlled, randomized trial of vitamin D (Vit D) supplementation in Tbilisi, Georgia. Subjects entered the trial within 7 days of initiation of conventional anti-TB drug therapy (retreatment cases were excluded). *M. tuberculosis* clearance from sputum cultures (LJ solid media) obtained 8 weeks after entry was determined. Plasma was obtained at baseline (before initiation of vitamin D3 or placebo) and metabolomics analysis performed using high-resolution liquid chromatography mass spectrometry (LC-MS). Individual regression models were analyzed for each detected metabolite with sputum culture conversion at 8 weeks (wks) as the independent variable and metabolite intensity as the

dependent variable, adjusted for MDR-TB status, diabetes status, body mass index, sex, age, treatment group (vit D vs. placebo), and plasma 25-hydroxyvitamin D level. Statistically significant ($P < 0.05$) metabolites were subsequently analyzed with a high-throughput metabolomics pathway analysis program (Mummichog).

Results: After 8 wks of anti-TB drug treatment, 52 subjects (85%) had a negative sputum culture and 9 (15%) remained culture-positive. Of 5715 metabolites detected, 251 differed ($P < 0.05$) between subjects who had achieved sputum culture conversion to negative versus those that remained culture positive (130 metabolites were decreased and 121 were increased, respectively). Nine specific metabolic pathways were significantly different between the two groups, including cytochrome P450 drug metabolism ($P = 0.013$), drug metabolism related to other enzymes ($P = 0.001$), glutamate metabolism ($P = 0.003$), aspartate and asparagine metabolism ($P = 0.003$), amino-sugar metabolism ($P = 0.021$), de novo fatty acid biosynthesis ($P = 0.02$) and leukotriene metabolism ($P = 0.027$).

Conclusion: In patients with pulmonary TB, plasma metabolomics analysis obtained early after TB diagnosis identified metabolic pathways related to drug metabolism, amino acid/nutrient metabolism and inflammation that differentiated those who did or did not become sputum culture-negative for *M. tuberculosis* after 8 wks of anti-TB drug treatment.

OA-474-06 A web-based interface to explore and analyze *Mycobacterium tuberculosis* whole genome sequence data

M Farhat,¹ J Honaker,² C Choirat,² T Ioerger,³ M Murray⁴
¹Massachusetts General Hospital, Boston, MA, ²Harvard University, Boston, MA, ³Texas A & M University, College Station, TX, ⁴Harvard Medical School, Boston, MA, USA.
 e-mail: marhat@gmail.com

Background: The study of genetic diversity, drug resistance and other clinical disease phenotypes through *Mycobacterium tuberculosis* whole genome sequences promises to improve our understanding of *M. tuberculosis* biology and management of TB Disease. Intuitive and open tools for data analysis can accelerate research and diagnostic development, and aid clinicians and laboratory personnel in interpreting these complex data. We sought to develop a web based interpretation and analysis tool for *M. tuberculosis* whole genome sequences.

Methods: We developed a web based tool using a core dataset of well characterized 123 strains with whole genome sequences, and 1397 strains with sequences from 28 known or putative drug resistance loci. We also developed a data pipeline that allow users to contribute to and expand this dataset. We trained a machine learning algorithm using the statistical language R that enables the prediction of drug resistance based on this data and drug resistance phenotypes, and developed a mapping tool to display the geographical distribution of

genetic variation, drug resistance, and lineage among other features.

Results and Conclusion: The interface enables the prediction of drug resistance phenotypes to 12 drugs from either whole genome sequences or a minimal set genetic variants from 21 genes or promoter regions. The interface also allows the geographic and statistical exploration of sequence, drug resistance, lineage data and others that the user may choose to input. To our knowledge, this tool is the first open access analysis tool of its type for *M. tuberculosis* genetic data.

23. TB in children, including MDR

OA-475-06 High frequency of pulmonary non-tuberculous mycobacteria in HIV-infected children with presumed tuberculosis in South-East Asia

B Dim,¹ S Goyet,¹ L Borand,¹ T N L Nguyen,² T H Pham,² S Godreuil,^{3,4} V Ung,⁵ O Marcy^{1,6}
¹Institut Pasteur in Cambodia, Phnom Penh, Cambodia; ²Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam; ³INSERM U1058, Montpellier, ⁴CHU Arnaud de Villeneuve, Montpellier, France, ⁵National Pediatric Hospital, Phnom Penh, Cambodia; ⁶ISPD - INSERM U897, Bordeaux, France. Fax: (+855) 2372 5606. e-mail: dbunnet@pasteur-kh.org

Background: Epidemiology, clinical impact and therapeutic management of Non-Tuberculosis Mycobacteria (NTM) in human immunodeficiency virus (HIV)-infected children are poorly studied in high tuberculosis (TB) burden countries. We studied NTM infections in HIV+ children suspect of TB in South-East Asia enrolled in the ANRS 12229 PAANTHER 01 study.

Design/Methods: HIV-infected children aged ≤ 13 years with a suspicion of intra-thoracic TB were enrolled after parental informed consent in pediatric HIV clinics in Cambodia and Viet Nam, from April 2011 to May 2014. Smear microscopy, Xpert MTB/RIF, and liquid culture (MGIT) were performed on respiratory and stool samples. NTM species identification was performed using GenoType Mycobacterium CM/AS® (Hain). Children were initiated on TB, NTM, and antiretroviral (ART) treatments per national recommendations and followed 6 months. We identified factors associated with NTM infection by logistic regression.

Results: We enrolled 250 children with 115 (46.0%) female, 112 (44.8%) on ART at inclusion, median age 6.9 years (IQR: 3.6 – 9.5), median weight for age Z-score -2.5 (IQR: -3.4 – -1.9), median CD4 15% (IQR: 3 – 25). Of 245 children with samples performed, 18 (7%) had culture-confirmed TB and 41 (17%) NTM (4 NTM/TB co-infections). Factors associated with NTM were CD4 count $< 5\%$ ($P = 0.037$) and absence of ART ($P = 0.027$) in univariate analysis, absence of ART only in multivariate analysis. Species identification in 74 of 88 NTM positive samples found 6 *M. simiae*, 7 *M. scrofulaceum*, 12 *M. fortuitum*, 42 *M. avium* complex (MAC), 2 *M. gordonae*, 2 *M. interjectum*, 2 *M. kansasii*, 1 *M.*

lentiflavum. 5 NTM-positive children had smear-positive samples, including 1 NTM/TB co-infection; 3 of 4 NTM/TB co-infections had a positive Xpert. Of 41 NTM-positive children, 28 received TB treatment, 17 received NTM-specific treatment, initiated 15 days (IQR: 7 – 53) after inclusion. At the end of the study (M6), 7 NTM-positive children had died, 1 had withdrawn from the study, 33 were followed -median weight gain from inclusion 2.1 (IQR: 1.0 – 3.0) kgs.

Conclusion: In HIV-infected South-East Asian children suspect of TB, 17% had culture confirmed NTM on respiratory and stool samples. Despite important NTM species diversity, MAC was the most common identified cause of lung disease in HIV-infected children. In the absence of rapid diagnostic test, and because of the high fatality rate, diagnosis and management of NTM are major issues in these children.

OA-476-06 Tuberculosis among adolescents and children along the cascade of HIV care in two regions of Ethiopia

D J Dare,¹ W Abebe,² K T Gari,³ M Aseresa Melese,¹ P G Suarez,⁴ A Ruff⁵ ¹Management Sciences for Health, HEAL TB Project, Addis Ababa, ²Addis Ababa University, Addis Ababa, ³Hawassa University, Hawassa, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, ⁵Johns Hopkins University, School of Public Health, Baltimore, MD, USA. Fax: (+251) 11 372 4473. e-mail: degujerene@gmail.com

Background: Understanding the magnitude of TB among adolescents and children has both public health and clinical significance. Since adolescents are socially more active than younger children and adults, their potential to transmit to their peers is high. Also, adolescents in general have more tendency to stop or interrupt treatment, which makes them important targets for prevention of drug resistant tuberculosis. On the other hand, younger children are at increased risk acquiring TB from adults and adolescents. HIV co-infection further compounds this challenge. However, there is limited data on the magnitude of tuberculosis in adolescents and younger children living with HIV. We report results from a cohort of HIV infected adolescents and children treated and followed at eight health facilities in two regions of in Ethiopia. Our objective was to determine the burden of tuberculosis among adolescents and children living with HIV along the cascade of chronic HIV care.

Methods: We conducted a retrospective cohort study in eight health facilities in two regions of Ethiopia. The study population constituted children (0-9 yr) and adolescents (age 10-19 years) enrolled in chronic HIV care between January 2005-December 31 2013. Trained study nurses assisted by site data clerks retrieved information from patient charts and registers. Patients' age category was the main predictor variable. Covariates included baseline WHO clinical stage, CD4, and IPT. Occurrence of new TB during follow up was the main outcome variable. We used SPSS for data analysis. We calculated TB incidence rates as new cases per 100 person-years of observation (PYO). We used Cox

regression analysis to control for confounders. The national research ethics committee approved the study protocol.

Results: Of 2058 participants (1072 adolescents and 986 children) included in this analysis, 54% were girls and 90% came from urban areas. Nearly a half (48.5%) were in advanced WHO stage at presentation. Previous history of TB was present in 13.9% of the participants. A further 12.1% had history of TB at enrollment. A total of 243 cases (142 in adolescents and 101 in younger children) of TB were reported during a pre-ART follow up period of 2422 PYO, making the overall incidence rate 10.03 (95%CI; 8.83, 11.35) per 100 PYO for the total cohort. The unadjusted incidence rate was higher in adolescents 16.32 (95%CI; 13.75, 19.24) than the rate in younger children (6.51 [95%CI; 5.29, 7.90]; $P < 0.0001$). After adjusting for WHO stage and INH use, adolescents were twice more likely to have TB diagnosis before ART. ART was associated with 85% reduction in TB incidence in both groups but the adolescent age group continued to have significantly higher rates even after ART.

Conclusion: The burden of TB was high both in children and adolescents but it was even higher in the adolescent age group, suggesting the need for targeting this age group for TB prevention. On the other hand, the lower TB rate in the younger age group could be due to poorer diagnostic capacity, warranting the need for better diagnostic tools for TB in the younger children. Therefore, both adolescents and children living with HIV should be prioritized for TB prevention interventions.

OA-477-06 Risk factors for active tuberculosis among child contacts of recently diagnosed adults with sputum smear-positive tuberculosis

U Egere,¹ T Togun,¹ S Abdoulai Daffay,¹ J Otu,¹ B Kampmann^{1,2} ¹Vaccines and Immunity Theme, Medical Research Council Unit, Fajara, The Gambia; ²Imperial College, London, UK. e-mail: uegere@mrc.gm

Background: Like in many settings, TB in children is under-diagnosed and poorly managed in The Gambia. Although WHO recommended, contact tracing is not done because of limited resources and lack of expertise. Better targeted screening might be achievable if particular risk factors are known. We identified risk factors for TB disease among child contacts of adults recently diagnosed with TB, which could guide such targeted strategies for national programs.

Design/Methods: Households of consenting adults diagnosed with sputum smear positive TB in The Gambia were visited, where a symptom screening questionnaire and Tuberculin skin testing (TST) were administered to all children <15 years. TST response of ≥ 10 mm was considered positive. Presence of cough of at least 2 weeks duration and at least one of other symptoms such as weight loss, failure to gain weight, fever, night sweats, was regarded as suggestive of TB. All children with symptoms suggestive of TB and/or positive TST result

had clinical examination, chest X-ray and sputum examination at the childhood TB clinic at the MRC. Children with active TB were commenced on anti-TB treatment according to national guidelines. Random effects logistic regression model taking into account clustering of contacts within households was used to access the relationship between TB disease and risk factors.

Results: Of 3565 child contacts screened in the community, 736 (20.6) were symptomatic and/or TST positive of which 702 had clinical and chest X-ray examination in the clinic. Sputum examination (smear, GeneXpert and culture) was then performed for all children. 44 of 702 (6.3%) were diagnosed with active TB. Record of BCG vaccination was not associated with protection against active TB. Odds of active TB increased with increasing gradient of exposure to the index case (OR 4.0 {1.16 – 13.8} $P=0.028$ for same room, OR 7.2 {1.83 – 28.2} $P<0.0005$ for same bed). Positive TST was associated with increased odds (OR 15.2 {5.7 – 40.8} $P<0.0005$ for TST 10-14mm) but odds did not increase further as TST increased beyond 14mm.

Conclusion: Child contacts in closest proximity to adult TB cases have the highest odds to develop active TB. Though not a new finding, this is significant in The Gambia where relatively large numbers of contacts live in separate house to the index case but would still be eligible for contact tracing. In the face of limited resources contact tracing could target the closest contacts only for the highest yield.

OA-478-06 Surveillance of childhood tuberculosis drug resistance in Cape Town, South Africa: increasing rifampicin mono-resistance

H S Schaaf,¹ E Walters,¹ A Hesselning,^{1,2} C Rautenbach,^{2,3} C Bosch,¹ A Garcia-Prats¹ ¹Stellenbosch University, Cape Town, ²Tygerberg Hospital, Cape Town, ³National Health Laboratory Service (NHLS), Cape Town, South Africa. Fax: (+27) 21 938 9138. e-mail: hss@sun.ac.za

Background: Consecutive 2-year tuberculosis (TB) drug resistance surveys amongst children have been ongoing in Cape Town, South Africa since March 2003 to evaluate trends of drug resistance and HIV co-infection amongst children with culture-confirmed TB. We found a decline in the prevalence of TB-HIV co-infection and multidrug-resistant TB (MDR-TB) in the most recent reporting period (2011-2013) compared to previous peak occurrences.

Design/Methods: A prospective 2-year surveillance (March 2013-Feb 2015) of drug resistance in all bacteriologically confirmed child TB cases (<13 years) at Tygerberg Hospital, Cape Town, South Africa. Initial drug susceptibility testing (DST) is done for isoniazid (INH) and rifampicin (RIF) on a single specimen from each child with culture-confirmed TB, and RIF DST if only the Xpert MTB/RIF is positive. Second-line DST was undertaken if culture-confirmed and resistant to RIF. HIV status was recorded.

Results: 292 children, 144 (49.3%) males, with a median age of 34 months (IQR 14-84 months) with bacteriologically confirmed TB were recorded; 276 were culture-confirmed and 16 only confirmed by Xpert. Of culture-confirmed cases, 241 (87.3%) were pan-susceptible, 20 (7.2%) were MDR, 8 (2.9%) were RIF-resistant/INH-susceptible and 7 (2.5%) were INH-resistant/RIF-susceptible. Of the 16 Xpert-positive only cases (culture-negative), 14 were RIF-susceptible, 2 RIF-resistant and 2 had indeterminate results. Of 290 (99.3%) children tested, 30 (10.3%) had any RIF-resistance. Of 26 RIF-resistant cases tested, ofloxacin and amikacin resistance were present in 5 (19%) and 4 (15%), respectively. Of 280 (95.9%) children tested, 45 (16.1%) were HIV-infected. Compared to previous surveillance periods, RIF mono-resistance has increased steadily over each period from 0 to 2.9%, now surpassing INH mono-resistance. The prevalence of MDR-TB has stabilised and the HIV prevalence has decreased significantly from a peak of 29% observed in 2007-2009, to 16% during the last two surveillance periods.

Conclusion: The steady increase in RIF-resistant/INH-susceptible cases is concerning, while the prevalence of MDR-TB appears to be stabilising. These data indicate recent transmission of DR-TB strains to young children, reflecting ongoing transmission. The increasing circulation of RIF mono-resistance has important implications for both treatment and preventive therapy in cases confirmed to be resistant by Xpert without further culture and DST.

OA-479-06 The pharmacokinetics and safety of ofloxacin for drug-resistant tuberculosis in children

A Garcia-Prats,¹ H R Draper,¹ K Dooley,² J Seddon,³ S Thee,⁴ H McIlleron,⁵ H S Schaaf,¹ A Hesselning¹

¹Desmond Tutu TB Centre, Stellenbosch University, Tygerberg, South Africa; ²Johns Hopkins University School of Medicine, Baltimore, MD, USA; ³Imperial College London, London, UK; ⁴Charite, Universitätsmedizin Berlin, Berlin, Germany; ⁵University of Cape Town, Cape Town, South Africa. e-mail: garciaprats@sun.ac.za

Background: Ofloxacin is a fluoroquinolone widely used for the treatment of multidrug-resistant tuberculosis (MDR-TB). Pharmacokinetic (PK) and safety data in children are limited, and it is not known whether the recommended pediatric dose of 15-20mg/kg achieves exposures reached by adults with TB. After a standard 800mg dose in adults, median PK measures are: area under the concentration-time curve (AUC) 0-24 103µg*h/mL, maximum serum concentration (C_{max}) 10.5 µg/mL, and oral clearance (CL/F) 0.12 L/h/kg.

Design/Methods: PK and safety of ofloxacin were assessed in children <15 years of age routinely receiving treatment or preventive therapy for MDR-TB. To assess a 20mg/kg dose, plasma samples were collected pre-dose and at 1, 2, 4, 8 and either 6 or 11 hours post-dose. Assays were performed using HPLC MS/MS. PK parameters were calculated by non-compartmental analysis. Children with MDR-TB disease were followed

longitudinally in the study for safety, with clinical and laboratory assessments 1-2 monthly. Adverse events were graded using standardized DAIDS criteria, and attribution to ofloxacin assessed.

Results: Of 85 children (median age: 3.4 years) 11 (13%) were HIV-infected and 14 (18%) were underweight. Mean (range) C_{max} and AUC₀₋₈ were 8.97 µg/mL (2.47-14.40) and 44.2 µg*h/mL (12.1-75.8), respectively. In multivariable linear regression, AUC₀₋₈ was reduced by 1.54 µg*h/mL for each additional year of age ($P=0.026$) and increased by 0.68 µg*h/mL for each additional kg of body weight ($P=0.009$). Controlling for age and weight, no other variables contributed to the model. Because of < 3 time points in the elimination phase in some patients, the half-life, CL/F, and AUC₀₋₂₄ were estimated only in 72 participants. The mean (range) AUC₀₋₂₄ was 66.7 µg*h/mL (18.8-120.7) and half-life was 3.47h (1.89-6.95). The mean (range) CL/F was 0.33 L/h/kg (0.10-1.04), and more rapid clearance was seen in younger children ($P < 0.001$). Among 46 patients with MDR-TB disease contributing 23.8 years of observation time, there were no Grade 3 or 4 events potentially related to ofloxacin.

Conclusion: Ofloxacin was safe and well tolerated in children with MDR-TB. In these children, C_{max} values approached those in adults after an 800 mg oral dose, however AUCs were well below reported adult values suggesting further dose modification in children may be required to optimize regimens for MDR-TB treatment in children.

OA-480-06 Developing Swaziland's first public pediatric MDR-TB contact clinic

G Mtetwa,¹ P Ustero,^{1,2} R Golin,^{1,2} J Glickman,¹ P Swamy,² B Tsabedze,¹ M Hlatshwayo,¹ A Mandalakas²
¹Baylor College of Medicine Children's Foundation - Swaziland, Mbabane, Swaziland; ²Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. Fax: (+268) 2404 0214. e-mail: golin@bcm.edu

Background and challenges to implementation: Baylor College of Medicine Children's Foundation - Swaziland (BCMCF-SD) provides comprehensive HIV-TB services, including a standardized approach to pediatric TB prevention, diagnosis, treatment, and contact tracing. The high TB incidence (1,382/100 000) together with the high rates of MDR-TB in Swaziland (7.7% of new cases, 34% of retreatment cases) led BCMCF-SD to develop the country's first public pediatric MDR-TB contact clinic.

Intervention: To meet the needs of MDR-TB exposed children and adolescents, BCMCF-SD established a monthly MDR-TB Contact Clinic Day. Contacts of household MDR-TB index cases are identified and referred to BCMCF-SD. Participating families receive reminder phone calls prior to their clinic day and receive transport reimbursement for their first visit. Children and adolescents are requested to attend clinic with a caregiver; patients and caregivers attend an education session on MDR-TB infection. TB screening and risk assessment is completed by all attendees. Sputum analysis (GeneXpert [GXP] and culture) and radiological

studies are available at no charge to support children's evaluation. The majority of patients will be followed for 1 year, with select patients requiring up to 2 years of clinical monitoring.

Results and lessons learnt: Since February 2015, a total of 25 children and adolescents were enrolled. The mean age was 6.6 years, with 40% (10/25) under 5 years old. 80% (20/25) were HIV negative, 20% (5/25) were HIV positive. On average, contacts attended clinic 17.7 months after the household index case started MDR-TB treatment. TB symptom screening was positive in 32% (8/25) of contacts. Of those, 75% (6/8) completed GXP testing; GXP testing did not detect MTB in any specimens. All patients with a positive TB screen had a normal chest radiograph. Drug sensitivity test results of the index cases could only be identified for 16% (4/25) of contacts.

Conclusions: Clinicians and parents welcomed referral to BCMCF-SD's pediatric MDR-TB contact clinic as they recognize the importance of monitoring this vulnerable population. Strategies are needed to reduce the financial barriers imposed by transport and radiological fees. The lack of national and international policy concerning preventive therapy for children and adolescents limits the full benefit of this program.

OA-481-06 Survival of children with HIV infection and drug-resistant TB in three provinces in South Africa, 2005-2010

S Morris,¹ E Hall,¹ S Smith,¹ N Ismail,² R Odendaal,³ N Ndjeka,⁴ H Menzies,¹ M Van Der Walt³ ¹U.S. Centers for Disease Control, Atlanta, GA, USA; ²National Health Laboratory Services, Johannesburg, ³South African Medical Research Council, Cape Town, ⁴Ministry of Health, Pretoria, South Africa. e-mail: feu3@cdc.gov

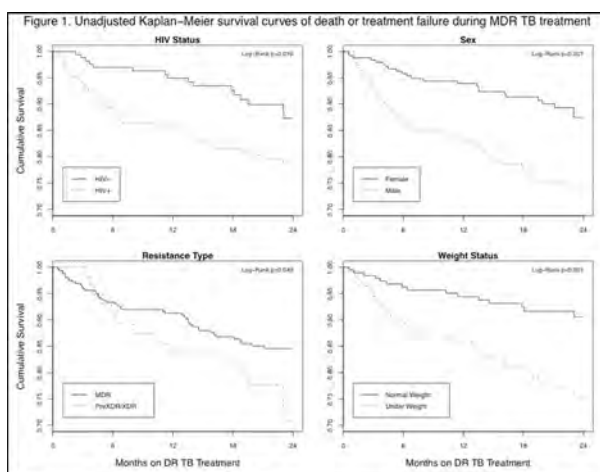
Background: Few studies describe treatment outcomes of pediatric patients co-infected with HIV and drug-resistant tuberculosis (DR-TB). The objective of this secondary analysis of a pediatric DR-TB study conducted in three South African provinces was to assess the survival of these patients based on HIV status and other risk factors.

Design/Methods: Demographic, clinical, and laboratory data from pediatric patients treated for DR-TB during 2005-2010 were retrospectively collected. Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) comparing the odds of experiencing a poor outcome (death or treatment failure) to a positive outcome (cure or treatment completion), while controlling for HIV status, sex, age, province, year of TB diagnosis, resistance pattern, weight and 6-month culture growth among patients diagnosed before 2009. A time-to-event analysis was conducted using days from start of treatment to outcome. Bivariate and multivariate stratified Cox proportional hazard models were used to estimate hazard ratios.

Results: Of 685 eligible participants, 55% were HIV-infected, 52% were underweight, and 42% were male. There were 434 participants with documented HIV

status and outcomes; cured or completed treatment (57%), died (16%), failed (1%), defaulted or lost to follow-up (9%), and still on treatment, transferred or unknown (18%). HIV-infected patients had a six fold increase in odds of poor outcome when compared to HIV-negative children (aOR=6.4; CI 2.1–19.1). Males, underweight, and severely underweight patients experienced an increase in odds of death or treatment failure (aOR=2.9; CI 1.1–8.2, aOR=2.6; CI 1.2–5.6, aOR=9.0; CI 3.4–23.5, respectively) than comparison groups. Among the HIV-infected patients, those that had never taken antiretroviral therapy (ART) died or failed treatment at three times the rate when compared to those who had taken antiretroviral therapy. The rate of dying or failing treatment at any point in time during the follow-up was 2.5 times higher among patients who were HIV-infected (aHR=2.4; CI 1.2–5.0).

Conclusion: HIV-infected, male, and underweight children with DR-TB were more likely to fail treatment or die when compared to other children with DR TB within this population. Targeted interventions and early use of ART are needed to improve clinical outcomes among HIV-positive and underweight children diagnosed with and at risk for DR-TB.



OA-482-06 The management of child multidrug-resistant tuberculosis contacts across Europe

A Turkova,^{1,2} M Tebruegge,^{3,4} F Brinkmann,⁵ M Tsoia,⁶ F Mouchet,⁷ B Kampmann,^{8,9} J Seddon⁹ ¹Medical Research Council Clinical Trials Unit at University College London, London, ²Imperial College Healthcare NHS Trust, London, ³University of Southampton, Southampton, ⁴University Hospital Southampton NHS Foundation Trust, Southampton, UK; ⁵Children's Hospital, Ruhr University Bochum, Bochum, Germany; ⁶National and Kapodistrian University of Athens School of Medicine, "P. & A. Kyriakou" Children's Hospital, Athens, Greece; ⁷Université Libre de Bruxelles, Brussels, Belgium; ⁸Medical Research Council

(MRC) Unit The Gambia, Banjul, Gambia; ⁹Imperial College London, London, UK. e-mail: a.turkova@ucl.ac.uk

Background: The burden of multidrug-resistant (MDR) tuberculosis (TB) is increasing globally, including in the WHO European region, where an estimated 75,000 cases occurred in 2013. Consequently, a large number of children are exposed to MDR-TB, become infected and/or develop disease. There are no data from clinical trials to inform the management of child MDR-TB contacts, and national and international guidance is inconsistent. However, observational studies suggest that the use of a multidrug regimen, tailored to the drug susceptibility results of the source case, can be safe and effective.

Design/Methods: From March to July 2014 we conducted a web-based survey using the Paediatric Tuberculosis Network European Trials group (pTbNet), the IUATLD Childhood TB Working Group, and the Childhood Subgroup of the WHO Stop TB Partnership. The aim of the study was to capture variations in the clinical management of children exposed to MDR-TB in the WHO European region.

Results: Of 176 specialists from 44 countries approached, 72 (41%) responded from 25 countries, including 28 from 6 countries outside the European Union/European Economic Area (EU/EEA). Sixty-six (92%) had >5 years of experience working with TB; 59 (82%) were at senior level and 41 (57%) managed ≥3 child MDR-TB contacts a year. Forty-two (58%) stated they were using preventive treatment (PT); 24 (57%) of those reported they were treating all children with evidence of latent TB infection, 16 (38%) reported treating exposed children without positive tests of infection in certain circumstances (young age or immunosuppression). Thirty-one (74%) used tailored regimens with ethambutol, pyrazinamide, high-dose isoniazid, levofloxacin/moxifloxacin and ethionamide being most commonly used. Twenty-one (50%) stated they were treating for 6 months, and 14 (33.3%) for >6 months. Most were following cases up for ≥2 years regardless of whether PT was given or not (71% & 86%, respectively). The only factor associated with the provision of PT was practice within the EU/EEA (vs. outside the EU/EEA); adjusted odds ratio: 4.07 (95% CI: 1.33–12.5; *P* = 0.014).

Conclusion: We identified a wide spectrum of practice in Europe regarding MDR-TB-exposed children. Over half of clinicians were using PT with varying indications, drug regimens and follow-up periods, reflecting poor evidence base and variable guidance. The data highlight that there is an urgent need for prospective studies to inform management decisions in the future.

24. The wide swath of vulnerable populations

OA-483-06 20 years of TB control in the penitentiary system of Azerbaijan: achievements and challenges

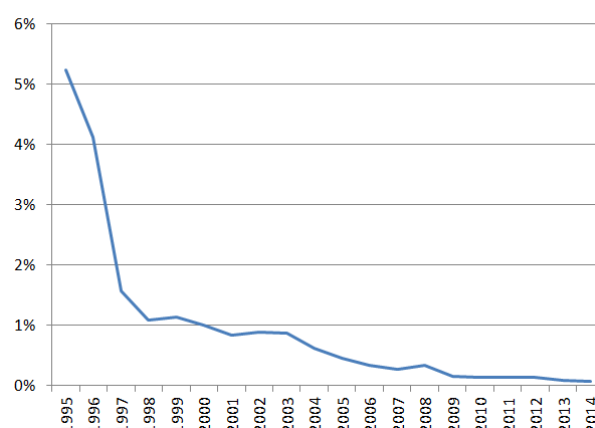
E Gurbanova,¹ R Mekhdiyev,¹ F Huseynov,¹ O Baghirov,² R Tahirli³ ¹Main Medical Department of the Ministry of Justice, Baku, ²Specialized Treatment Institution for Detainees with Tuberculosis, Baku, ³Laboratory of the Specialized Treatment Institution for Detainees with Tuberculosis, Baku, Azerbaijan. e-mail: e.gurbanova@prisonhealth.az

Background: The Main Medical Department (MMD) of Azerbaijan Ministry of Justice provides healthcare including TB services to 24 penitentiary institutions with 16 000 population. Design and methods: Following political commitment, a TB Control Program has been successfully developing in accordance with WHO recommendations over 20 years. It includes early TB case finding, qualitative and rapid diagnostics, standardized TB treatment, strict compliance to DOT and infection control (IC) protocols as well as uninterrupted supply with certified drugs. Quality assured TB laboratory is equipped with phenotypic and genotypic diagnostic tools for precise TB diagnostics. Both drug-susceptible (DS) and drug-resistant (DR) TB treatment is centralized at the Specialized Treatment Institution (STI) with approximately 900 bed-places. IC include administrative (patient segregation in accordance with infectiousness, drug sensitivity profile, treatment phase and detention regimen) environmental (input and extract ventilation, UV lamps) and individual. Patients are offered permanent support of adherence via additional food and hygienic packages as well as psychological support to overcome stress related to disease and imprisonment. Uncompleted TB treatment, initiated within the PS, proceeds after release. Having ensured appropriate juridical basis MMD has been collaborating with MoH and NGO to provide support and follow-up of TB patients in civilian sector.

Results: Comparing with 1995 in 2014 mortality from TB among Azerbaijan prison population decreased >65 times (Diagram). The Programme achieved significant treatment success rate both for new smear positive DS-TB and MDR-TB cases equal 91% and 80% respectively. 100% of inmates pass through TB screening in pre-trial isolators and 95% of the prisoners pass through annual mass screening for TB including questionnaire, X-ray, and sputum investigation. Special attention is paid to identification and prevention of TB among HIV-infected. Training Center functioning since 2012 at the STI was declared WHO CC on TB prevention and control in prisons and trained >700 medical and non-medical staff of PS. Moreover, delegations from >15 countries visited the Program to get acquainted with the practice. Operational researches are performed on the Programme's theoretical and practical basis.

Conclusions: Today Azerbaijan TB Control in prison Programme is internationally recognized model for penitentiaries in and beyond the European Region.

Diagram. TB mortality among Azerbaijan prison population



OA-484-06 Deaths due to tuberculosis and social inequality: a spatial analysis in a priority municipality for disease control, Brazil, 2006-2012

M Yamamura,¹ M Popolin,¹ M Santos Neto,² L H Arroyo,¹ F Chiaravalloti Neto,³ J Crispim,¹ A Belchior,¹ R Arcencio¹ ¹Nursing School of Ribeirão Preto - University of São Paulo, Ribeirão Preto, SP, ²Federal University of Maranhão, Imperatriz, Maranhão, ³Public Health School - University of São Paulo, São Paulo, SP, Brazil, e-mail: mellinayamamura@yahoo.com.br

Background: Death due to tuberculosis (TB) is as an avoidable event there due to the availability of diagnostic technologies and treatment. The objective was to analyze the spatial relationship of preventable deaths from TB with social inequity indicators in Ribeirão Preto - São Paulo, Brazil.

Design/Methods: An ecological study that considered the primary cause of deaths from TB recorded between 2006 and 2012 in the Mortality Information System. It was possible to consider literacy variables of household heads, number of residents per household, and per capita income obtained through Census of the Brazilian Institute of Geography and Statistics, in 2010. The Analysis of Principal Components (PCA) for the construction of social inequity indicators was applied in the Statistica 10.1 software. The geocoding of deaths was performed in Terraview 4.2.2. TB mortality rate calculation happened through local and empirical Bayesian method. It was necessary to define, as geographical units, the areas covered by Primary Health Care Services. Multiple linear regression and spatial regression were used to test the spatial dependence between social inequity indicators from TB mortality rates, in the R software.

Results: Death rates, in regions under study, ranged from 0.00 to 797.31 deaths per 100 000 inhabitants/year. In the APC, three indicators were built with a total variance

of 79.5%. They were named as low, high and intermediate social inequity indicators with a variation of 46.21%, 18.76% and 14.61%, respectively. In multiple linear regression, the median social inequity indicator or intermediate was statistically significant ($P=0.0005$), R^2 adjusted by 28.98% and there was spatial dependence (Moran $I = 0.21$, $P = 0.0034$). Spatial Lag Model to address the existent dependency resulted in the best one, and it enabled to verify which areas with median social inequity or intermediate indicator showed the highest mortality rates.

Conclusion: Despite evidence of relationship between TB deaths and extreme social inequality indicators, it was possible to observe in the study a relation between TB and areas where families are literate and have incomes above the minimum wage. Perhaps, the resources are still insufficient for the social development of communities, which is an important and protective factor in TB geography.

OA-485-06 Active case finding: a science of delivery on the ground

S Pandurangan,¹ S Chadha,¹ S Mohanty,¹
P Banuru Muralidhara,¹ B Entoor Ramachandran,¹
B Thapa,¹ A Das¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India.
Fax: (+91) 11 46 05 40 30. e-mail: sripriya14@gmail.com

Background and Challenges: Universal access to tuberculosis (TB) services is critical for timely diagnosis and treatment. Early case-detection and ensuring complete treatment of sputum-positive TB patients has always been a major public health challenge for TB control programmes. The current programme strategies have been able to cater to only those patients who visit public health institutions or those who were identified by community-based healthcare workers.

Intervention: Project Axshya, supported by the Global Fund, is being implemented by The Union in 300 districts of India in partnership with 9 Sub-Recipients and a network of more than 1200 community based organisations. The primary aim of Project Axshya is to enhance the access of vulnerable and marginalized populations to TB services through advocacy, communication and social mobilisation activities. Under the Project, Active case finding a strategy being implemented to identify the 'missing' three million TB cases with a focus on enhancing accessibility to TB services among the households. Trained community volunteers visits nearly 1000 households per month per district to sensitize about TB followed by identification of TB symptomatics (having cough of 2 weeks) in these households. Identified symptomatics are either referred to the nearest designated microscopy centres or if required sputum collection and transportation is being done. If the symptomatics found to be positive, they are linked to treatment services.

Results and lessons learnt: A total of 6.2 million households were visited by the community volunteers during the period April 2013 – March 2015. About 435979 TB symptomatics were identified. Of these 181 107 persons sputum were collected and transported and

the remaining persons were referred to the nearest microscopy centres. A total of 232 298 (53%) cases were examined at DMCs and 17 584 (8%) were found to be positive and 97% of those diagnosed were put on DOTS.

Conclusion: The Active case finding through community based organisations successfully enhances access to diagnosis and treatment of TB for vulnerable and marginalised populations.

OA-486-06 TB risk perceptions among medical residents at a tertiary care center in India

G Pardeshi,¹ M Parande,¹ D Kadam,¹ A Chandanwale,¹
A Deluca,² R Bollinger,³ J Farley,⁴ N Suryavanshi⁵
¹Byramjee Jeejeebhoy Medical College/Sassoon General Hospital, Pune, India; ²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ³Johns Hopkins University School of Medicine, Baltimore, MD, ⁴Johns Hopkins University, Baltimore, MD, USA; ⁵Byramjee Jeejeebhoy Medical College/Johns Hopkins, Pune, India. e-mail: kanugeet@gmail.com

Background: Risk perception influences an individual's behavior. Resident doctors in India are at high risk for tuberculosis (TB). To optimize uptake and effectiveness of prevention guidelines, we assessed their risk perceptions regarding occupationally acquired TB.

Methods: The study using mixed methodology was undertaken at BJ Government Medical College, a tertiary health care center in Pune, India in September 2014. Consenting post-graduate medical resident doctors completed a self-administered anonymous structured Knowledge, Attitude and Practice questionnaire about factors perceived to increase their risk of TB. Data were analyzed using χ^2 /Fishers Exact test. An open-ended question and two focus group discussions assessed concerns about their personal risk of acquiring TB. Responses were analyzed to identify key themes with exemplary quotes.

Results: Of 305 (94%) residents contacted, 263(86%) consented and completed the questionnaire. Many (55%) reported daily exposure to active TB cases. Thirteen (5%) reported a previous episode of TB and 114(45%) knew of another resident who had been diagnosed with TB. Almost all medical residents reported concern with developing TB and drug-resistant TB (98% & 88%, respectively). Compared to 1st year residents, more experienced residents (2nd and 3rd year) were more likely to report specific infection control and workplace concerns as contributing to their TB risk. For example, not using Personal Protective Equipment (PPE) was identified as increasing the risk of TB in 23 (24%) of 97 1st year residents and in 80 (49%) of 163 other residents ($P < 0.05$). Residents who knew a colleague with TB were more likely to report risk factors, compared to those who did not know a colleague with TB. For example, 71(62%) of those with a TB-infected colleague reported workload as a TB risk factor, compared to 59 (43%) of those without a colleague with TB ($P < 0.05$). Key themes identified as increasing their personal risk, included overexposure to TB patients,

high-risk procedures/sites, patient cough etiquette, poor use of PPE, poor ventilation, crowded working and living conditions.

Conclusions: Our study found a high concern for occupational TB, among medical residents in a large urban hospital in India. Poor implementation of standard infection control and workload were frequently identified as contributing to their perceived risk of TB. Less concern expressed for known TB risk factors among 1st year residents and among those who did not know a colleague with TB highlights the need for increased TB prevention education and better implementation current TB prevention guidelines.

OA-487-06 Integrating tuberculosis screening in mother and child health clinics: a policy change could overcome the challenges of the second sputum sample

S Maosa,¹ M Kumwenda,^{2,3} A Chilembwe,¹ B Chikuse,⁴ B Chikuse,⁴ A Dimba,⁵ C Shaw,⁶ B-T Nyang'wa,⁷ M Brouwer⁸ ¹Sue Ryder Foundation in Malawi, Balaka, ²Malawi Liverpool Wellcome Trust, Blantyre, ³University of Malawi, Blantyre, ⁴District Health Office, Balaka, Malawi, ⁵Ministry of Health, Lilongwe, Malawi; ⁶Target Tuberculosis, Brighton, ⁷Independent Consultant, London, UK; ⁸PHTB Consult, Tilburg, Netherlands. e-mail: soniamaosa@yahoo.com

Background: The Malawian National Tuberculosis (TB) Program (NTP) guidelines require a presumptive TB patient to submit two sputum samples: one at the time of consultation and the second one produced early next morning (the spot-morning or standard approach). A project integrating active TB screening in mother and child health clinics found that not all presumptive TB patients submitted the morning sample. The same day approach provides the required two samples in a single visit. In this study we explored reasons why women do not submit the morning sample. We also compared the yield between the same day approach and the standard approach.

Methods: Mixed methods study. Qualitative: focus group discussions with (presumptive) TB patients and health care workers. Quantitative: comparison of the standard with the same day approach through inclusion of consecutive presumptive TB patients at Balaka District Hospital. Participants provided a second spot sample one hour after the first spot sample in addition to the standard morning second sample. We collected demographic and clinical data. A TB case was any participant with at least one positive sputum sample by the standard approach as per NTP guidelines.

Results: Reasons for not submitting a morning sample included: long distance to the health facility, financial burden of a repeat visit, fear of TB-HIV diagnosis, long waiting time at the facility and discourteous attitude of health care workers. The culturally subordinate position of women within a household made it difficult for married women to comply with morning sample requirements. Being very ill or slackness contributed to failing to go for a second visit. The same day approach

evaluation has so far included 187 participants; 21 (11%) and 19 (10%) were bacteriological positive according to the standard and same day approach respectively. Of the 21 positive patients, 18 had all 3 sputum samples positive. Two of the remaining 3 were positive on the morning sample only and the third had both the second spot and the morning sample positive. Five percent of patients failed to bring the morning sample versus 1% for the second spot sample.

Conclusion: Women face many barriers in the health system, at home and in themselves for submitting the morning sample. A simple policy change from the spot-morning to the same day approach could overcome the individual and social-economic barriers. Health systems improvements are necessary to remove some of the other barriers.

OA-488-06 Tuberculosis-entry screening for asylum seekers in the Netherlands: challenges and solutions in a pressurised immigration context

Y Aartsma,¹ J Den Boer,¹ M Urban,¹ M Vermue,¹ Q Waldhoer,² E Kloeze,³ R Van Hest^{1,4} ¹Regional Municipal Health Service Groningen, Groningen, ²Association of Community Health Services and Regional Medical Emergency Preparedness and Planning Offices in the Netherlands, Utrecht, ³University Medical Centre Groningen, Groningen, ⁴Regional Municipal Health Service Rotterdam-Rijnmond, Rotterdam, Netherlands. Fax: (+31) 10 4339 950. e-mail: nah.vanhest@rotterdam.nl

Background and challenges to implementation: The Netherlands operates a centralised system of asylum application. Apart from a small minority at the national airport Schiphol and unaccompanied minors, the majority of asylum seekers must file their request at the national reception centre in Ter Apel, almost 22 000 persons in 2014. Within 72 hours their procedure of registration and identity verification by the Alien Police, an interview with the Immigration and Nationalisation Service and mandatory radiographic screening for intrathoracic tuberculosis (TB), must be completed. We describe process and yield of daily entry screening, including a time of a sudden high influx of asylum seekers, predominantly from Syria and Eritrea. Apart from the logistics, maintaining good standards of medical practice under pressure of timely processing of the asylum application procedure is challenging.

Intervention or response: Chest X-ray (CXR) screening for TB at the Dutch national reception centre for new asylum seekers, since April 2012 on a daily basis. CXRs are digitally transferred for reading (within maximum 24 hours) to the TB Department of the Regional Public Health Service of Groningen, also allowing teleradiology in the weekends. Apart from making CXRs, upon request of the TB Physician, the team of medical technical assistants at the centre, can also take standardised questionnaires with telephone translators, collect sputum for bacteriology or perform tuberculin skin testing for further examination and can isolate individuals.

Results and lessons learnt: The average daily number of screenings increased from 22 in 2012, 34 in 2013 to 67 in 2014, with outliers above 200 persons per day in 2014. Of all entrants 1.6% were further examined of which 4.5% were diagnosed with TB. Entry screening during 3 years identified 30 TB cases, of which 8 (27%) were smear-positive, 26 (87%) culture-positive and 4 (13%) multidrug resistant. TB was common among Eritreans but not among Syrians. The annual yield of entry screening was 114, 57 and 64 cases per 100 000 persons respectively. A flexible and efficient practice model for daily radiographic TB screening of a varying influx of asylum seekers was feasible.

Conclusions and key recommendations: This unique early diagnosis practice model was effective, with potential for other European countries. The number of TB cases found actively and passively after entrance will be further researched, also as quality assessment of entry screening.



OA-489-06 Rapid expansion of TB prevention and care programs: are the elderly left behind?

B Kerschberger,¹ I Ciglenecki,² G Mchunu,³ L Rusike-Pasipamire,¹ I Zabsonre,¹ M M Win,¹ B Rusch,² S M Kabore¹ ¹Médecins Sans Frontières (Operational Centre Geneva), Mbabane, Swaziland; ²Médecins Sans Frontières (Operational Centre Geneva), Geneva, Switzerland; ³National TB Control Programme, Ministry of Health, Manzini, Swaziland. e-mail: benadi11@yahoo.de

Background: Southern African countries scaled-up TB care with focus on younger adults which are severely affected by the intertwined HIV-TB epidemic. This public health approach for care expansion, however, risks leaving certain populations behind. Little is known on TB notification rates and treatment outcomes for elderly populations from high HIV-TB prevalence settings.

Design/Methods: We compared first line TB drugs age-specific notification rates (2009-2014) and treatment outcomes (2009-2013) between the elderly (≥ 50 yrs) and younger adults (20-49 yrs) in the rural Shiselweni region (210,000 population), Swaziland. Annual population figures were obtained from the 2007 census. Logistic regression models adjusted for baseline factors (sex, registration year, TB case definition, HIV status,

health care level) were utilized to compare adjusted odds ratios (aOR) of treatment success between age-groups.

Results: Out of 7539 TB notifications, 21% were among the elderly. TB notification rates in the HIV negative and positive population were higher in the elderly (HIV-: 616/100 000; HIV+: 4558/100 000) when compared to younger adults (HIV-: 283/100 000; HIV+: 3216/100 000) ($P < 0.01$). Among HIV+elderly, notifications were higher among males (5530/100 000) when compared to females (3437/100 000) ($P < 0.01$). The overall decline in notification rates from 2009-2014 was higher in younger adults (elderly: 1957 to 572/100 000 vs. younger adults: 2466 to 790/100 000; $p < 0.01$). At TB treatment commencement, 12% among the ≥ 60 had an unknown HIV status compared to 7 and 6% in the 50-59 yrs and younger adults ($P < 0.01$). HIV co-infection was lowest in the ≥ 60 yrs (34%) and higher in the 50-59 yrs (66%) and younger adults (82%) ($P < 0.01$). Among new PTB cases ($n = 5342$), success rate was 68% in ≥ 60 yrs compared to 74% in each of the other age-groups ($P < 0.01$). The likelihood of treatment success among all treatment cases was decreased in the ≥ 60 yrs (aOR 0.56, 95%CI 0.47-0.67) and similar in 50-59 yrs old (aOR 1.01; 95%CI 0.83-1.23) in comparison to younger adults.

Conclusion: The elderly only contributed one fifth to total adult TB notifications explained by demographic patterns. However, the ≥ 50 yrs old had the highest age-adjusted notifications rates, while HIV testing utilization and treatment outcomes were inferior in ≥ 60 yrs old. More attention is needed in TB prevention and care programs for older populations, specifically in the context of a maturing HIV-TB co-epidemic.

OA-490-06 Effectiveness of routine TB screening in central Tanzanian prisons using digital chest X-ray and Xpert® MTB/RIF assay

J Van Den Hombergh,¹ C Mangu,² D Kowuor,² J Malewa,³ E Chilolo,¹ M Hoelscher,^{4,5} P Clowes^{2,5} ¹Stichting PharmAccess International (PAI), Dar Es Salaam, ²NIMR Mbeya Medical Research Centre, Mbeya, ³Tanzania Prisons, Dar Es Salaam, Tanzania; ⁴Medical Center of the University of Munich, Munich, ⁵German Centre for Infection Research, Munich, Germany. e-mail: janushom@gmail.com

Background and challenges to implementation: Penitentiary institutions are proven to be a permanent source for active TB transmission, but data on TB prevalence in prisons, as well as associated risk factors, are scarce, especially in Africa where 26% of newly diagnosed cases occur. Effective and sustainable TB screening followed by prompt treatment for those found to have active TB is needed to curb TB transmission in prison settings.

Intervention: As part of a TB REACH grant, all inmates and new admissions to 3 Tanzanian prisons in Dar es Salaam are actively screened for TB by using chest X-ray and the X-pert MTB/RIF® assay. In one of the three prisons Xpert is only applied for those showing any abnormality on the chest X-ray. In this prison computer-aided diagnosis for TB (CAD4TB) is applied to the X-ray images. PITC for HIV is offered as an opt-out strategy as

part of the screening protocol. Those who are found to have active TB and/or HIV infection are registered for immediate care and treatment following national guidelines.

Results and lessons learnt: From July 2013 to March 2015, a total 6003 inmates and remandees in three central prisons in Dar es Salaam were screened. Overall prevalence of bacteriologically proven TB was 2500 per 100 000 (range 1800 to 3100). In the prison with digital radiography, 2139 prisoners were screened with chest X-ray and 688 were found to have abnormalities on the X-ray (32%). Among those, 7.8% tested positive on Xpert, versus 3.6 and 1.8% of all tested with Xpert in prison 2 and 3 respectively. All TB patients detected were treated promptly, often the same or the next day following screening. In all 3 prisons TB notifications rose markedly after introduction of the screening protocol and treatment could be initiated early, thus preventing further transmission in the prisons and in the community after release.

Conclusions: Screening prisons populations for TB using Chest X-ray and Xpert identifies infectious cases of TB early and facilitates effective treatment, reducing further transmission. Using a protocol including chest X-ray reduces the number of Xpert tests required and is potentially cost-effective. Continuation of TB treatment after release from the prison remains a major challenge. Sustained effective TB screening in prisons will eventually bring down the incidence and prevalence of active TB in prisons and contribute to reduction of transmission in the community at large. Periodic screening of resident inmates, followed by ongoing routine screening of new admissions, should therefore become a core activity of the prison health services.

25. Engagement of CSOs, communities and patients in TB management and control

OA-491-06 The yield of TB among contacts of TB patients treated in the last three years (retrospective screening) in Ethiopia

Z Dememew,¹ M Ensermu,¹ D J Dare,¹ D Habte,¹ M Aseresa Melese,¹ K Alemu,² N Demmelash,¹ P G Suarez³ ¹Management Sciences for Health, Addis Ababa, ²Management Sciences for Health, Bahir Dar, Ethiopia; ³Management Sciences for Health, Arlington, VA, USA. e-mail: zgashu@msh.org

Background and challenges to implementation: As part of the strategy to strengthen tuberculosis (TB) prevention and control efforts in Ethiopia, the USAID-funded Help Ethiopia Address the Low Performance of TB (HEAL TB) project has collaborated with regional health bureaus of Oromia and Amhara to implement innovative enhanced community based TB interventions.

Table Activity of enhanced active TB case search and household contact tracing

Indicators	Enhanced active TB case finding	Retro-spective household contact tracing	Total enhanced household contact tracing
Number of households visited	682,236	-	682,236
Number of index TB cases	-	20,805	20,805
Number of individuals screened for TB	2,452,635	77,626	2,530,261
Number (%) with presumptive TB cases	52,262 (2.1%)	9,142 (11.8%)	61,404 (2.4%)
Number (%) evaluated at Health center	18,262 (34.9%)	4,967 (54.3%)	23,229 (37.8%)
All forms of TB identified (% yield)	479 (2.6%)	249 (5.0%)	728 (3.1%)
Number (%) of smear positive TB cases ¹	362 (75.6%)	184 (74.0%)	546 (75%)
Number (%) of smear negative TB cases	49 (10.2%)	24 (9.6%)	73 (10.0%)
Number (%) of extra-pulmonary TB cases	68 (14.2%)	41 (16.5%)	109 (15.0%)

¹ The proportion of SS + is high here because all smear negative and EPTB suspects are referred to hospitals for diagnosis and our data had not captured all of them

Intervention or response: We conducted this study in six selected zones of Oromia and Amhara regions between June-September 2014. We recruited and trained lay providers (high school graduates) to do active case search through two approaches; (a) tracing household contacts of TB index cases who completed treatment in the last three years which we labelled as “retrospective” contact screening; and (b) screening other households in the community without index cases. They first visited the houses of index TB cases and then the remaining households in the neighboring area using the WHO symptom screening criteria. They referred the presumptive TB cases to health centers for evaluation.

Results and lessons learnt: The community workers visited household contacts of 20,805 index TB cases and screened 77 626 contacts of which 11.8% had presumptive TB. Similarly, of 682,236 other households visited in the catchment area, 2 452 635 household members were screened for symptoms of TB of which 2.1% had presumptive TB which was significantly lower than the yield among contacts ($P < 0.01$). Of 23 229 presumptive TB cases evaluated, 728 (3.1%) all forms of TB were identified including 546 (75.0%) smear positive (SS+), 109 (15.0%) extra pulmonary TB and 73 (10.0%) smear

negative TB cases (SS-). Larger proportion of TB cases were identified among TB contacts than the comparison group (5% vs. 2.6%, $P < 0.05$). Over the same period, the routine community TB activity by health extension workers yielded 659 (2.9%) all forms of TB from 22 426 presumptive TB cases evaluated at the health centers and the yield was less than that of “retrospective” contact screening ($P < 0.05$).

Conclusions and key recommendations: The yield of retrospective community based contact screening was significantly higher than the routine community TB activity and therefore should be considered as additional case finding approach in the routine health extension workers community based TB care activities.

OA-492-06 Role of peer educators to increase HIV testing among TB patients in two ART hospitals and one TB clinic, Jakarta, 2014-2015

Y Gunawan,¹ H Agustine,² F Susanti,³ M C J Tumbelaka,⁴ T Handayani,¹ W Bruary,¹ S Aditya,¹ D P Setyawati⁵ ¹RED Institute, Jakarta Timur, ²Persahabatan Hospital, Jakarta Timur, ³Budhi Asih Hospital, Jakarta Timur, ⁴Jakarta Respiratory Center, Jakarta Selatan, ⁵FHI360 Indonesia, Jakarta Pusat, Indonesia. e-mail: msamsuri@fhi360.org

Background and challenges to implementation: HIV testing among TB patients in Indonesia is low due to TB staff time constraint and PITC skills. Although, several CSOs are working on TB and HIV, only few of them are working with both. RED Institute, a CSO with TB-HIV experience in prisons, commenced its works in 2014 in two ART hospitals and one TB clinic in Jakarta to promote HIV testing among TB patients, with TGF's financial support.

Intervention or response: RED staff played the role as peer educators, conducted TB-HIV IEC for all TB patients at DOTS clinic in 2 hospitals (Persahabatan Hospital, Budhi Asih Hospital) and 1 TB clinic (JRC Clinic) to motivate TB patients to take HIV testing. All of those who agreed to be tested were referred to HIV laboratory and HIV treatment, when HIV results were positive.

Results and lessons learnt: Results of increase on HIV testing among TB patients in 2 hospitals and 1 TB clinic are as in attached Table.

Conclusions and key recommendations: HIV testing among TB patients increased in all 3 sites. Major contributing factor is the role of CSO's peer educators that provided information and education about TB-HIV to TB patients. The authors recommend other TB and HIV CSOs to duplicate in other facilities.

Indicator	Jan-Dec 2013		Jan – Sept 2014	Apr 2014 – Mar 2015		Okt 2014 – Mar 2015
	Persahabatan Hospital	Budhi Asih Hospital	JRC Clinic	Persahabatan Hospital	Budhi Asih Hospital	JRC Clinic
# TB Patients	1347	751	323	1315	702	190
# HIV Testing among TB Patients	23	10	11	362	315	106
%	2%	1%	3%	28%	45%	56%
	Before Interventions			After Interventions		

OA-493-06 Effectiveness of sputum collection and referrals from community screening for active tuberculosis case finding in Mombasa County, Kenya

T Kiptai,¹ C Mwamsidu,¹ A Munene,¹ T Abongo,¹ M Mungai,¹ C Kamau,² G Moemi,³ B Ulo¹ ¹AMREF Kenya, Nairobi, ²Christian Health Association of Kenya (CHAK), Nairobi, ³Kenya Association for the Prevention of Tuberculosis and Lung Diseases (KAPTLD), Nairobi, Kenya. e-mail: titus.kiptai@amref.org

Background and challenges to implementation: In Kenya notified TB cases dropped from 99 159 in 2012 to 89 760 in 2013 (9.48% decline). Mombasa County notified 4726 TB cases in 2013 giving a case notification rate of 469 per 100 000 that is above the national average of 208 per 100 000. In response to the high TB burden, Global fund approved funds for National TB program's request to undertake active TB case finding in Mombasa County. AMREF Kenya is implementing the Grant's Civil Service Organization (CSO) component through two CSOs, CHAK and KAPTLD. The CSOs work with public and private facilities that include chemists as well as informal ones like herbalists respectively to implement activities through the community strategy.

Intervention or response: Between May 2014 and March 2015, AMREF Kenya through the CSOs trained and engaged 136 community health volunteers (CHVs) and 76 laboratory technicians. Ten new laboratory technologists were hired and posted to high volume TB diagnostic facilities to enhance examination of the additional sputum load. CHVs implemented active case finding of TB through door to door screening of household members. Presumptive TB clients identified were referred to the nearest diagnostic facilities and sputum collected for clients who were either not able to visit the facilities due to lack of transport or unwillingness. CHVs also followed up the presumptive TB clients referred by private facilities to diagnostic facilities. CHVs were provided with bicycles and monthly stipend to aid their activities.

Results and lessons learnt: Of the 21 099 people screened, 9383 (44.5%) presumptive TB cases were identified. Of these, 3279 (34.9%) were referred for investigations, out of which 2508 (76.5%) reached the facilities and 435 (17.3%) diagnosed with TB. For the 6104 (65.1%) who were not able to visit the facilities, sputum was collected and transported for examination, out of which sputum for 5492 (90%) were examined and 368 (6.7%) diagnosed with TB. In total 803 TB cases were identified, increasing notified cases referred by CHVs from 4% to 28% during the implementation period.

Conclusions and key recommendations: Door to door screening is core in increasing case detection. Sputum collection and referral reduces diagnostic delays. There is need to carry out the same activities in areas with high notifications rates to combat TB infections in the regions.

OA-494-06 Sputum collection and transportation in vulnerable and marginalized communities in India: experiences from community driven TB project Axshya

B Thapa,¹ A Das,¹ S Mohanty,¹ P Banuru Muralidhara,¹ B Entoor Ramachandran,¹ J Tonsing,¹ S Chadha¹

¹International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: bthapa@theunion.org

Background: Community case finding interventions in vulnerable and marginalized communities are underway in Global Fund supported civil society driven Tuberculosis (TB) prevention and care project, "Axshya" in India. Identified presumptive TB patients (PTBP) are linked with diagnostic and treatment services through referrals and sputum collection and transportation (SCT). The objective is to determine how SCT has contributed to TB patient diagnosis and treatment in comparison to referrals.

Design/Methods: Phase II of project Axshya was implemented in 300 districts in India from April 2013. Case finding interventions included; active case finding (ACF), community meetings, mid-media activities, engagement of rural health care providers, facility based SCT, and engaging groups and networks of people living with HIV. The intervention wise aggregated data on number of interventions, PTBP identified, referrals, SCT, TB diagnosed and initiated on treatment were collected from the quarterly progress reports from April 2013 to September 2014 and analysed.

Results: Project identified 665 577 PTBP, 357 972 (54%) were referred and SCT was done from 307 605 (46%). Of those referred, 30% (106 689) could be examined. PTBP whose SCT was done through all activities were 3.4 times more likely to get their sputum examined than referrals. This increased to 4.3 times if SCT was done following ACF. Altogether, 62% (414 294) PTBP were examined and 34 900 TB patients were diagnosed and 33 837 (97%) were initiated on treatment. Highest yield was from was ACF (12 692, 38%). The smear positivity rate was higher in referrals (8.7%) than SCT (8.3%) ($P > 0.05$) with overall positivity rate of 8.4%. TB patients diagnosed through SCT were 1.03 times more likely to be initiated on treatment than referrals ($P < 0.01$). If the project was able to examine all the referrals that did not reach the microscopy centre through SCT, an additional 20 857 TB patients would have been diagnosed.

Conclusion: Sputum collection and transportation has provided accessibility for diagnosis to 46% of those PTBP identified, diagnosed 25,636 and initiated treatment on 25,062 TB patients. SCT coupled with community case finding interventions has shown remarkable success for providing access to diagnostic, diagnosing TB patients and decreasing initial defaults in marginalized and vulnerable communities in India.

OA-495-06 Empowering faith-based community health volunteers as partners in TB control

J Teves,¹ F Agbayani,² T Yu,³ S Dela Cruz,³ S Masulit³

¹Diocese of Ipil, Zamboanga, ²Integrated Provincial Health Office, Zamboanga, ³Philippine Business for Social Progress, Manila, Philippines. e-mail: virgilbelen@gmail.com

Background and challenges to implementation: With a TB cure rate (new smear-positive) of 82% in 2011, Zamboanga Sibugay province (population: 576 232) in southern Philippines needed to improve case holding to meet the national target of 85%. However, distance, poor road infrastructure, limited availability of transportation, and high transportation fare made it difficult for public health workers to access the province's geographically isolated areas. The Integrated Provincial Health Office (IPHO) expanded its coverage by working with the Catholic church's Community-based Health Program (CBHP) that had a cadre of over 1000 parish volunteers distributed across 19 parishes in the 16 municipalities of the province, all committed to serve the community at practically no cost to the IPHO.

Intervention or response: With USAID/Philippines technical assistance, the IPHO trained more than 600 CBHP community volunteers to conduct TB education and counseling sessions and serve as treatment partners to ensure treatment compliance and completion. They were also trained to identify individuals with TB symptoms, refer them to the nearest TB-DOTS center, and regularly maintain records and submit reports.

Results and lessons learnt: The CBHP volunteers helped identify 20 new smear-positive (NSP) cases in 2012, 78 in 2013, and 91 in 2014 contributing 4%, 15%, and 16%, respectively to the province's CDR (NSP). Correspondingly, the volunteers served as treatment partners to 6, 17, and 30 of the NSP cases who were initiated on treatment. This resulted in a treatment success rate (TSR) of 84% in 2012 and 95% in 2013. TSR for the 2014 cohort is unavailable as yet.

Conclusions and key recommendations: Mobilizing faith-based community health volunteers is a low-cost, viable, and sustainable strategy for TB case finding and case holding, particularly in geographically challenged, access-poor areas.

OA-496-06 Role of community volunteers in finding missed TB cases: lessons from Three I's implementation in Zambia

A Nota,¹ S Kaminsa,¹ M Chizyuka,¹ E Chiyeke,¹

M Amofa-Sekyi¹ ¹FHI360/TB CARE I, Lusaka, Zambia. Fax: (+260) 211 257 329. e-mail: amosnota@yahoo.com

Background and challenges to implementation: Countries with a high TB-HIV co-infection rate, like Zambia, are encouraged to focus on Intensified Case Finding (ICF), Infection Control, and Isoniazid Preventive Therapy; referred to as the "3 I's" to control the TB epidemic. Tracing household (HH) contacts of smear-positive TB cases is an effective ICF tactic, but not often employed in Zambia.

Intervention or response: HH contact tracing was implemented in 15 communities attached to 15 health facilities in six districts, of Central and Copperbelt provinces in Zambia. A total of 124 community volunteers were engaged across these communities from May 2013 to March 2015. The community volunteers collected details of all patients diagnosed with TB by either smear or GeneXpert MTB/RIF from the TB register with facility staff support. Each volunteer arranged a convenient meeting time with the HH members of this diagnosed individual, ensuring that the majority were present during the visit. The community volunteer screened all HH members for cough, night sweats, weight loss and fever. All symptomatic HH contacts submitted two spot sputum specimens to the volunteer. The sputum samples were either sent for AFB smear microscopy (HIV-seronegative) or GeneXpert MTB/RIF examination (HIV-seropositive). HH contacts with a sputum or Xpert MTB positive result were referred or escorted to the health facility for TB treatment. HH contacts were also encouraged to test for HIV.

Results and lessons learnt: Among the 7455 HH contacts identified and screened for symptoms of TB, 1607 symptomatic contacts submitted sputum for examination, and 180 (11.2%) were bacteriologically confirmed with TB. All confirmed contacts were started on TB treatment. These cases were identified in the community by community volunteers within a period of 10 months. **Conclusions and key recommendations:** We found, like many others, that HH contact tracing is an extraordinarily effective way to increase case detection. The cases found over a 10 month period extrapolates to a population-based case rate of approximately 2,414/100 000 population, 6 times greater than the estimated TB case in the general Zambian population. Engaging the community actively in ICF efforts is a very effective mechanism for finding some of the missing TB cases within a local population. Involving local communities in primary health care, may help resource-poor health systems achieve the goal of universal access for all.

OA-497-06 Active case finding activities performed by former TB patients: experience from South-Kivu Province, Democratic Republic of Congo

E Andre,¹ D Bahati Rusumba,² E Musafiri,² D Muzigo,² D Kasereka,² D Kalumuna,² O Le Polain De Waroux³

¹Universite de Louvain, Brussels, Belgium; ²Coordination Provinciale Lèpre et Tuberculose du Sud-Kivu, Bukavu, Democratic Republic of the Congo; ³London School of Hygiene & Tropical Medicine, London, UK. e-mail: olivier.lepolain@lshtm.ac.uk

Background: Late and under-detection of TB is one of the most important challenges towards TB control in the Democratic Republic of the Congo. We here report the results of the first 14 months of implementation of an Active Case Finding (ACF) programme in the South Kivu Province (population ~ 6 million), where former TB

patients are being trained to undertake ACF in their communities. Material/

Methods: ACF activities were performed by screeners in their close environment, before extending it geographically ('stone in the pond' approach). Information on socio-demographic characteristics were recorded for each individual screened, as well as information on cough lasting for ≥ 15 days. Cases with a cough were offered a laboratory test (Ziehl Nielsen). We performed descriptive statistics and explored differences in the prevalence of cough and TB by socio-demographic characteristics, through the use of negative binomial regression.

Results: A total of 14 043 individuals from 2900 households were screened by the 141 screeners in communities living in 15 of the 34 health districts of the Province. Overall, 2,103 (15%) individuals reported a cough for ≥ 15 days. This proportion increased linearly with age from 4.5% in <5 y olds to 28.6% among adults aged 40 years and above, was higher in males than females ($P < 0.0001$), and cases tended to be clustered within households. About 92% of individuals with a cough accepted to be tested, of whom 38 (1.8%) were confirmed with smear positive pulmonary TB (SPP). TB incidence increased linearly with age and was higher in males, with a 5% increase in the proportion of diagnosed cases by 5 year age increase (adjusted incidence rate ratio for age (aIRR) 1.05 (95%CI 1.04 – 1.06)) and sex (aIRR males 1.31 (95%CI 1.01 – 1.69)). The cumulative incidence of SPP TB in the province, as reported through the national surveillance system, was 53 per 100 000 (95%CI 50 – 55). In comparison, the incidence of SPP TB from the ACF activities over the same period was 231 per 100 000 (95%CI 154 – 334).

Discussion: Our preliminary results suggest that almost 2% of individuals reporting a cough lasting for more than 15 days were diagnosed with SPP TB. The higher incidence among communities targeted by ACF activities is likely due to a combination of increased detection, as well as the targeting of more high risk communities, and suggest ACF activities are important to help curtail the burden of TB in South Kivu.

OA-498-06 Improving treatment success rate by use of community mobilizers in Juba, South Sudan

J Mogga,¹ H Lasu,¹ S Macharia,² S Kia,³ B Woldemariam⁴

¹Ministry of Health, South Sudan, Juba, ²Management Sciences for Health, Juba, ³AIDS Resistance Trust, Juba, South Sudan; ⁴Management Sciences for Health, Addis Ababa, Ethiopia. e-mail: smacharia@msh.org

Background and challenges to implementation: Treatment success has stagnated below 80% in the last three years. The treatment success rate dropped to 72% in 2012 compared to 75% in the 2011 cohort. Juba is estimated to have a population of over 1 million which is served by only three TB Management Units (TBMU) contributing to over 40% of all defaulters in South Sudan. No community based TB control strategies

applied in Juba city. Directly Observed Treatment (DOT) is not strictly adhered nor is there a concrete treatment follow up strategy utilized in Juba to date.

Intervention: To address these challenges, the National TB, Leprosy and Buruli ulcer Programme (NTLBP), with support from the Global Fund and USAID-funded TB CARE I project, implemented a project from October 2013 to 31st March 2014 to retrieve loss follow-up TB patients in Munuki Primary Health Care Center (PHCC). A list of these patients was given to a network of 20 community mobilizers who traced the patients to their respective residence or through telephone contact provided in the TBMU register. The treatment success rate after the intervention was compared with the reports previously reported to the NTLBP.

Results and lessons learnt: A list of 539 TB patients had defaulted from the TBMU register from 1st January 2012 to 31st December 2012 out of which 2 had inadequate personal information and could be dropped from the study. A total of 87.2% patients were traced and made to complete treatment, 4.7% could not be located, 7.8% had moved to another facility to continue with treatment and 0.4% died. There were no significant differences in outcomes according to age and gender. After the intervention, treatment success rate among new TB cases increased from 61% to 84%. Challenges encountered include incomplete recording of patient's data, highly mobile population and crisis on 15th December 2013 that resulted in displacement of TB patients.

Conclusions and key recommendations: The use of community mobilizers in TB control can improve on adherence to treatment. Close coordination between the health facility and community mobilizers is required to provide timely list of loss to follow up. Completeness of data is of essence to ensure consistence in information in all patient's data sources. This approach can be replicated in other urban centers where the defaulter rate is high.

26. Lung health: pneumonia, COPD, asthma and cystic fibrosis

OA-499-06 A controlled human aerosol model to study respiratory hygiene interventions to prevent airborne transmission

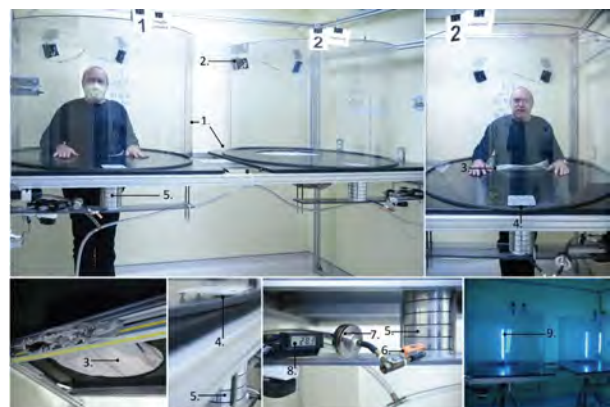
K Vanden Driessche,^{1,2,3} J Zlosnik,² N Hens,^{1,4} B Quon,² B Marais,⁵ R De Groot,³ D Speert,² M Cotton⁶ ¹Hasselt University, Center for Statistics (CenStat), Diepenbeek, Belgium; ²University of British Columbia, Vancouver, BC, Canada; ³Radboud University, Nijmegen, Netherlands; ⁴University of Antwerp, Vaccine and Infectious Disease Institute, Antwerp, Belgium; ⁵University of Sydney, Marie Bashir Institute for Infectious Diseases and Biosecurity and Children's Hospital at Westmead, Sydney, NSW, Australia; ⁶Stellenbosch University, Cape Town, South Africa. e-mail: koen.vandendriessche@radboudumc.nl

Background: *Mycobacterium tuberculosis* is a notorious airborne transmitted pathogen. Ongoing transmission in high incidence areas drives the global TB epidemic

including drug resistant disease. There are increasing concerns about other bacteria being transmitted by air: *Burkholderia cepacia complex* and *Pseudomonas aeruginosa* are associated with increased morbidity and mortality in cystic fibrosis (CF) patients and both have been isolated from CF clinic room air. The recently updated CF Foundation (USA) infection control guidelines now advise all CF patients to wear surgical masks in healthcare settings. While generally accepted that covering one's cough (with a mask or by practicing cough etiquette) prevents droplet spread, the effect on airborne transmission has not been conclusively evaluated. We have developed a model to measure concentration and particle size distribution of viable (myco-)bacteria from human cough aerosols. We set out to improve this model and validate it as a tool to study interventions against airborne bacterial spread. Design We recruited CF patients who were chronically colonized with *P. aeruginosa*. Participants were asked to cough in two cylindrical chambers from which the air was extracted through cascade impactors (Figure). Participants moved between a chamber where they wore a surgical mask while coughing and a control chamber where they coughed without a mask (42 coughs in total equally divided over the two chambers). We took delayed aerosol samples and excluded microorganisms from stage 1 in the impactors which captures droplets, as evaluation of airborne transmission was our primary experimental outcome measure. Generalized linear mixed models were used to measure the effect of masks on airborne *P. aeruginosa* load.

Results Eleven CF patients, aged 16-77 years, participated. Viable *P. aeruginosa* was isolated during 12 sessions from 6/11 (55%) participants. Wearing a surgical mask reduced the airborne *P. aeruginosa* load by an average of 88% (95%CI 81-96%).

Conclusions The controlled human aerosol model used in our study produced relatively precise results despite a small sample size. Our data show that surgical masks reduce the airborne spread of *P. aeruginosa* in CF, supporting the new recommendation that CF patients should wear surgical masks in healthcare settings. Next, we intend to evaluate the potential impact of different public health interventions, including cough etiquette, aimed at reducing *M. tuberculosis* transmission.



1: two cylindrical cough chambers 2: two fans in each chamber to homogeneously disperse airborne particles 3: a kayak seal for particle containment 4: the exhaust hole is covered by a plate to prevent direct droplet impact 5: a six-stage viable Andersen cascade impactor can sample the air in the cough chamber 6: valve 7: HEPA filter 8: flow regulator 9: UV light is used during the decontamination process

OA-500-06 The correlation between IL-16-295 polymorphism and risk of asthma: evidence from a meta-analysis

Q Wu,¹ Y Ji,¹ C Wu,¹ Y Wang,¹ Q He¹ ¹Sichuan University, Chengdu, China. e-mail: 76201313@qq.com

Background: IL-16 is one of the immunomodulatory cytokine whose expression is elevated in the bronchial epithelium, bronchoalveolar lavage fluid and induced sputum of asthmatic patients. It promotes the migration of T cells to target sites, plays a critical role in the development of coronary artery disease. Several researches reveal that giving medication of antibodies to IL-16 can decrease development of airway hyper-responsiveness, without having impact on airway eosinophilia in a mouse model of allergic asthma. The aim of this study is to research the relationship between il-16-295 polymorphisms and asthma disease risk by meta-analysis.

Design/Methods: We searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and China National Knowledge Infrastructure (CNKI) (<http://www.cnki.net/>) web databases to cover all studies based on association between IL-16-295 polymorphisms and risk of asthma until April 2015. The meta-analysis was performed for selected case-control studies. At the same time, pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were counted for all genetic models.

Results: A total of 1693 asthma cases and 777 controls were included from five case-control studies conforming to our included criteria. Results from overall pooled analysis suggested no evidence of significant risk between il-16-295 polymorphism and asthma risk in all genetic models, such as, allele (C vs. T: OR = 1, 95%CI = 0.86 to 1.18, $P = 0.96$), homozygous (CC vs. TT: OR = 0.89, 95%CI = 0.57 to 1.39, $P = 0.6$), heterozygous (TC vs. TT: OR = 1.06, 95%CI = 0.87 to 1.29, $P = 0.57$), dominant (CC + TC vs. TT: OR = 1.03, 95%CI = 0.86 to 1.25, $P = 0.73$) and recessive (CC vs. TT + TC: OR = 0.86, 95%CI = 0.56 to 1.34, $P = 0.51$) models. Publication bias was not detected in this meta-analysis.

Conclusion: The results of this meta-analysis indicating that IL16-295 polymorphism may not have the relationship with asthma. Thus, future large-scale studies with group of populations are needed to analyze the association between IL-16-295 and asthma.

OA-501-06 Use of Google Earth Pro and mobile technology in preparation for evaluation of the Practical Approach to Lung Health in rural Malawi

B Chisunkha,^{1,2} H Banda,^{1,2} K Mortimer,^{2,3} B Ngwira,^{1,2} H Mtengo,^{1,2} J Smedley,³ I Namakhoma,^{1,2} S B Squire^{2,3}
¹REACH Trust, Lilongwe, Malawi; ²Collaboration for Applied Health Research & Delivery (CAHRD), Liverpool, ³Liverpool School of Tropical Medicine, Liverpool, UK. e-mail: blessingschisunkha@gmail.com

Background: In low and middle income countries (LMIC), surveys in health research have relied on manual processes and methodologies like mapping study areas,

household listing and household tracing plus paper-based questionnaires for data collection. Similarly, there is physical data transfer of questionnaires to central office and manual data entry by assigned clerks. To reduce challenges faced using these traditional approaches we used Google Earth Pro (GEP) to electronically map a rural area for population-proportional sampling and for definition of clusters in preparation for a cluster-randomised controlled trial of the Practical Approach to Lung Health in rural districts of Dowa and Ntchisi in Malawi.

Design/Methods: GEP was used to create catchment-area clusters around Health Facilities (HFs), buffer zones between clusters and list of every household with coordinates without requiring field visits. A random sample of 6,480 households was then obtained from within each of the clusters. 24 smartphones with installed GPS Essentials were used by 14 research assistants to navigate to the selected households. An electronic questionnaire installed in the smartphones was used to collect data which was then electronically transferred to a secure server for storage and management.

Results: We were able to delineate cluster boundaries with buffer zones around each of the 27 HFs in the two districts, taking into account geographical features likely to enhance/hinder patient access, and identify individual households (figure). This reduced time and costs by eliminating traveling to conduct household listing and associated activities. The approach proved accurate, effective and easy in tracing households. Time and cost were further saved as both data collection and entry were done at the point of interviewing. Data were directly transferred to the server, reducing the risk of data loss.

Conclusion: Using GEP and Mobile technology in health research has the potential to reduce duration and costs of field-based projects since electronic mapping performed on a computer eliminates travel and upkeep costs. This is especially true in rural and remote regions of LMICs. It also reduces project costs by removing a separate data entry exercise. Data cleaning is eased as most errors are checked at the time of data collection-with automatic validation checks and skip patterns. Furthermore, it reduces probability of selection bias by listing and sampling teams and reduces data loss.



OA-502-06 Short-term health impact of stove intervention in reducing household air pollution and illnesses among rural women in Pakistan

T Jamali,¹ A Shahid,¹ A Shahid,¹ Z Fatmi,¹ M M Kadir¹

¹Aga Khan University Hospital, Karachi, Pakistan. e-mail: tanzil.jamali@aku.edu

Background: Improved stoves are considered the main-stay intervention to reduce household air pollution due to biomass cooking fuel. This paper evaluated stove intervention programs in two provinces, Sindh and Punjab, of Pakistan, to determine the short term impact in reducing household air pollution and illnesses among rural women, who were the main cook in the household.

Design/Methods: A cross-sectional survey was conducted from June to September 2014 in the villages of Kasur, Punjab and Dhabeji, Sindh. A total of 83 improved and 209 traditional stoves in Dhabeji and 134 improved and 179 traditional stoves in Kasur were included for comparison. Interviewers administered the questionnaire inquiring respiratory (IUTALD), eye and skin symptoms. Blood pressure was recorded and peak expiratory flow was measured to determine lung function. 24-hour particulate matter (<2.5 µm) and carbon monoxide levels were measured, in a subsample, in intervention and control kitchens.

Results: Significant reduction for particulate matter and carbon monoxide were observed among improved stoves kitchens. Among women in Dhabeji, Sindh program, significant risk reduction was observed for cough (aRR: 0.27, CI: 0.20, 0.38), phlegm (aRR: 0.27, CI: 0.18, 0.40), shortness of breath (aRR: 0.16, CI: 0.11, 0.22), chest tightness (aRR: 0.23, CI: 0.17, 0.31) and attack of asthma (aRR: 0.33, CI: 0.22, 0.49) ($P < 0.001$). Risk reduction were also observed for sandy eyes (aRR: 0.63, CI: 0.47, 0.97) and itching in eyes (aRR: 0.62, CI: 0.41, 0.95) ($P < 0.050$). While in Kasur, Punjab program, risk reduction was observed for phlegm (aRR: 0.60, CI: 0.45, 0.81) and also protection from burns (aRR: 0.56, CI: 0.34, 0.91). Mean peak expiratory flow among improved stoves users was higher in both Sindh (19.30, CI: 12.90, 25.70) and Punjab (11.70, CI: 6.10, 17.30) programs.

Conclusion: Improved stoves showed substantial emission reduction and improved health indicators over traditional stoves. However, variation and differential health gains were noted among the two programs. Further intervention experience and its evaluation, standardization of stoves and adaptation according to the local environmental and social needs is required to scale up the stove intervention programs.

OA-503-06 Respiratory failure in the medical intensive care unit at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

A Work,¹ A Sultan,¹ A Shumet,¹ K Gsilasie,¹

A Binegdie Bekele,¹ C Sherman,² M Parekh,³

N Schluger^{3,4} ¹Addis Ababa University, Addis Ababa, Ethiopia; ²Brown University, Providence, RI, ³Columbia University, New York, NY, ⁴World Lung Foundation, New York, NY, USA. e-mail: madhavi.j.parekh@gmail.com

Background: There is limited data regarding intensive care unit (ICU) outcomes and specifically for those respiratory failure in the developing world. In the United States, ICU mortality is estimated between 10-30% (SCCM, 2015), but is approximately 25-50% in developing countries, and higher for those requiring mechanical ventilation (Anesthesia, 2007). The purpose of this study is to assess characteristics and outcomes of patients with respiratory failure at tertiary care center in Addis Ababa, Ethiopia.

Design/Methods: A prospective observational study included all patients admitted to the MICU from June 2014-April 2015. Demographics, admission diagnosis, comorbidities, need for mechanical ventilation, etiology of respiratory failure, and ICU mortality were included in the analysis. The Mortality Prediction Model (MPM0-II) was used to estimate severity of illness.

Results: During the study period, 197 patients were admitted to the MICU. Of these, 34% had respiratory failure. The mean age of those with respiratory failure was 35.4 years; 53.8% were female. Hospital acquired pneumonia was the leading cause of respiratory failure (22%) followed by pulmonary embolism (17%), aspiration pneumonia (15%), neuromuscular weakness including Guillain-Barré Syndrome and tetanus (13%), community acquired pneumonia (11%), cardiogenic pulmonary edema (11%), pneumocystis jiroveci pneumonia (9%), severe asthma exacerbation (9%), tuberculosis (6%) and sepsis-related acute respiratory distress syndrome or ARDS (6%). HIV/AIDS (25.5%) was the most common comorbid condition, followed by COPD or asthma (20.9%), and hematologic malignancy (18.6%). Sixty two percent of those with respiratory failure required mechanical ventilation, and 34% met criteria for ARDS. Mortality for those with respiratory failure was 47.6% as compared to an overall ICU mortality of 34.8%, despite a similar severity of illness (mean MPM0-II 18.8 and 17.8, respectively).

Conclusion: This study highlights that respiratory failure is common in a tertiary care hospital ICU in Ethiopia, and is associated with a high mortality rate. The majority of patients with respiratory failure (nearly 50%) were due to acute bacterial pneumonia (hospital or community acquired, and aspiration). Future study will include analysis of antibiotic use and ventilator management in these patients.

OA-504-06 Spectrum and outcomes of patients admitted with respiratory disease to the medical wards at Tikur Anbessa Specialized Hospital

A Shumet,¹ K Gsilasie,¹ A Work,¹ F Oumer,¹ A Binegdie Bekele,¹ C Sherman,² M Parekh,³ N Schluger^{3,4} ¹Addis Ababa University, Addis Ababa, Ethiopia; ²Brown University, Providence, RI, ³Columbia University, New York, NY, ⁴World Lung Foundation, New York, NY, USA. e-mail: madhavi.j.parekh@gmail.com

Background: Very little published data exists regarding the characteristics and outcomes of respiratory diseases requiring inpatient admission in Ethiopia. This study aims to assess the spectrum of respiratory diseases and their outcomes among adults admitted to medical wards at TASH, a tertiary care center in Addis Ababa, Ethiopia.

Design/Methods: A prospective observational study of patients admitted to the medical wards of TASH between November 2014 and March 2015 was performed. All subjects were identified via chart review of inpatient admissions; their demographic, comorbid conditions, and clinical data were included in the analysis.

Results: During the study period, 102 patients admitted to medical wards with a respiratory diagnosis. The mean age was 44 years, men comprised 55% of patients, and 59% of patients were from rural areas. History of smoking was present among 25% of patients, and was exclusively among men. Those with HIV comprised 12%; 17% of patients had a history of tuberculosis treatment. Active tuberculosis was the primary diagnosis that required admission in 25% of patients (pulmonary tuberculosis 15%, disseminated tuberculosis 10%), followed by lung cancer/mass (17%), bacterial pneumonia (14%), pleural effusion (11%), pulmonary embolism (7%), and decompensated pulmonary hypertension (5%). More than one third (35%) of patients had more than one concurrent respiratory diagnosis; the most common secondary diagnosis was exudative pleural effusion (11% of all patients). The most frequently observed comorbid conditions were hematologic disorders in 21% of patients (most commonly leukemia or lymphoma), diabetes (17%) and solid malignancies (11%). The average length of stay was 21.4 days. Thirty one percent of those studied died during their hospitalization; the majority of these deaths were related to tuberculosis and lung cancer.

Conclusion: Tuberculosis and lung cancer were the most frequent causes of admission and death among those admitted with respiratory disease to the inpatient wards at TASH. In-hospital mortality was strikingly high in the study population. Future study will include a larger sample size and analysis of management strategies.

OA-505-06 COPD among patients with obstructive airway disease in Ethiopia

K Gsilasie,¹ A Work,¹ A Shumet,¹ F Oumer,¹ A Binegdie Bekele,¹ C Sherman,² M Parekh,³ N Schluger^{3,4} ¹Addis Ababa University, Addis Ababa, Ethiopia; ²Brown University, Providence, RI, ³Columbia University, New York, NY, ⁴World Lung Foundation, New York, NY, USA. e-mail: madhavi.j.parekh@gmail.com

Background: While chronic obstructive pulmonary disease (COPD) is considered very common worldwide, its magnitude and risk factors are not known in Ethiopia. Physician based clinical diagnosis may be challenging given the relative low rate of tobacco use overall. However, COPD may be more common than expected given significant exposure to biomass fuel smoke in this population. The aim of this study is to determine the magnitude of and risk factors for COPD in an outpatient chest clinic in a tertiary care hospital in Addis Ababa, Ethiopia.

Methods: A prospective, cross-sectional study of patients with a diagnosis of obstructive airway disease (asthma, COPD, bronchiectasis) was performed from December 2014-March 2015. The first phase of the study included a structured questionnaire of demographic, socioeconomic, and clinical information. The second phase of the study included pulmonary function testing, specifically pre-and post-bronchodilator spirometry.

Results: The results of the first phase are reported here. Fifty-one patients with a physician diagnosis of obstructive airway disease were identified during the study period. The mean age was 49 and women accounted for 60%. Nearly all (93%) of patients were from an urban area. Asthma was the most common clinically diagnosed obstructive lung disease (69%), followed by COPD (11%), and bronchiectasis (11%); 13% of patients were given more than one clinical diagnosis. Four patients shared a diagnosis of COPD with asthma and/or bronchiectasis. All 8 patients with any tobacco use history were men, and the majority (63%) were given a diagnosis of COPD; 80% of patients given a diagnosis of COPD were men. Only 6% of women were given a diagnosis of COPD; nearly all were diagnosed with asthma, despite significant biomass fuel smoke exposure (83%).

Conclusion: While obstructive lung diseases are common in Ethiopia, it is unclear if physician-based clinical diagnoses of specific diseases, notably COPD as opposed to asthma or bronchiectasis, are correctly identified by clinical characteristics alone, especially in a population where tobacco use is uncommon. Perhaps patients who have COPD are mislabeled as asthma or bronchiectasis, based on traditional risk factors. Phase one of this study is reported here, and identifies various diagnoses among those with obstructive disease, but proper classification will require spirometry with bronchodilator testing.

OA-506-06 Impact of the 13-valent pneumococcal conjugate vaccine on clinical and hypoxemic childhood pneumonia over three years in central Malawi

E Mccollum,^{1,2} B Nambiar,² R Deula,³ B Zadutsa,³ A Bondo,³ C King,² N Lufesi,⁴ A Costello,² T Colbourn²

¹Johns Hopkins School of Medicine, Baltimore, MD, USA;

²University College London, London, UK; ³Parent and Child Health Initiative Trust, Lilongwe, ⁴Ministry of Health, Lilongwe, Malawi. e-mail: ericdmccollum@gmail.com

Background: The impact of the pneumococcal conjugate vaccine (PCV) on childhood pneumonia during programmatic conditions in Africa is unknown. Following PCV13 introduction in Malawi, we evaluated the case burden and rates of childhood pneumonia.

Design/Methods: Between January 1, 2012-June 30, 2014 we conducted active surveillance for pneumonia in children <5 years at seven hospitals, 18 health centres, and with 38 community health workers in two districts, central Malawi. Eligible children met non-severe, severe, or very severe World Health Organization clinical pneumonia criteria. Oxygenation <90% defined hypoxemic pneumonia. We quantified the case burden and rates of clinical pneumonia, hypoxemic pneumonia, and hospital pneumonia deaths following PCV13 introduction using multivariable time-series regression.

Results: Of 30 630 clinical pneumonia cases, 76.7% were non-severe or severe, and 19.5% very severe. Hypoxemic pneumonia occurred in 8.3% of cases and 3.2% with hospitalized pneumonia died. At 75% PCV13 coverage, versus 0%, non-severe cases increased 58% (95%CI, 20%-96%), however, very severe cases decreased 63% (95%CI, 22%-100%) and hypoxemic pneumonia fell 62% (38%-85%) in children <5 years. Among hospitalized cases <5 years, very severe disease, hypoxemic pneumonia, and fatality rates declined 65% (22%-100%), 51% (19%-82%), and 39% (10%-67%). Very severe and hypoxemia incidence also dropped 46% (10%-83%) and 76% (39%-100%) at health centres. Community health worker-diagnosed hypoxemic pneumonia rates declined 85% (17%-100%).

Conclusion: Two and a half years after PCV13 introduction, the health system burden and rates of the most severe forms of pneumonia substantially decreased in Malawian children.

POSTER DISCUSSION SESSIONS

50. TB tidbits: diagnosis, surgery and outcomes

PC-1122-06 Discrepancies between line probe assays and phenotypical DST for detection of MDR- and XDR-TB

E Ardizzoni,^{1,2} S Asnong,¹ C Mathieu,² T Sebastiani,³ I Zabsonre,³ G Torrea,¹ F Varaine,² B De Jong¹ ¹Institute of Tropical Medicine, Antwerp, Belgium; ²Médecins Sans Frontières (MSF), Paris, France; ³MSF, Geneva, Switzerland. Fax: (+32) 3 247 63 33. e-mail: eardizzoni@itg.be

Background: While WHO recommends to use line probe assays (LPAs) like the MDR-TBplus and -sl for the rapid detection of MDR-TB, MDR-TBsl has shown incomplete sensitivity for fluoroquinolones (FQ) and injectables agents (IA) resistance detection. In this descriptive study we compared LPAs and conventional drug susceptibility testing (DST) during one year of testing, and assessed the impact of discordant results on treatment decisions.

Design/Methods: On samples sent for routine tuberculosis (TB) diagnosis by Médecins Sans Frontières to the Institute of Tropical Medicine, Antwerp, LPAs MDR-TBplus Vs2 and MDR-TBsl Vs1 were used to detect multi-drug resistant (MDR) and extensively drug-resistant TB (XDR). Samples were tested by Xpert®MTB/RIF (Xpert) elsewhere. The LPAs were confirmed by DST on liquid (MGIT) or solid medium. Gold standard for RMP was rpoB sequence, and DST for the other drugs. Results were collected from routine databases and clinical information from patients' files.

Results: Samples from 34 patients, of whom 23 (67.6%) were MDR and 11 (32.4%) were isoniazid (INH) and RMP susceptible by the gold standard, were also tested with MDR-TBplus. LPA correctly identified all susceptible cases but missed 5 (21.7%) MDR; 3 MDR that were false RMP-susceptible in LPA were also missed by Xpert (mutations Phe251, Phe572), and another 2 were false INH-susceptible in LPA. On the other hand, MGIT missed 2 (8.7%) RMP-resistant cases, detected by Xpert and LPA (Asn526 and Leu526). All cases started MDR treatment based on Xpert results, except for the 3 false RMP-susceptible cases in MGIT. In total 20 patients started XDR empiric treatment by WHO recommendation before their isolates were tested with MDR-TBsl and DST. Five (25%) were XDR, 3 (15%) were pre-XDR FQ resistant, and 12 (60%) FQ and IA susceptible by DST. Four XDR cases were missed by LPA, 1 for both FQ and IA, and 3 for IA alone. Another pre-XDR was missed for FQ. All susceptible cases were correctly identified. Treatment was not modified following testing, whether correct or not.

Conclusion: MDR-TBplus missed about 13% of RMP resistant cases due to mutations out of the rpoB core region, but detected the cases missed by MGIT, related to "disputed" mutations (Van Deun 2013), also identified by Xpert. MDR-TBsl on the other hand missed the majority

of XDR cases. In settings where Xpert is used as first test, LPA tests did not impact on treatment decisions.

PC-1124-06 Comparison of pre- and post-Xpert® tuberculosis treatment outcomes among people living with HIV in Botswana

T Agizew,¹ S Nyirenda,¹ A Mathoma,¹ U Mathebula,¹ A Date,² B Kgwaadira,³ P Pono,³ A Finlay^{1,2} ¹Centres for Disease Control and Prevention, Gaborone, Botswana; ²U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ³Ministry of Health, Gaborone, Botswana. Fax: (+267) 393 2904. e-mail: agizewt@bw.cdc.gov

Background: Xpert MTB/RIF (Xpert), a rapid molecular diagnostic test, has a high sensitivity for diagnosing *Mycobacterium tuberculosis* among people living with HIV (PLHIV) compared to smear microscopy and can potentially reduce time to diagnosis and treatment leading to improved tuberculosis (TB) treatment outcomes.

Methods: From Aug 2012 - Mar 2014, PLHIV initiating antiretroviral therapy at 22 HIV care and treatment centers in Botswana were enrolled and underwent systematic screening for TB. GeneXpert instruments were deployed following a step-wedge design in 13 sites from Nov 2012 - Jun 2013 to serve the centers. National pre- and post-Xpert intensified case finding algorithms were followed: initially symptomatic patients were evaluated by testing sputum samples using smear microscopy and after GeneXpert instruments were installed, testing with Xpert. TB treatment outcomes were compared between patients with drug sensitive TB diagnosed pre- and post-Xpert, adjusting for intra-site correlation.

Results: Among 6136 patients, 1878 were enrolled pre- and 4258 post-Xpert implementation. Upon initial consultation, 1449 (23.6%) screened positive for one of four TB symptoms (cough, fever, night sweat, weight loss) and 244 (4.0%) diagnosed with and treated for drug-sensitive TB. By Apr 2015, TB treatment outcomes were available for 219/244 (89.6%); 41 were pre-Xpert and 178 post-Xpert (Table 1). Among these, 18 patients were transferred out. Treatment outcomes were unfavorable (died, defaulted or failure) for 8/39 (20.5%) pre- and 32/162 (19.8%) post-Xpert resulting in a risk ratio of 1.03 (95% confidence interval [CI]: 0.63-1.71). When stratified by smear microscopy results, treatment outcomes among patients with a negative smear result ($n = 149$) were similar (risk ratio 1.36, 95%CI: 0.66-2.79). Half of smear negative post-Xpert patients had a positive Xpert test result, 64/127 (50.4%). The median number of days from initial diagnostic test to TB treatment among patients with smear negative disease was 23 (Interquartile Range [IQR]: 2-34) pre-Xpert compared to 6 (IQR: 3-19) post-Xpert ($P = 0.16$).

Conclusions: Our preliminary findings indicate that overall treatment outcomes, including those with smear negative TB disease, were similar among patients treated for drug-sensitive TB disease, pre- and post-Xpert. However, Xpert was useful for bacteriologically confirming TB among patients with smear negative disease.

Table. Comparison of TB treatment outcome pre- and post-Xpert implementation among people living with HIV in Botswana

	PreXpert	PostXpert	Risk ratio	95% CI*
Treatment outcomes among all TB patients	n=41	n=178		
Unfavorable outcome (death, default, failure)	8	32	1.03	0.63-1.71
Favorable outcome (cured/completed)	31	130		
Sub Total	39 (95%)	162 (91%)		
Transferred out or not evaluated	2 (5%)	16 (9%)		
Treatment Outcomes among patients with smear negative disease	n=30	n=119		
Unfavorable outcome (death, default, failure)	6	17	1.36	0.66-2.79
Favorable outcome (cured/completed)	22	91		
Sub Total	28 (93%)	108 (91%)		
Transferred out or not evaluated	2 (7%)	11 (9%)		

*Adjusted for intra-site correlation

PC-1125-06 Trends in treatment outcome of new and retreatment tuberculosis cases in two regions of Ethiopia

K Melkieneh,¹ Z Dememew,¹ M Nigussie,² I Jemal Abdulahi,³ Y Anteneh Kassie,¹ D J Dare,¹ M Aseresa Melese,¹ P G Suarez⁴ ¹Management Sciences for Health, Help Ethiopia Address the Low Tuberculosis Performance (HEAL TB) Project, Addis Ababa, ²Amhara Regional Health Bureau, Bahar Dar, ³Oromia Regional Health Bureau, Addis Ababa, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, USA. e-mail: Kmelkieneh@yahoo.com

Background and challenges to implementation: Ethiopia is one of the 22 high tuberculosis (TB) burden countries. To address this challenge, the USAID-funded Help Ethiopia Address the Low TB Performance (HEAL TB) project in collaboration with the national TB program has been supporting comprehensive TB prevention and control interventions in two regions of Ethiopia, covering 50% of Ethiopia's 90 million population since 2011. Here we present trends in treatment outcome in HEAL TB supported regions.

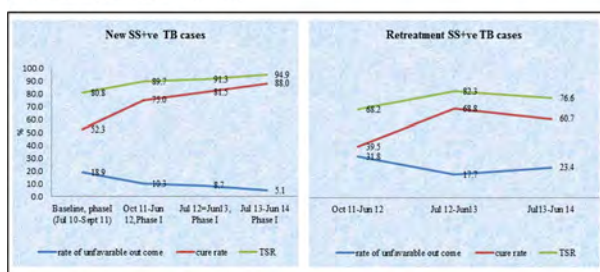
Intervention or response: The interventions included capacity building for TB program managers at different levels, training of health professionals, laboratory capacity building including quality assurance, drug supply management, mentoring and supportive supervision. In this report, we analyzed the trends in TB treatment outcomes for the 10 zones which were included in the initial phase of project implementation.

Results and lessons learnt: We supported treatment of 34,045 new smear positive pulmonary TB (SS+) patients in the two regions between October 2011 and June 2014. Treatment success rate (TSR) for the SS+ improved from

81% at baseline to 95% at the end of the third year, and cure rate (CR) improved from 52.3% to 88.0% ($P < 0.05$). Of 1737 smear positive TB patients on retreatment regimen treated over the same period, TSR and CR improved from 68.2% to 76.6% and from 39.5% to 60.7% respectively ($P < 0.05$) [Figure]. The annual increment in CR among retreatment cases was 10.6% which is significantly higher than the 6.5% increment in new SS+ ($P < 0.001$). Moreover, the average TSR and CR for new SS+ was high: 92% and 88% respectively.

Conclusions and key recommendations: Treatment outcomes improved steadily in both new and retreatment cases because of better adherence of patients to treatment, improved clinical and lab follow ups, and uninterrupted drug supplies.

Figure 1: Trend of favorable and unfavorable outcome for TB patients on new and retreatment regimen (Oct 11-Jun 14)



PC-1126-06 Treatment interruption: the vicious cycle

B Naik,¹ K G Deepak,¹ Y Patel,¹ S Shastri,² A Sreenivas,¹ A Singarajipura² ¹World Health Organization Country Office for India, New Delhi, ²Department of Health & Family Welfare, Bangalore, India. e-mail: naikb@rntcp.org

Background: Treatment interruption is a problem underestimated. The treatment interruption rates among tuberculosis (TB) patients seem to be within the acceptable range at country level but masking the inter-state/ regional variations which are significant and not addressed adequately. We attempted to see the trends of the treatment interruption {programmatically called as “lost to follow-up” (erstwhile called as defaulters)} among new smear positive cases (NSP), relapse cases and treatment after loss to follow-up cases in the country vis a vis the state of Karnataka (population: 63 million) which even after having a programme whose processes were well appreciated (by national and international evaluation teams); is having a persistently high rate of loss to follow-up.

Design/Methods: Secondary data from the national annual status reports of India and Karnataka state quarterly reports were analysed and trends were matched.

Results: As shown in the table; the trend of lost to follow-up patients in the state of Karnataka has remained higher than the national average in all the 3 types of cases (new smear positive, relapse and treatment after loss to follow-

up) even after more than a decade into implementation of the programme. Among NSP the national average lost to follow-up rate is around 6% of registered NSP cases compared to 8% in Karnataka. Every fourth treatment after loss to follow-up patient is again lost to follow-up. Significant proportions of these “lost to follow-up” cases become MDR-TB and come with the challenges of holding them on a more complex and prolonged treatment.

Conclusion: The treatment interruption rates are glaringly high among the TB cases (especially among retreatment TB cases) in Karnataka (population: 63 million) when compared with national averages. Health systems need to be adequately strengthened to handle this situation. Focused interventions targeted at the most at risk groups are needed to address this problem at the earliest stage of care to avoid complications in the patient management and reduce burden on the health system.

Year	Loss to follow-up rates among notified new smear positive TB cases (%)		Loss to follow-up rates among notified Relapse TB cases (%)		Loss to follow-up rates among notified “treatment after loss to follow-up” TB cases (%)	
	India	Karnataka	India	Karnataka	India	Karnataka
2005	7	9	14	17	20	25
2006	6	10	14	19	19	26
2007	6	9	12	16	18	26
2008	6	8	12	16	17	26
2009	6	8	12	15	17	27
2010	6	7	12	15	18	26
2011	5	7	11	15	17	25
2012	6	7	11	18	17	26

PC-1127-06 Surgical interventions for drug-susceptible and drug-resistant tuberculosis in Mumbai

L Anande,¹ A Dalal,² S Shirodkar,² M Das,³ H Mansoor,³ D Remartinez,³ P Isaakidis³ ¹Sewri GT Hospital, Mumbai, ²Jupiter Hospital, Mumbai, ³Médecins Sans Frontières, Mumbai, India. e-mail: msfocb-asia-epidemiology@brussels.msf.org

Background: There is a little documented evidence on surgical interventions carried out in tuberculosis (TB) patients including drug-resistant TB (DR-TB) patients. However, there is an urgent need to include surgical interventions in TB treatment guidelines. We aimed to describe experiences and programmatic challenges while providing surgical interventions to TB patients registered for care in two tertiary-care hospitals in Mumbai, India. **Design/Methods:** This was a retrospective cohort study of TB patients receiving surgical interventions in G.T.B tertiary-care Sewri hospital and Jupiter hospital in Mumbai, India between March 2012 and March 2015.

Results: A total of 113 TB patients who had undergone surgical interventions were included in the study. The cohort consisted of young adults with median (Inter-quartile range) age of 27 (22-35) years. Majority (74%)

of them were males. Among all TB patients, more than a quarter (26%) had DR-TB [Multi-drug resistant TB (MDR-TB): Pre-extensive DR-TB: Extensive DR-TB: Extremely DR-TB: 16:4:7:2]. Approximately half of the patients (46%) were operated for pleural thickening and/or partial/complete lung collapse. About 12% of the patients were intervened for post-surgical complications such as broncho-pleural fistula, wound gap or discharging sinus. The most common surgical interventions carried out were pneumonectomy (32%, 36/113) and decortications (29%, 33/113) for drug-susceptible TB patients, while pneumonectomy (45%, 13/29) was the most common surgical intervention for DR-TB patients. There were three post-operative deaths recorded in this cohort.

Conclusion: With increase in complex drug-resistance forms of tuberculosis and limited number of effective drugs surgery has become an adjunct to tuberculosis treatment. Sometimes it remains the only effective option for XDR-TB and worse form of DR-TB. One-eighth of patients presenting with post-operative complications highlight the need for close monitoring. The selection of cases in need of surgery and appropriate surgical interventions warrants discussion. Non-resection surgical options for patients with bilateral disease are urgently needed as long as the current pharmacological treatment options remain limited.

PC-1128-06 Factors associated with mortality among TB patients in Kenya

J Njenga,¹ A Wairia,^{1,2} B Mungai,¹ F Ngari,² E Masini,² P Agunga,^{1,2} M Maina³ ¹Centre for Health Solutions - Kenya, Nairobi, ²Ministry of Health, Kenya, Nairobi, ³USAID Kenya, Nairobi, Kenya. e-mail: jnjenga@chskkenya.org

Background: Kenya targets to have less than 5% of TB case fatality by 2018. Available statistics however suggest that TB case mortality is on the increase from 5.9% in 2012 to 6.6% in 2013. Understanding factors associated with mortality among TB patients is necessary if the country is to achieve her set targets.

Design/Methods: We abstracted data from the national TB surveillance system, TIBU, for all patients started on TB treatment between January 2012 and December 2013 and who had a treatment outcome assigned by the time of data abstraction. The outcome of interest was death. The explanatory variables assessed were whether the health facility was public, private or prisons, type of patient, type of TB, DOT by, HIV status, CTX and ART uptake, nutrition support, sex, age, and patient referral. Binary logistic regression data analysis methods were applied using SPSS version 21.

Results: Out of 187 907 patients assessed, 10 973 (5.8%) died during treatment. Dot by, referred by and CTX uptake variables were not associated with death outcome. Facility type, sex, age, TB Type, patient type, HIV status, ART uptake and nutrition support were all found to be significant variables associated with mortality. Combined, these factors explained 64% of variation in the death outcome. Patients in private health facilities

were 19.8% (95%CI 15.7% to 23.8%) less likely to die compared to patients in public facilities. Females were 16.5% (95%CI 13.0% to 19.8%) less likely to die compared to males patients while adults were 78.9% (95%CI 64.8% to 94.3%) more likely to die than children below 15 years. PTB smear negative, PTB smear positive and EPTB patients were 24.1% (95%CI 17.9% to 29.9%), 60.4% (95%CI 56.9% to 63.6%) and 14.8% (95%CI 7.4% to 21.5%) less likely to die compared to PTB smear not done patients respectively. Relapse smear positive and relapse smear negative, return after default and relapse extra-pulmonary cases were all more likely to die compared to new patients ($P < 0.0001$). HIV negative patients were 73.5% (95%CI 71.5% to 75.3%) less likely to die compared to HIV positive patients and being on ART reduced the likelihood of death by 38.5% (95%CI 36.0% to 42.6%) compared to being not on ART for HIV positive patients. Patients who received micro nutrients and food support were 8% (95%CI 2.8% to 13.7%) and 49.9% (95%CI 41.7% to 58.5%) more likely to die compared to those who received no nutrition support respectively.

Conclusion: TB case mortality in Kenya is associated with facility type, age, sex, patient type, TB type, HIV status, ART uptake and nutrition support. There is need to borrow best practices in private and prison facilities, come up with innovative interventions targeting men and ensure all pulmonary TB patients receive smear microscopy in order to reduce TB case fatality. HIV prevention and ART uptake among HIV positive patients should be scaled up. Food support should be provided at the right time. Severely malnourished patients could benefit more from being admitted and their progress monitored closely instead of being provided with food support and left on their own.

PC-1129-06 Osteoplastic thoracoplasty with minimally invasive access in the complex treatment of patients with destructive pulmonary tuberculosis

D Krasnov,¹ V Krasnov,¹ D Skvortsov,¹ I Felker¹

¹Novosibirsk Tuberculosis Research Institute, Novosibirsk, Russian Federation. e-mail: felkeririna@sibmail.com

Background: The collapse surgical operations for patients with pulmonary destructive TB are accompanied by a significant number of complications, severe pain, cosmetic defects and poor adherence of patients to this surgical method. The aim of our study was to develop and to test a new low-traumatic version of osteoplastic thoracoplasty (OT) which is performed from minimally invasive access.

Methods: We conducted a randomized study of 414 patients with complicated destructive TB. OT was performed for all patients. In the main (I) group ($n = 191$) - from minimally invasive access, in the control group (II) ($n = 223$) - according to classical method. Lung resection in all patients was contraindicated. Before surgery: Radiological signs of TB progression were identified in 167 (87.4%) persons of I group and in

179 (80.3%) persons of II group ($p = 0.05$, χ^2). Poly cavernous lung lesion (2 or more cavities (CV)) was observed in 118 (61.8 %) and 138 (61.9%) patients ($P = 0.98$, χ^2). Bilateral subtotal lung damage was in 178 (93.2%) and 213 (95.5%) cases ($P = 0.30$, χ^2), new infiltrative foci in the opposite lung – in 39 (20.4%) and in 42 (18.8%) patients ($P = 0.69$, χ^2) accordingly. Bilateral CV localization was registered in 43 (22.5%) patients of I group and in 61 (27.4%) patients of II group ($P = 0.26$, χ^2). Smear and culture positive before surgery were 179 (93.7%) and 207 (92.8%) patients from I and II accordingly ($P = 0.72$, χ^2). MDR-TB was registered in 71.2% and 72.2% of cases ($P = 0.82$, χ^2).

Results: Intraoperative blood loss less than 400 ml in the main group noted in overwhelming number of patients - 187 (95.4%), whereas in the control group - only in 105 (44.1%) ($P = 0.0001$, χ^2). Various postoperative complications in I group occurred in 28 (14.7%) patients, in II group they were registered more frequent - in 69 (30.9%) persons ($p = 0.0001$, χ^2). OT application led to bacteriological conversion in 144 (80.4%) patients of I group and 143 (69.3%) of II group ($P = 0.01$, χ^2). CV closure was achieved in 159 (83.2%) and 156 (70.0%) patients, respectively ($P = 0.001$, χ^2).

Conclusion: The proposed method is more sparing, the risk of intraoperative blood loss (RR = 10.10; 95%CI 9.20-11.01), and complications in the early postoperative period (RR = 1.46; 95%CI 1.38-1.54) for classical OT is much higher. Application of new techniques from minimal access allowed to achieve better results than traditional method, such as bacteriological and cavity closure (OR = 3.7; 95%CI 3.4-4.01).

PC-1130-06 Persistent sputum smear positivity in pulmonary tuberculosis patients during treatment follow-up

C M Muvunyi,¹ N Bizimungu,² J C Ngabonziza Semuto,² J B Mazarati² ¹University of Rwanda, Kigali, ²Rwanda Biomedical Center, Kigali, Rwanda. e-mail: clmuvunyi@gmail.com

Background: In resource poor setting, sputum smear microscopy still remains the method of choice used for tuberculosis diagnosis and treatment monitoring. At the same time, identification of acid-fast bacilli (AFB) in the sputum smear during tuberculosis therapy is considered a predictor of patient infectivity and treatment failure.

Design/Methods: The study was conducted at national reference Laboratory in Rwanda to evaluate the magnitude of prolonged positivity of sputum smear during treatment follow-up in Rwanda. We retrospectively evaluated a cohort of 205 adult patients (142 men and 63 women) diagnosed with new case pulmonary tuberculosis.

Results: Of the 205 patients, delayed sputum smear and culture conversion occurred in 91 (44%) and 47 (23%) patient beyond 2 months, respectively. Sputum smears remained positive for AFB beyond 5 months of therapy in 13 patients (6%). Of the 13 patients with positive smears after 5 months, 10 (77%) converted to negative culture

results before negative smear results, and 3 (23%) had persistently positive culture results. Thus, in this study population, there were only three true treatment failures beyond 5 months.

Conclusion: Persistent sputum smears positive for AFB at the end of treatment do not necessarily indicate treatment failure but is more likely to be associated with negative culture results due to the presence of nonviable mycobacteria. Based on the data presented here, we proposed to investigate the pretreatment risk factors associated delayed sputum smear and culture conversion in Rwanda where microscopy remains the only tool widely accessible for TB treatment monitoring.

PC-1131-06 Compliance with tuberculosis diagnostic guidelines in South African public health facilities

Z McLaren,¹ A Sharp,¹ M Triyana,² J Zhou,¹ A Nanoo³

¹University of Michigan, Ann Arbor, MI, USA; ²Nanyang Technological University, Singapore, Singapore; ³National Health Laboratory Service, Johannesburg, South Africa. e-mail: zmclaren@umich.edu

Background: The quality of tuberculosis diagnostic care and treatment varies across health facilities and affects patient health outcomes. Both health system factors and patient population factors contribute to non-compliance with clinical guidelines. National TB Laboratory Registers can be used to generate information about compliance with clinical protocol at the patient and health facility level. Information on where compliance is poor enables the targeting of additional resources to locations where it can save the greatest number of lives. This is the first study on clinic and treatment quality in South Africa using national laboratory register data for full sample of public health facilities.

Design/Methods: We use data from the National Health Laboratory Service database on tuberculosis tests performed on patients in public health facilities for the period Jan 2004 - Dec 2011, which includes over 30 million test records from over 10 million patients at health facilities. Culture-confirmed TB-positive cases are based on the presence of at least one positive result from TB culture, PCR test or Xpert MTB/RIF. We examine compliance with clinical guidelines for TB diagnosis and follow up testing of patients with suspected pulmonary TB. We perform multivariate regression analysis of the effect of facility and patient characteristics on the facility compliance rate using supplemental data from the District Health Information System (DHIS) and Census. **Results:** Overall, 5.2% of patients received two tests within the first two days, 7.3% of TB+ patients received a test at the end of the intensive phase, and 3.6% of TB+ patients received a test at the end of treatment. Among patients who received at least two tests, these values were 35.0%, 40.0%, and 18.4%. Compliance was generally higher in hospitals than in clinics and varied considerably by province.

Conclusion: Our results demonstrate that directing additional health resources to facilities in Limpopo

province, rural areas and in the bottom decile of the compliance rate distribution could improve compliance and lead to better patient TB outcomes in these facilities. The facility TB care indicators we produced are useful as a standardized measure of quality of care and provides a source of continuous monitoring.

51. M/XDR treatment: toxicity and stigma

PC-1132-06 Adverse events among MDR-TB patients receiving second-line treatment in Cubal, Angola

M L Aznar,¹ C Bocanegra,¹ E Gabriel,¹ A Zacarías,¹ I Molina,² R De Carvalho,¹ M Moreno,¹ T Lopez¹ ¹Hospital Nossa Senhora da Paz, Cubal, Angola; ²University Hospital Vall d'Hebron, PROSICS Barcelona, Barcelona, Spain. e-mail: cristinabocanegra@gmail.com

Background: Second-line treatment for multi-drug resistant tuberculosis (MDR-TB) has recently started in Angola. There is little data about the real burden of adverse events of this treatment in rural, low-resources context in wide areas of Sub-Saharan Africa.

Design/Methods: This is a descriptive, prospective study, performed at Hospital Nossa Senhora da Paz, a 400-bed rural hospital located in Cubal, in Benguela Province of Angola. We included all adult patients who started second-line treatment for MDR-TB between May 2013 and January 2015. Standard treatment in this setting includes amikacin or kanamycin or capreomycin plus ethionamide or prothionamide, ofloxacin, cycloserine and pyridoxine for eight months, followed by twelve months of treatment with ethionamide or prothionamide, ofloxacin and cycloserine. Prospective data were analyzed to determine the frequency and characteristics of adverse effects.

Results: One hundred and twenty-eight patients were included, with a mean age of 32.3 years (SD 9.4). 56.3% were male and 8 (6.3%) were co-infected with HIV. The minimum time of follow-up was three months, with a mean of 12.1 months (SD 5.9). Overall 90 (70.3%) patients presented at least one adverse effect; among these, 29 (22%) were severe. 77 (35%) patients had to discontinue or lower the dose of at least one drug and 2 (1.5%) abandoned the whole treatment due to adverse effects. Ototoxic (32%), gastrointestinal (25.8%), peripheral neuropathy (25.8%), together with increased creatinine (38.3%) were the most commonly adverse events reported, whereas ototoxic and psychiatric were the most debilitating. Mean of time for development of adverse effects was 123 days (SD 107.3); overall, 38.1% resolved within one month. No differences were observed in risk of adverse effects between infected and non-infected HIV-patients. Similarly, age was not significantly associated with adverse events.

Conclusion: Patients on second-line treatment experienced a wide range of secondary adverse events, many of them severe and disabling, at very moment of follow-up. Appearance of these effects often difficult correct

compliance of the treatment. Management of these symptoms requires early identification and prompt management by experienced professionals at all levels of healthcare. Safer regimens for drug-resistant TB are advocated.

PC-1133-06 QTc interval in patient treated with a 9-month regimen for multidrug-resistant tuberculosis

M-L Mbulula-Mawagali,¹ Z Kashongwe Munogolo,² J Toloko,³ F Kassa,⁴ M Gninafon,⁴ W Bekou,⁴ A Trebucq,⁵ K G Koura⁵ ¹Action Damien, Kinshasa, ²University of Kinshasa, Kinshasa, ³Provincial Coordination of Tuberculosis and Leprosy, Kinshasa, Democratic Republic of the Congo; ⁴National Tuberculosis Programme of Benin, Cotonou, Benin; ⁵International Union Against Tuberculosis and Lung Disease, Paris, France. e-mail: kgkoura@theunion.org

Background: The QT interval represents the time taken for ventricular depolarisation and repolarisation. The corrected QT interval (QTc) estimates the QT interval according to the heart rate. Moxifloxacin and clofazimine have been shown to cause QTc prolongation with an increased risk of ventricular arrhythmia. Our goal was to describe the QTc interval before and one week after initiation of treatment in multi-drug resistant tuberculosis (MDR-TB) patients treated with a 9-month regimen including these two drugs at a normal dosage.

Design/Methods: Data on the patients included in the prospective study in Benin and Democratic Republic of Congo between September 2013 and January 2015 were used. Socio-demographic characteristics and human immunodeficiency virus (HIV) status were collected at inclusion. An electrocardiogram was performed before initiation of treatment and one week later. The QT interval was manually measured and corrected according to the linear regression Framingham formula: $QTc = QT + 0.154 (1-RR)$, RR represents the time between two RR waves. QTc is prolonged if the measure is higher than 440 milliseconds (ms) in men or 460 ms in women. Student's paired *t* test was used to compare the means of QTc before and one week after initiation of treatment.

Results: One hundred and twenty-two patients were included. The median age was 35 years, 40% were female and 16% of patients were HIV positive. The mean QTc [95%CI] before initiation of MDR-TB treatment was 375.0 ms [368.8-381.2] and two patients had a QTc prolongation: 461 and 522 ms. One week later, the mean QTc [95%CI] was 388.0 ms [381.0-395.2], which is significantly higher ($P < 10^{-3}$) than the mean QTc before treatment. One patient increased its QTc over the threshold (from 354 to 603). The two patients with a QTc prolongation before initiation of the treatment kept it high: 456 and 543. These three patients, with a QTc prolongation, are still alive: one has finished his treatment and has been declared "Cured". Treatment is still ongoing for the other two patients.

Conclusion: The slight but significant increase in mean QTc after initiation of treatment is consistent with the cardiac effect of moxifloxacin and clofazimine. However, few patients had a QTc prolongation and the 9-

month “Bangladesh regimen” was not modified nor interrupted for these patients.

PC-1134-06 Aminoglycoside ototoxicity in tuberculosis treatment: a review of the World Health Organization global pharmacovigilance database

E Sagwa,¹ P C Souverein,¹ I Ribeiro,² H G M Leufkens,¹ A Mantel-Teeuwisse¹ ¹Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; ²Centre for Health Technology Assessment and Drug Research, Coimbra, Portugal. Fax: (+264) 220 361. e-mail: esagwa@yahoo.com

Background: Ototoxicity due to long-term aminoglycoside use in tuberculosis treatment (TB) is a potentially debilitating problem. The comparative risk of streptomycin, amikacin, kanamycin and capreomycin in causing ototoxicity in the context of TB treatment is still unclear. Our aim was to evaluate the association between aminoglycosides used for TB and the reporting of ototoxicity as well as its determinants, using the pharmacovigilance information that is spontaneously reported by countries to the Vigibase maintained by the WHO Collaborating Centre for International Drug Monitoring at the Uppsala Monitoring Centre (UMC) in Sweden.

Design/Methods: Case/non-case study among TB patients treated with aminoglycosides, with cases being reports of ototoxicity, and non-cases being reports of other adverse drug reactions (ADRs). The influence of the concomitant use of medications for HIV was also studied. The strength of the association between amikacin, kanamycin and capreomycin use in TB treatment, in comparison with streptomycin use, and the risk of ototoxicity was expressed as reporting odds ratio (ROR), a measure of disproportionality in pharmacovigilance databases, with 95% confidence intervals (CI).

Results: Up to mid-2014, 3693 individual case safety reports (ICSRs) were submitted in Vigibase where streptomycin, amikacin, kanamycin and capreomycin indicated for TB treatment were suspected of causing the adverse reaction. Of these ICSR, ototoxicity was reported in 602 cases, the rest being other ADRs (non-cases). The reported types of ototoxicity included deafness ($n = 80$), tinnitus ($n = 95$), vertigo ($n = 404$) and 23 unspecified ototoxicity. In multivariate analysis (Table1), amikacin was associated most with reported cases of deafness (adjusted ROR=6.5; 95%CI 2.8-15.1), followed by kanamycin (adjusted ROR=4.0; 95%CI 1.2-13.4). On the other hand, the use of capreomycin compared to streptomycin use, was inversely associated with the reporting of vertigo (adjusted ROR=0.1; 95%CI 0.01-0.4). None of these three drugs were disproportionately associated with the reporting of tinnitus. Patient age was an effect-modifier: <25yrs (reference), 25-49yrs (aROR=1.4; 95%CI 1.0-1.8), 50-74yrs (aROR=2.0; 95%CI 1.5-2.7) and 75yrs and older (aROR=3.2; 95%CI 2.1-5.0). Sex and concomitant HIV medication appeared not to influence the risk of reported ototoxicity.

Conclusion: Compared to streptomycin, amikacin use was associated with the greatest risk of deafness reported in the Vigibase, followed by kanamycin. We advise national TB control programs to closely monitor patients for ototoxicity when using these aminoglycosides in the long-term treatment of TB. Appropriately designed studies are needed to confirm the comparative risk of the various types of ototoxicity occurring in the long-term treatment of drug-resistant tuberculosis using amikacin, kanamycin and capreomycin.

Table 1: Univariate (crude RORs) and multivariate (adjusted RORs) analysis of risk of categories of ototoxicity by type of aminoglycoside

Exposure	Deafness (n=80)	Tinnitus (n=95)	Vertigo (n=404)
	Adjusted ROR*	Adjusted ROR*	Adjusted ROR*
Streptomycin	Reference	Reference	Reference
Kanamycin	4.0 (1.2-13.4)	1.8 (0.4-7.5)	NA
Amikacin	6.5 (2.8-15.1)	2.3 (0.7-7.5)	0.3 (0.1-1.4)
Capreomycin	1.1 (0.9-2.3)	0.5 (0.1-2.1)	0.1 (0.01-0.4)

*Reporting odds ratios (RORs) adjusted for sex and human immunodeficiency virus (HIV) co-treatment. Age not adjusted for because it was an effect-modifier. NA= not possible to calculate.

PC-1135-06 The effect of moxifloxacin and clofazimine on the corrected QT interval (QTc) in patients treated with a 9-month regimen for MDR-TB in Niger

S Hassane Harouna,¹ A Piubello,¹ B Souleymane,¹ S Morou,¹ I Boukary,¹ A Sala,² K G Koura³ ¹Damien Foundation, Niamey, ²Regional Hospital, Maradi, Niger; ³International Union Against Tuberculosis and Lung Disease, Paris, France. e-mail: hassoul20@yahoo.fr

Background: Normal dose of moxifloxacin and clofazimine are currently prescribed as part of a 9-month treatment regimen for multidrug-resistant tuberculosis (MDR-TB) in Niger. Both are known to cause a prolongation of the corrected QT Interval (QTc), with the resulting risk for fatal arrhythmias. The aims of this study are to describe the QTc interval at baseline and during the first month of treatment.

Design/Methods: Between October 2013 and December 2014, a prospective study on a 9-month regimen to treat MDR-TB patients was conducted in Niger. Breakfasts were provided 30 min prior to the intake of the drugs. An electrocardiogram (ECG) was recorded before the start of the treatment (D0), as well as seven days (D7), and thirty days (D30) later. The QT interval was manually measured and corrected according to the linear regression Framingham formula [$QTc = QT + 0.154(1-RR)$]. QTc was considered prolonged if higher than 450 milliseconds (ms) in men and 470ms in women. All the ECGs were over-read by a cardiologist blinded, to time, date, treatment and any data identifying the subject.

Results: Fifty-three patients were included, of whom twelve (23%) were female. The median age was 36 years and 11% of patients were HIV positive. At baseline the mean $\pm$ standard deviation (SD) for the QTc was 370.4 $\pm$ 24.5 and one patient had QTc prolongation (male

with QTc=455ms). The QTc remained within normal limits on day seven after the start of treatment, with a mean ($\pm$ SD) of 374.9 ± 24.8 . Thirty days after the treatment initiation, the QTc mean ($\pm$ SD) was 376.1 ± 29.7 which is not significantly higher than QTc before treatment ($P = 0.075$). The single patient who had QTc prolongation at D0, had a normal value at D7 (422ms) and QTc prolongation at D30 (468ms). This patient's treatment was not modified but he was monitored daily for one week until his QTc prolongation resolved. Furthermore, no patient manifested a QTc longer than 500ms or a QTc prolongation longer than 60ms from baseline when we compared the variation between D7 and D30 versus D0. No other significant ECG changes were observed.

Conclusion: Moxifloxacin and clofazimine administered in a 9-month regimen for MDR-TB appear to be safe and well tolerated. An ECG should be performed before the initiation of treatment to identify patients with QTc prolongation. Patients with pre-existing QTc prolongation require close monitoring to ensure safety.

PC-1136-06 Hearing thresholds of drug-resistant tuberculosis patients: baseline audiogram configurations and associations

M Fadeyi,¹ A Sogebi,² V Ibeziako,³ A Agbaje,³ E Usoroh,³ S Dutt,³ P Dakum³ ¹Sacred Heart Hospital DR-TB treatment centre, Lantoro Abeokuta, Ogun State, ²Olabisi Onabanjo University, Ago Iwoye, Ogun State, ³Institute of Human Virology Nigeria, Fct, Abuja, Nigeria. e-mail: vizeziako@ihvnigeria.org

Background: The treatment of DR-TB involves the use of aminoglycosides which have been shown to cause varying degrees of ototoxicity. Majority of DR TB patients in Nigeria are previous CAT 11 failures most of which already have varying degrees of hearing loss as a result of Streptomycin which poses a challenge to clinical management. This study was aimed at using baseline audiogram parameters to determine the occurrence of hearing loss among DR-TB patients and the relationship between sociodemographic and clinical parameters with abnormal audiogram configurations.

Design/Methods: One year prospective study of patients managed at the Ogun state drug resistant-Tuberculosis center. Patients' initial (baseline) audiometry was performed within two weeks of admission to assess hearing thresholds, using pure tones ranging 0.25-8.0kHz for the air conduction, and 0.25-4.0 kHz for bone conduction in each of the ears separately. Patients' socio demographic and clinical data were also obtained. Data was collated and analyzed

Results: Age range was 8-82 years, Mean $\pm$ SD= 34.5 ± 12.6 years, Male: Female =2:1, 78.0% of the patients were domiciled outside the home state, 13.6% were retroviral positive, 94.7% had previous drug regimen failure. <10% of the patients had normal audiograms, 78.8% had sensorineural hearing loss (SNHL) and two configurations; ascending (40.9%) and sloping (19.7%) were most common. Pure tone averages at the low and high frequencies were 33.0 and

40.0 dB HL respectively. 27.3% had normal hearing in the better ear, 50.8% had mild (25.1-40.0 dB), and others with higher degrees of hearing loss. Male sex was associated with deranged audiometric configurations, while there was no association with age, positive retroviral status, previous regimen failure and admission weight <50.0kg.

Conclusion: Many patients with DR-TB in Nigeria had mild, suboptimal sensorineural hearing levels bilaterally with male gender being the only factor associated with abnormal configurations.

PC-1137-06 Prevalence of depression and anxiety during treatment of MDR-TB patients in a tertiary care hospital

Z Barry,¹ Sara Khan,¹ S Khan,¹ O Qureshi,² A Pasha,² S Rehman,² H Hussain,² A Malik² ¹Indus Hospital, Karachi, ²Interactive Research and Development, Karachi, Pakistan. e-mail: zainab.barry@industbcontrol.org

Background: Mental health is associated with every illness. There is scarce literature about mental health condition of TB patients undergoing prolonged treatment. There are fewer studies on the impact of TB treatment on a patient's mental health, especially MDR-TB. The aim of this study is to measure depression and anxiety in Multi-Drug Resistant-(MDR-TB) patients during Intensive and continuation phases of TB treatment. Method: We conducted a prospective study to see the pattern of depression and anxiety at Indus Hospital from January to December 2014. All patients are counseled at baseline and during their monthly follow up visits. A random sample of 171 patients was selected from both phases of treatment. The Aga Khan University Anxiety and Depression scale (AKUADS) validated for Pakistani population was administered. The tool has 25 questions with four responses - never, sometimes, often, and always. Each question is scored from 0-3. A score from 0-20 ensures no depression or anxiety; 21-40 is categorized as mild depression and anxiety; 41-60 is categorized as moderate depression and above 61 is labeled as severe depression and anxiety.

Results: Of the 171 patients assessed 48% were females and 52% were males with the mean age of 28 years. Of these 58.5% were in intensive phase of treatment and 41.5% were in the continuation phase. Of the patients in intensive phase 44% had no depression and anxiety, 53% had mild and 3% were severely depressed. Where as, in continuation phase 53% of the patients had no depression and anxiety, 16% had mild depression and 2% were still severely depressed.

Conclusion: Given the high rates of depression and anxiety, counselling should be an essential part of therapy to ensure adherence.

PC-1138-06 Occurrence of adverse events in patient receiving community-based therapy for multidrug-resistant tuberculosis in Pakistan

A Javaid,¹ M A Khan,² S Mehreen,² A Basit,¹ K Afsarafridi,² U Ullah,² M Khan³ ¹Lady Reading Hospital Peshawar, Peshawar, ²Lady Reading Hospital, Peshawar, ³Peshawar Medical College, Peshawar, Pakistan. e-mail: mali_smile2005@yahoo.com

Background: Pakistan is one of the top listed countries ranking 4th among top 22 multidrug resistant tuberculosis (MDR-TB) countries. The increasing rate of MDR-TB in Pakistan underscores the importance of effective treatment programs of drug-resistant TB. Clinical management of MDR-TB requires lengthy multidrug regimens that often cause adverse events (AEs).

Design/Methods: We retrospectively reviewed records of patients who began MDR-TB treatment during 2012 cohort at a tertiary care hospital in Peshawar, Pakistan. We sought to ascertain the occurrence of treatment related adverse events and factors associated with these events. We also examined the frequency of and reasons for changing drug regimens. We further sought to determine whether the occurrence of adverse events negatively impacts the treatment outcome and management of adverse effects without requiring the discontinuation of MDR-TB therapy. Analysis was performed using SPSS (SPSS version 16, SPSS Inc., Chicago, IL).

Results: Among 200 enrolled patients 52.5% were female and most of the patients (81.5%) were from group age ≤ 44 years. Among these patients 155 (78.27%) experienced at least one adverse event during treatment. The most commonly reported events were depression (70%), nausea (52.5%) followed by joint pain (47.5%) and body aches (42.5%). Other events like hearing loss, gastritis, decrease in sleep, vomiting, tinitis, anorexia, vertigue and skin rashes occur 22%, 18%, 17%, 11.5%, 10.5%, 9.0%, 8.5% and 7.5% respectively. A change in drug dose due to an adverse events occurred in 26% cases, while 6% cases had at least one drug discontinued temporarily. Older age and lung cavities at baseline were positive association with occurrence of adverse events. Also association was found between adverse events and outcomes (OR 0.480, 0.236-0.978, $P=0.041$)

Conclusion: Adverse events were prevalent among MDR-TB patients treated at PMDT unit Lady Reading Hospital Peshawar. All patients who were older aged and cavitary lungs should be closely monitored for treatment adverse events.

PC-1139-06 The experiences of adolescents with multidrug-resistant tuberculosis and participation in clinical research

K Zimri,¹ P Rose,¹ A Garcia-Prats,¹ A Hesselting,¹ H S Schaaf,¹ G Hoddinott,¹ L Viljoen¹ ¹Desmond Tutu TB Centre, University of Stellenbosch, Cape Town, South Africa. e-mail: klassinaz@sun.ac.za

Background: Adolescents experience a large burden of tuberculosis (TB), including multidrug-resistant (MDR)-

TB. There is limited knowledge of adolescents' experiences of MDR-TB, which may pose considerable emotional and physical burden. The experiences of adolescents participating in clinical research have been poorly described to date, particularly in resource-limited settings, but are important to improve involvement of this neglected group in future research

Methods: We undertook a qualitative study using in-depth interviews. Adolescents aged 10-18 years routinely diagnosed and treated for MDR-TB in Cape Town, South Africa, and who participated in an observational pharmacokinetic study of secondline TB drugs were included. Individual interviews were conducted with each participant followed by a "body-mapping" session where participants could identify how their bodies were affected by MDR-TB. Interviews were conducted in Afrikaans, Xhosa or English and were recorded, transcribed and translated in English. Data were analysed through a thematic analysis.

Results: Nine adolescents were enrolled and 5 included in the analysis. During analysis several themes emerged. Participants had to deal with key challenges including (1) the burden of the medication, including the pill burden, medication taste, and pain and fear of injectable drugs; (2) stigma (including rejection from peers); (3) dealing with social isolation, including the exclusion from their family due partly to hospital stay; (4) multiple fears in terms of health and mortality; and (5) emotional loss associated with MDR-TB, including many who were affected by the death of a relative. While facing all of these challenges, several patients displayed resilience and good coping mechanisms. Participants found the experience of participation in clinical research empowering, as they were able to learn about their disease and most of them expressed interest in sharing their experiences.

Conclusions: Adolescents diagnosed with MDR-TB face many challenges including stigma, exclusion from their families due to hospitalisation, and dealing with the emotional aspects of losing family members. An improved understanding of these challenges in this vulnerable group may help target supportive interventions. Adolescents overall had a positive view of participation in research, and were very interested in sharing their experiences with other adolescents, which is key to planning research and clinical care.

PC-1140-06 Improving pharmacovigilance of drug-resistant tuberculosis drugs

N Misra,¹ I Master¹ ¹King Dinuzulu Hospital Complex, Durban, South Africa. Fax: (+27) 31 242 6008. e-mail: nirupa.misra@kznhealth.gov.za

Background and challenges to implementation: King Dinuzulu Hospital Complex (KDHC) is the centralized drug resistant tuberculosis (DR-TB) centre in EThekweni, KwaZulu Natal (KZN), South Africa (SA). KDHC has a high burden of disease with patient numbers increasing from 205 in 2000 to 686 cases in 2006 to approximately 2500 patients monthly in 2014. Activation of decentralised sites and satellite sites has increased the need to

strengthen pharmacovigilance activities in EThekweni. The armamentarium for drug resistant tuberculosis consists of old drugs, repurposed drugs and new drugs. Treatment regimen consists of many drugs with overlapping toxicities. This coupled with antiretroviral therapy in patients co-infected with HIV increases the risk of adverse drug reactions (ADRs). Despite most patients presenting with ADRs, the reporting of these at facility level is very poor as seen by the small number of non-ARV ADRs that are reported by facilities to the District Health Information System (DHIS) compared to ARV related ADRs. Strengthening ADR reporting in EThekweni is a priority especially with the introduction of new drugs with limited experience. Using the model of targeted spontaneous reporting adopted in the ARV programme, targeted spontaneous reporting of ADRs related to DR TB medicine is being proposed in EThekweni.

Intervention or response: Almost every patient initiated on DR-TB treatment will experience some form of ADR ranging from mild nausea to severe life threatening conditions. The completion of ADR reports for every ADR experienced is not practical and because of the large number of drugs completion of the standardized MCC ADR reporting form is too time consuming. Although a dedicated pre-printed DR-TB ADR reporting form was introduced by NDOH challenges still existed with reporting due to the high workload of doctors and uncertainty as to what to report. The form was reviewed and changes made to make it more user friendly. A core list of ADRs that should be reported was developed by the experts at KDHC and training was conducted on spontaneous targeted reporting.

Results and lessons learnt: A list of ADRs was developed to guide clinicians as to what ADR to report. A pre-printed DR-TB ADR reporting form was implemented. The number of ADRs related to DR-TB treatment reported increased following the intervention.

Conclusions and key recommendations: Targeted spontaneous reporting will improve pharmacovigilance activities in EThekweni.

Design/Methods: The methods and samples included review of meeting reports, programme documents and reports, policy documents, and interviews with provincial, district and sub-district managers and TB Coordinators; healthcare workers providing services in the facilities. Thematic content analysis was used to minimally organise and describe the data set in rich detail, and to interpret various aspects of the research topic.

Results: Results from the analysis identified key behavioural, structural, communication and relationship issues that together determine the quality of services delivered. The following major recurring systems barriers were identified: poor communication between levels of care, poor knowledge of DR-TB programmatic management (PMDT) at district level and clinical management at decentralised levels, DR-TB recording and reporting challenges, lack of financial and other resources (e.g. availability of vehicles for outreach teams; inadequate infrastructure and equipment for infection control). A causal loop diagram (CLD) was developed as an analytical tool to attempt to understand how the issues interact through a series of positive and negative feedback loops to drive quality at a systems level. Using this framework as a guide, we can develop an understanding of the key issues, opportunities and obstacles that drive quality in decentralised MDR-TB management and to systematically explore TB control intervention options. Solutions include capacitation on PMDT (including communication systems and referral links between levels of care), MDR-TB clinical training for health care workers (including infection control, side effects monitoring, contact tracing), and regular reviews of TB and DR-TB programmes, and integration of TB services into primary health care teams.

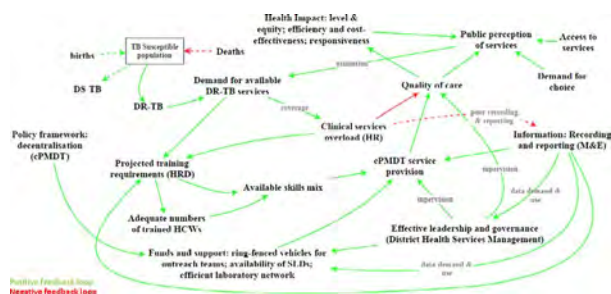
Conclusion: This pilot project demonstrates the utility of the system dynamics method, rather than rigorous policy analysis based on empirical evidence. The approach offers a way to make sense of the complex relationships and information flows between multiple stakeholders. The CLD framework will help to enhance the quality of traditional TB control efforts.

52. Community-based and self-administered treatment of drug-resistant TB

PC-1141-06 A causal loop analysis of the rollout of community-based MDR-TB care in South Africa

R Chimatira¹ ¹Right to Care, Johannesburg, South Africa., e-mail: raymond.chimatira@gmail.com

Background: South Africa adopted the community-based MDR-TB care model in 2009. This paper describes an exploratory operational research project using a qualitative system dynamics approach to identifying the factors potentially influential on systems performance for the effective delivery of decentralised DR-TB care at district level.



PC-1142-06 Self-administered treatment for the continuation phase of drug-resistant tuberculosis treatment: feasibility and impact on patient outcomes

E Mohr,¹ H Cox,² L Wilkinson,¹ G Van Cutsem,³ V Cox,¹ J Daniels,¹ O Muller,¹ B Beko,¹ J Hughes¹ ¹Médecins Sans Frontières (MSF), Khayelitsha, ²University of Cape Town, Cape Town, ³MSF, Cape Town, South Africa. e-mail: mohrek27@gmail.com

Background: Daily directly observed therapy (DOT) is recommended for drug-resistant tuberculosis (DR-TB) patients throughout treatment. This potentially poses a barrier to treatment adherence, particularly during the continuation phase of treatment when patients have clinically improved and can return to normal activities. A pilot program to provide community supported, self-administered treatment (SAT) for patients in the continuation phase of treatment was initiated progressively from January 2012 as part of decentralized DR-TB treatment in Khayelitsha, South Africa. In order to assess feasibility and impact of SAT, we compared 12 month outcomes among patients receiving treatment from primary care clinics with the SAT program to those from clinics still using DOT.

Methods: All DR-TB patients still receiving treatment at the end of the intensive phase within four clinics offering SAT from January 2012 through December 2013 were compared to those in the remaining five clinics using DOT. Patients were assessed for eligibility for SAT by clinicians based on previous adherence record and clinical condition. SAT patients were assigned a community treatment supporter who maintained contact on a weekly basis, and patients were seen at their clinic monthly to monitor treatment progress and collect medication.

Results: There were 163 patients entering the continuation phase in SAT clinics and 160 patients in DOT clinics during the study period. Due to phased implementation of the pilot 97/163 (60%) patients were considered for SAT. Eighty two (50%) were enrolled for SAT; reasons for exclusion of 15 patients from SAT included adherence concerns, patient choice, HIV-related issues, or poor clinical condition/potential treatment failure. Four of the 82 (5%) patients later returned to clinic DOT due to adherence concerns. Rates of LFT in the first 6 months of the continuation phase were 10% (15/158) compared to 11% (16/153) for all patients in SAT versus non-SAT clinics, respectively. Similarly, there was no difference in mortality with 4% and 5% death rates in SAT and non-SAT clinics, respectively.

Conclusion: While the LFT rate remains high, preliminary outcomes for patients receiving SAT are not worse than for clinic based DOT. It was feasible to integrate the pilot into existing primary health care services and findings suggest that SAT may improve quality of life for adherent DR-TB patients, while decreasing the burden placed on clinics by compulsory daily DOT.

PC-1143-06 Decentralization of drug-resistant tuberculosis: translating policy into practice

N Misra,¹ I Master,¹ H Sunpath,² S Fynn² ¹King Dinuzulu Hospital Complex, Durban, ²Ethekwini District Office, Durban, South Africa. Fax: (+27) 31 242 6008. e-mail: nirupa.misra@kznhealth.gov.za

Background and challenges to implementation: King Dinuzulu Hospital Complex (KDHC) is the centralized drug resistant tuberculosis (DR-TB) centre in EThekweni, Kwazulu Natal (KZN), South Africa (SA). Patients diagnosed with extremely drug resistant tuberculosis (XDR TB), pre-XDR-TB and multidrug resistant tuberculosis (MDR-TB) treatment failures are referred to KDHC from facilities throughout KZN. Patients with MDR-TB from all facilities in EThekweni and three other districts in KZN also refer to KDHC. Patient numbers increased from 205 in 2000 to 686 cases in 2006 to approximately 2500 patients monthly in 2014. Staff shortages at KDHC and a shortage of beds have resulted in a waiting list for patients to be initiated on DR-TB treatment with the time to treatment initiation in excess of 3 weeks. Activation of decentralized sites to initiate patients on MDR-TB treatment and activation of satellite sites to manage stable MDR-TB patients was identified as the solution to this challenge.

Intervention or response: Despite policy to guide decentralization, implementation in KZN was slow. Barriers included fear of DR-TB, lack of training and capacity. A steering committee was established to drive the process. It was decided that implementation will be done in a collaborative way with stakeholder buy-in being key to success. A facility assessment tool was designed and sites assessed for readiness. Workshops were convened with the multidisciplinary team from each site. The results of the assessment were presented and draft standard operating procedures (SOP) to guide decentralization were presented. The SOPs were finalized following robust discussions on the practicality of implementation. Training was also provided on pharmacovigilance and clinical management of TB.

Results and lessons learnt: Criteria for down referral of patients to satellite sites were finalized. Four CHCs were identified as ready to manage patients down referred. SOPs were finalized and signed off by the District Manager. Three sites in EThekweni and one each in Amajuba, UThukela and ILembe were activated as decentralized sites. Stable MDR-TB patients are being transferred to satellite sites with pre-dispensed medicine and patients are being initiated at decentralized sites.

Conclusions and key recommendations: Discussions of implementation challenges and barriers prior to finalization of the SOP is key to success. Translating policy into practice must be done in a collaborative way.

PC-1144-06 HIV and drug-resistant TB co-management: the importance of strengthening pharmacovigilance in South Africa

N Ndjeka,¹ S Berrada,² M Dheda,¹ J Jooste² ¹National Department of Health, Pretoria, ²SIAPS, Management Sciences for Health, Hatfield, South Africa. e-mail: sberrada@msh.org

Background and challenges to implementation: As the high burden of drug resistant tuberculosis (DR-TB) is putting increasing pressure on the health system, the South African National Department of Health (NDoH) has identified the need to decentralise the management of these DR-TB patients. In the South African context of high HIV burden, strengthening clinical and pharmaceutical management is critical to support the effective implementation of the decentralised model of care. With new medicines, complex DR-TB regimens and various co-morbidities, the detection, assessment, understanding and prevention of adverse drug effects are not sufficient to improve patients' outcomes. Pharmacovigilance needs to include a management component of the adverse reaction (ADR) that will take into consideration many patient, personnel, drug interactions, concomitant conditions and health infrastructure-related confounders.

Intervention or response: NDoH has developed, piloted and rolled out a decentralised antiretroviral therapy (ART) pharmacovigilance model. The decentralised pharmacovigilance model is based on multidisciplinary clinical clusters where a hospital and its feeder clinics work together to manage ADRs. The clinical teams meet once a month to review the ADR reported by the hospital and the clinics. The ADRs are discussed and recommendations made on the most appropriate clinical management for these patients.

Results and lessons learnt: This patient centered approach to pharmacovigilance appears to be perfectly suited to the decentralisation of DR-TB patient care. Building on the lessons learned from the ART programme, the decentralised pharmacovigilance model has now being tested in three DR-TB hospitals in three provinces in South Africa. The mixed responses to the pilot highlighted the need to customise the data collection forms and training approach to suit the complexity of the DR-TB programme.

Conclusions and key recommendations: The patient centered approach for pharmacovigilance has proven successful for the HIV programme. Although the lessons learned from the ART programme can be applied to DR-TB programme, customisation of the approach is needed to ensure a successful implementation of the decentralised pharmacovigilance for DR-TB and improved management of the patients.

PC-1145-06 Community-based M/XDR-TB care in South Africa: feasibility and lessons learnt

J Hughes¹ ¹Médecins Sans Frontières, Cape Town, South Africa. e-mail: msfocb-khayelitsha-tbdoc@brussels.msf.org

Background and challenges to implementation: In the context of routine hospitalisation and delayed access to

treatment for patients diagnosed with drug-resistant tuberculosis (DR-TB) in South Africa, a decentralised model of care was implemented in collaboration with local stakeholders in Khayelitsha in 2007 to enable clinically stable DR-TB patients to be diagnosed and managed by clinicians at a primary health care (PHC) level.

Intervention or response: Primary care facility staff were trained, DR-TB monitoring and evaluation systems established, treatment regimens optimised, patient support staff employed and infection control measures enforced, while ensuring integration into existing TB and HIV services.

Results and lessons learnt: Management and responsibility of the decentralised DR-TB programme was handed over to local authorities at the end of 2013 following notable successes such as increased DR-TB case detection (~200/year), improved treatment initiation rates (>95% of those diagnosed), reduced time from diagnosis to treatment initiation (72 days in 2007; 6 days in 2014) and implementation of a routine standardised counseling model for all patients starting treatment. Costing studies indicated that this decentralised model of care is 42% less costly than a fully centralised hospital model. While treatment outcomes remained largely the same as those reported from other areas in South Africa, a higher proportion of prevalent DR-TB cases in the community were able to access care due to decentralisation of services. Despite intensive patient support, loss from treatment rates remain high (~30%), suggesting that current toxic, lengthy, and poorly efficacious standardised DR-TB regimens remain a major challenge.

Conclusions and key recommendations: Clinically stable DR-TB patients can feasibly be managed in PHC and within their community however treatment outcomes are still adversely affected by the many challenges related to provision of adequate adherence support for DR-TB patients, as well as access to shorter, more tolerable and more effective treatment regimens. Innovative patient support strategies along with better access to improved treatment regimens are required to improve outcomes and optimise DR-TB care within the community.

PC-1146-06 The impact of decentralization of Programmatic Management of Drug-resistant Tuberculosis services in Swaziland

Z Tfwala,¹ N Dlamini,¹ G Mchunu,¹ F Khumalo,¹ W Sikhondze¹ ¹Ministry of Health, Mbabane, Swaziland. e-mail: tmzethy@gmail.com

Background and challenges to implementation: Drug resistant TB presents a major challenge for TB control globally. TB patients with drug-resistant strains require more resources to diagnose and treat successfully than those without. In 2009, Swaziland conducted a Drug Resistance Survey (DRS) which revealed a high prevalence strains resistant to both isoniazid and rifampicin (multidrug-resistant; MDR-TB) among new patients at 7.7% - more than double the 3% average of the African Region -and a prevalence of 33.7% among previously

treated patients, three times higher than the regional average of 12 – 13 %. This implies that about 390 (range: 240-530) MDR-TB cases are expected among new pulmonary TB patients notified by the programme in 2013 and another 250(210-290) among previously treated cases. For a country with an estimated population of 1.2 million this represents a formidable concern.

Intervention or response: In response to MDR-TB situation, the National TB Control Programme (NTCP) developed and successfully implemented a plan for the decentralization of DR-TB services and established Programmatic Management of DR-TB (PMDT) according to WHO guidelines to provide guidance for DR-TB management. Presented is the review of PMDT by WHO as part of an end-evaluation of the National TB Strategic Plan (2010-2014) in April 2014.

Results and lessons learnt: Since the decentralization of PMDT services, there has been a progressive improvement in the treatment success rate among MDR-TB patients from 18% in the 2007 cohort to 58% currently in the 2011 cohort. PMDT services have been decentralized from one central National TB Hospital in 2010 to 8 more regional DR-TB health facilities by the end of 2014. These facilities have been reinforced to provide quality comprehensive treatment care and support services to all DR-TB patients across the country including community outreach services and home assessments for Infection Prevention and Control.

Conclusions and key recommendations: Increasing investment of resources to intensify treatment adherence through community and family support for MDR-TB patients, as well as improving access to diagnosis, treatment and care is key to DR TB control. Swaziland is now planning to repeat a nationwide, representative drug resistant survey in 2016 to determine the burden of drug resistance in the country and possibly any changes since the last survey in 2009.

PC-1147-06 Community-based management of MDR-TB patients: experience from Malawi

H S Kanyerere,¹ J Mpunga,¹ H Banda,² C Kang'ombe,¹ I Dambe¹ ¹Ministry of Health, National TB Program, Lilongwe, ²Research for Equity and Community Health Trust, Lilongwe, Malawi. Fax: (+1) 301 941 8427. e-mail: asmitharthur@urc-chs.com

Background: Malawi started routine surveillance of MDR-TB among previously treated TB cases in late 1990s. All reported cases were only offered isoniazid and ethambutol (as these drugs were believed to reduce excretion of *Mycobacterium tuberculosis*). The NTP planned for an MDR-TB survey 2001 and successfully applied to the Green Light Committee for access to concessional quality 2nd line TB drugs for community-based management of MDR-TB patients.

Intervention: In 2007, NTP adapted WHO MDR-TB treatment guidelines including recording and reporting tools. District teams were trained in MDR-TB management. Malawi Government procured the first consignment of 2nd line drugs. Since there are no specialised

facilities in Malawi, NTP has opted for community-based management of MDR-TB patients.

Results: In September 2007, 8 MDR-TB patients were initiated on 2nd line TB drugs. By December 2007, 11 MDR-TB patients were on treatment. Since 2007, 186 patients have been diagnosed with MDR-TB and 120(65%) have been started on 2nd line TB treatment. 52 patients (28%) died before treatment initiation. Majority of patients diagnosed were previously treated patients with 1st line anti-TB drugs. In 2014 the NTP diagnosed 17 MDR-TB patients and 13(76%) were started on 2nd line treatment. On average, it takes 4 weeks from the time of MDR-TB confirmation to start of treatment. The HIV status varied from 73% in 2007 to 18% in 2014. Almost all MDR-TB patients had their specimens sent to a supranational laboratory for confirmation and 2nd line drug susceptibility testing. No XDR-TB patient has been reported. The treatment success rates among MDR-TB patients have varied from 62% to 67%. For 11 MDR-TB cases started on treatment in 2007, only 7 (63%) were successfully treated. On the other hand, the death rates have been very high ranging from 20% to 38%. Psychosocial and nutritional supplementation is the unmet need for the patients.

Conclusions and recommendations: Community-based management of MDR-TB patients is feasible in Malawi; however, more needs to be done. There is need to expedite diagnosis and treatment initiation to reduce time leads for the same. Treating these patients at a specialized MDR-TB facility may improve the treatment outcomes since most patients may have access to psychosocial and nutritional support including management of adverse effects. Furthermore, continuous in-service training on MDR-TB patient management for front-line staff is critical

MDR-TB cases registered and treatment outcomes (2007 to 2011)

Year	MDR-TB cases reg	No. started on Treatment	Treatment success	Died	Lost to follow-up	treatment failed	Not evaluated
2007	17	11 (65%)	7 (64%)	3 (27%)	1 (9%)	0	0
2008	16	16 (100%)	10 (63%)	6 (38%)	0	0	0
2009	15	9 (60%)	6 (67%)	3 (33%)	0	0	0
2010	40	26 (65%)	18 (62%)	7 (27%)	1 (4%)	0	0
2011	26	15 (58%)	10 (67%)	3 (20%)	1 (7%)	1 (7%)	0
2012	27	19 (70%)					
2013	28	11 (39%)					
2014	17	13 (76%)					

PC-1148-06 MDR-TB treatment outcomes: task-sharing is effective in improving access without compromising outcomes

J Farley,¹ N Ndjeka,² C Budhathoki,¹ E Bergren,^{1,2} N Mlandu,³ M Van Der Walt⁴ ¹Johns Hopkins University, Baltimore, MD, USA, ²National Department of Health, Pretoria, ³Jhpiego-South Africa, Pretoria, ⁴Medical Research Council, Pretoria, South Africa. e-mail: ebergre1@jhu.edu

Background: Treatment outcomes for multidrug-resistant tuberculosis (MDR-TB) in South Africa remain poor, particularly in patients with HIV. Interventions that increase access to quality, timely care are essential. Task-sharing by a clinical nurse practitioner (CNP) and a medical officer (MO) of MDR-TB-HIV patients is a potential human resource solution, yet evidence is required to support this approach.

Design/Methods: Treatment outcomes were evaluated among MDR-TB patients jointly managed by a CNP and an MO in an MDR-TB unit in a peri-urban city of KwaZulu Natal, South Africa. We followed a prospective cohort who began treatment between January 1 and December 31, 2012 and followed through January 31, 2015 for treatment outcomes. Patients were assigned a primary provider (CNP or MO) with task-sharing throughout patient care. A competing risk analysis with death, failure or default as competing negative outcomes is evaluated including primary provider assignment as an independent variable. A z-test was used to compare the cohort treatment success rate with the national norm in 2012.

Results: We enrolled 197 patients, 51% females with 75% unemployment with a mean age of 33 years and mean BMI 19.7. HIV co-infection was 74% (median CD4 count 250, Q3-Q1 385-141); 75% on ART for those HIV+ at baseline. MDR-TB treatment outcome included 58% success (i.e. cure/completion), 6% failure, 17% death, and 20% default. In comparison, treatment success for the 2012 cohort across South Africa is 45%; success rate in our study cohort was significantly higher than the national norm ($z = 3.70$, $P < 0.001$). In the competing risk analysis, there was no difference by HIV infection status for either failure or default after adjusting for age, sex and provider type. However, hazard for death was reduced by 64% in HIV negative patients ($P = 0.044$).

Conclusion: Overall outcomes in this cohort with task-sharing between CNPs and MOs were better than the country average for the same year. Despite high ART use, HIV continues to hasten death among this group.

PC-1149-06 High treatment success for multidrug-resistant tuberculosis in Africa: initiation and scale-up of the Ethiopian countrywide collaborative treatment

D Kokebu,^{1,2} J Andrews,³ R Hurtado,^{2,4} E D Ejara,^{2,5} K Abato,² T Daniel,² T Sok,⁶ A Goldfeld^{2,7} ¹St Peter's Tuberculosis Specialized Hospital, Addis Ababa, ²Global Health Committee, Addis Ababa, Ethiopia; ³Stanford University School of Medicine, Palo Alto, CA, ⁴Massachusetts General Hospital, Boston, MA, USA; ⁵University of Gondar Hospital, Gondar, Ethiopia; ⁶Cambodian Health Committee, Phnom Penh, Cambodia; ⁷Children's Hospital, Boston, Massachusetts, USA. Fax: (+1) 617 726 7653. e-mail: rh1927@gmail.com

Background: Fewer than half of patients receiving therapy for multidrug-resistant tuberculosis (MDR-TB) in Africa are successfully treated, with particularly poor outcomes reported for HIV co-infected patients. We report outcomes from the first four years of scale-up of MDR-TB treatment in Ethiopia.

Methods: A standardized second-line drug (SLD) regimen was used in an NGO-MOH collaborative community- and hospital-based program that provided initial courses of SLD during program start-up and included intensive side effect monitoring, home-based adherence strategies and nutritional supplementation. Clinical charts and outcomes for patients with at least 24 months of follow-up were reviewed and predictors of treatment failure or death were evaluated by Cox proportional hazards models.

Results: From February 2009 to December 2014, 1044 patients were initiated on SLD. 612 patients had at least 24 months of follow-up, 565 (92.3%) had confirmed MDR-TB and 44 (7.7%) were suspected MDR-TB cases. 603 (98.5%) had prior TB treatment, 133 (21.7%) were HIV co-infected, and median BMI was 16.6. Three hundred and ninety-six (64.7%) were cured, 85 (13.9%) completed treatment (composite treatment success: 78.6%), 10 (1.6%) failed, 85 (13.9%) died, and 36 (5.9%) were lost to follow-up. Of 479 HIV un-infected patients, 388 (81.0%) were successfully treated and 58 (12.1%) died and of 133 HIV co-infected patients, 93 (69.9%) were successfully treated and 27 (20.3%) died. HIV co-infection (AHR 2.48, $P < 0.001$) and cor pulmonale (AHR 6.98, $P < 0.001$) were predictive of treatment failure or death.

Conclusion: We report here the highest MDR-TB treatment success outcomes to be achieved to date in Africa in a population with advanced disease and profoundly low BMI in a setting with severe resource constraints, through an NGO-MOH partnership program using a standardized second-line regimen. Intensive treatment of side effects, nutritional supplementation, and adherence strategies facilitated by flexible funding, were key strategies.

53. Infection control

PC-1150-06 Tuberculosis and its presentation in in-patient units of a university hospital

W De Andrade Pereira De Brito,¹ F Dias E Sanches,^{1,2} C Cângani De Araújo,¹ V Gutterres Silva¹ ¹Pedro Ernesto University Hospital / UERJ, Rio De Janeiro, RJ, ²Thorax Diseases Institute / UFRJ, Rio De Janeiro, RJ, Brazil. e-mail: enfermeirofernando@hotmail.com

Background and challenges to implementation: Controlling tuberculosis (TB) in Brazil and in the world still represents a challenge to be conquered, especially in Rio de Janeiro where it is very common to find a TB case at hospital it could represent an extra issue to be solved.

Intervention or response: This descriptive study with a quantitative approach was developed after another study at the same hospital with the intention to verify the impact of the first study. The following objectives: Identify the inpatient units at risk for exposure to TB; analyze the number of sputum smears and cultures required in inpatient units; classify the samples of sputum smears and positive cultures of the type of TB; correlate the TB cases reported with positive samples of sputum smear and cultures. The data was collected during January-September 2012.

Results and lessons learnt: Clinical units with the highest rate of cases were found in an internal medicine ward where there isn't a proper isolating room. Lack of correlation of institutional profile with the data presented in the municipality of Rio de Janeiro which means undernotifications. It still remains an urgent need to continue speaking about TB with patients and their visitors, during shifts with healthcare workers and residents; as well as classes with students. Those strategies should be put in practice to avoid the sense of trivialization and / or no perceived risk of infection and subsequent illness.

Conclusions and key recommendations: More and more people are at risk. There isn't enough measures to evaluate a real impact of TB at hospital. There isn't enough quantitative of isolating rooms. Need for development new strategies focused on biosafety. It is necessary create forums for discussion under multiprofessional's perspectives.

PC-1151-06 Implementation of infection control practices to prevent TB transmission among PLHIV in five healthcare facilities, Belize, 2014-2015

D Forno,¹ F Morey,² R Lorenzana,³ M Briggs,⁴ V Lipke⁴

¹Centers for Disease Control and Prevention, Guatemala City, Guatemala; ²Belize Ministry of Health, Belmopan, Belize;

³University Research Company, Guatemala City, Guatemala;

⁴U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: dforno@cdc.gov

Background: Belize has the highest HIV prevalence (1.5%) and TB-HIV incidence (8.6 per 100 000) in Central America. The most common infectious cause of

death among people living with HIV (PLHIV) is TB and PLHIV are at high risk of contracting all types of TB disease. Risk for TB transmission is higher in crowded facilities where staff does not practice TB infection control (IC) activities. Based on World Health Organization policy, we implemented the CDC TB IC training package in health facilities to reduce TB transmission.

Design/Methods: The TB IC package was implemented in the two highest burden districts for TB-HIV in Belize: three facilities in Belize district and two facilities in Cayo district. The package included a toolkit to conduct TB IC risk assessments and to develop site-specific TB IC plans, training materials, visual aids for clinics, and an educational video. Facilities were assessed with a 37 item risk assessment tool measuring managerial, administrative, environmental, and personal protective equipment (PPE) categories at baseline.

Results were classified as red if the activity was implemented incorrectly; yellow if it was in progress; or green if it was implemented correctly. A total of 25 healthcare workers received a three-day TB IC training and completed a 13-question pre-/post-test to assess their knowledge.

Results: Two baseline TB IC activities scored red across all sites: separation of coughing patients and outdoor collection of sputum samples (Table 1). Four sites had a National IC policy, an IC committee, and an IC nurse assigned to the site, but had no site-specific TB IC plans. Across sites, an average of 39% of managerial, 35% of administrative, 29% of environmental, and 66% of PPE activities were implemented correctly. Average pre and post-test scores improved from 77% to 92%. A specific TB IC plan was developed for each site.

Conclusion: The standardized risk assessments showed poor implementation of several TB IC activities. An increase in knowledge was shown in most trainees. Site-specific TB IC plans developed during the training will be implemented to increase TB IC activities. We will conduct a six month follow-up evaluation to assess improvement in TB IC practices following each clinic's plan.

Figure Baseline TB IC risk reduction activities, Belize

	Clinic A	Clinic B	Clinic C	Clinic D	Clinic E
National IC Policy is available on-site	Green	Green	Green	Green	Green
An IC practitioner or nurse has been assigned to carry out IC in the facility	Green	Green	Green	Green	Green
An IC Committee/Team has been designated at this site	Green	Green	Green	Green	Green
A written site-specific IC plan has been written and is available to staff	Red	Red	Yellow	Red	Red
TB IC practices are monitored on a daily basis	Red	Red	Green	Red	Red
All staff have been trained on TB IC	Yellow	Yellow	Red	Red	Red
Patients that are coughing are separated from others and "fast tracked" to a clinician	Red	Green	Red	Red	Red
A "Cough Monitor" or other designated person gives cough etiquette guidance and assists with separation and triage	Red	Green	Red	Red	Red
Sputum collection is collected outdoors	Red	Red	Red	Red	Red
Staff receive annual TB screening	Red	Red	Red	Red	Green
Staff monitor natural and/or mechanical ventilation daily	Red	Red	Red	Red	Green
Patient waiting areas are out-of-doors or have good cross-ventilation	Red	Green	Red	Red	Green
Surgical masks are available and worn by coughing patients	Yellow	Yellow	Red	Yellow	Red
N-95 or FFP2 respirators are readily available and used by staff	Red	Red	Red	Red	Green

Conducted, available or correct
Not conducted, not available or not correct
In process



PC-1152-06 Airborne infection control within drug-resistant tuberculosis centres in Tamil Nadu, India: does practice follow policy?

S R Holur,¹ P Rahul,² D Ranganathan,³ M Lakshmi⁴

¹World Health Organization Country Office, Chennai, ²DTO Office, Vellore, ³Madras Medical College, Chennai, ⁴State TB Office, Chennai, India. e-mail: srkholur1979@gmail.com

Background: In 2012, more than 300 000 multidrug resistant tuberculosis (MDR-TB) cases occurred globally, of which, approximately 20% were in India. In India, all MDR-TB cases are required to complete at least 7 days of inpatient treatment at Drug-resistant Tuberculosis (DRTB) centres during the initiation of treatment. The Revised National Control Programme (RNTCP) has published air-borne infection control (AIC) guidelines. This study aims to assess the AIC knowledge and practices among health staff and MDR patients within DR-TB centers.

Design/Methods: We evaluated airborne infection control procedures and practices using a standard checklist developed by the RNTCP designed to capture the three major tenants of AIC: administrative controls, environmental controls and availability and use of personal protective equipment (PPE) in the 6 DR-TB centres in Tamil Nadu. We assessed the knowledge, attitudes and practices of all DR-TB centre staff using a standardized questionnaire. We also selected a convenient sample of patients undergoing treatment at each DR-TB center to better assess patient AIC knowledge and practices using a standardized questionnaire.

Results: administrative controls: 3(50%) of DR-TB centres had formal Infection Control Committees in place and among those, only 1 (17%) had routine and standing meetings to review performance and practice. 1(17%) had developed a site-specific infection control plan available. Only 1 center conducted annualized training and refreshers in AIC. Environmental controls: air ventilation and exchange (natural or mechanical) was observed to be adequate at all centers, however, none of the centers had upper room ultraviolet light for germicidal irradiation or HEPA-filtration. PPE: Respirators were available in only 2 of 6 centers, however, none conducted recommended fit testing. A total of 34 staff members were interviewed. Only 6 (18%) were aware of AIC, and only 3 (8%) had received formal AIC training. About a third of staff, (12/34) felt that isolating TB patients from patient with HIV was not necessary. Among the 21 patient interviewed, 12 (57%) were not aware of proper cough etiquette.

Conclusion: This study highlights the urgent need for immediate standardized AIC training of the administrators and all cadres of staff working in India, especially those working in high-risk settings like DR-TB centers.

PC-1153-06 Natural human-to-guinea pig model to test TB transmission interventions in South Africa: ten years later

A Stoltz,¹ E De Kock,² J A Kruger,³ S Keulder,¹ A Dharmadhikari,⁴ P Jensen,⁵ I Orme,⁶ E Nardell⁴

¹University of Pretoria, Pretoria, ²Retrasol, Pretoria, ³Rietvallei Animal Hospital, Pretoria, South Africa; ⁴Harvard Medical School, Boston, MA, ⁵U.S. Centers for Disease Control and Prevention, Atlanta, GA, ⁶Colorado State University, Fort Collins, CO, USA. e-mail: anton.stoltz@up.ac.za

Background: A quarter of the global 9.0 million reported TB cases are found in the African Region. Hospitals and other congregate settings are highly efficient sites of TB transmission, but most recommended interventions have not been validated in real hospital settings. For the past 10 years we have employed the well-established human-to-guinea pig transmission model of Wells and Riley to assess a series of conventional and novel infection control interventions.

Design/Methods: The Sidney Parsons Airborne Infection Research Facility was established in 2005 to test TB transmission interventions (UVGI air disinfection, masks on patients, effective treatment, BCG vaccine, inhaled drugs, and portable room air cleaners) to prevent TB transmission. In most experiments, 90 guinea pigs (intervention" chamber) are exposed to exhaust air from a 6-bed TB ward on days when the intervention being tested is turned on, and another 90 guinea pigs (control chamber) are exposed to the exhaust air from the same ward on alternate days when the intervention is turned off. The difference between the rates of guinea pig infections in the two chambers, determined by tuberculin skin testing, is a precise measure of the efficacy of the intervention. The alternate day strategy controls for temporal differences in patient infectiousness. In each study, up to 6 patients at a time occupy the facility – serving simply to generate aerosolized Mtb. Admission criteria include subjects recently diagnosed and early in treatment, preferably sputum smear positive with lung cavitation. Most subjects have MDR-TB, but some turn out to have XDR-TB, and are the most likely to transmit on conventional treatment.

Results: As previously reported, UVGI proved to be highly effective (80%), masks on patients (56%), but room air cleaners and inhaled colistin dry powder were ineffective. As shown by Riley, effective treatment was shown to be rapidly highly effective. Preliminary results of BCG vaccination of guinea pigs to prevent infection demonstrate some efficacy.

Conclusion: As first conceived of by Wells and Riley, the natural human-to-guinea pig model has for the past 10 years proven to be highly effective in testing conventional and novel TB transmission interventions and in understanding TB transmission.

PC-1154-06 Results of a baseline infection control assessment at identified decentralized MDR-TB facilities in South Africa

A Peters,¹ J Farley,^{1,2} J Pienaar,¹ M Mphahlele,¹ I Asia¹

¹Jhpiego SA, Pretoria, South Africa; ²Johns Hopkins University, Baltimore, MD, USA. e-mail: jacqueline.pienaar@jhpiego.co.za

Background and challenges to implementation: South Africa's MDR-TB burden ranks third highest in the world. South Africa also has the highest number of people living with HIV. Before 2011, national guidelines mandated that all DR TB patients be initiated on treatment in the country's handful of specialized TB hospitals. New cases outstripped the bed capacity and the country had to move to the decentralized approach to the transfer of responsibility for treating MDR-TB patients to lower levels of care. Infection Control (IC) is one of the requirements for decentralised MDR-TB care. The objective of the study is to conduct operational evaluations of IC in identified MDR-TB decentralized facilities.

Intervention or response: A cross-sectional descriptive study of 56 decentralized MDR-TB facilities was conducted from October 2014 to March 2015 using a standard assessment instrument comprising of five categories (IC officer, fit testing, IC Policy, UVGI, N95 Respirators availability).

Results and lessons learnt: Analysis of the 56 clinics assessed revealed that 14 (25%) have IC officers; 0 (0%) have done fit testing for N95 Respirators; 2 (3, 57%) do have IC policies in place, 2 (3, 57%) have working UVGI lights and only 5 (8, 93%) have N95 respirators available. One facility implemented 4 of the 5 requirements (1, 79%); 1 implemented 3 of the five requirements (1, 79%); 1 implemented 2 of the five requirements (1, 79%) and 11 implemented 1 requirement (19, 64%) while 42 did not implement any of the requirements (75%). IC practices were poorly implemented in most of the facilities.

Conclusions and key recommendations: These findings demonstrate the need to improve infection control practices and avail resources in identified decentralized MDR-TB settings before MDR-TB decentralization can safely and effectively be implemented.

PC-1155-06 A comparative study of the design of two hospitals on the Cape Flats with regard to user risk of contracting TB

K Bingham¹ ¹University of Pretoria, Pretoria, South Africa. e-mail: kgbingham@gmail.com

Background: The incidence levels of Tuberculosis amongst the population of the Cape Flats, Cape Town, South Africa, is well documented. This area is served by 2 hospitals, viz. Khayelitsha and Mitchells Plain Hospitals, both having been designed from a similar architectural brief, but being markedly different in composition. One hospital is high-rise with mechanical ventilation, while the other is low-rise, being predominantly reliant on

natural ventilation, with only selected areas of mechanical ventilation.

Design/Methods: This study compares the architectural responses of the 2 facilities and the inherent risk of lung disease through air-borne infection due to these responses. The contextual environment, and its climatic conditions and prevailing winds are recorded and compared with the footprints and layouts of the 2 facilities, to assess the impact of external air-flow on the buildings. Selected floor plan layouts, spatial volumes, patient flow, and the design of public-staff interfaces are considered, as well as the intervention of forced draught ventilation and directional air flow. This is weighed against the design of room fenestration and the provision of natural ventilation, and the inherent uncertainty that this brings.

Results: The mechanically ventilated areas, where extraction is provided near to areas of infection risk, allows for the least risk to staff and visitors. Where provision has been made for natural ventilation, the effect of the external environment has an adverse effect of air-flow patterns within the facilities, negating the design intentions of mechanical systems and producing the risk of infection to others, particularly in hot climatic conditions.

Conclusion: Mechanical ventilation and effective differential pressure zones are essential in all health facilities where there is the risk of infection through air-borne diseases. Uncontrolled natural ventilation adds to the risk of infection.

PC-1156-06 Establishment of a TB infection control demonstration site and training base for better TB control in Tajikistan

Z Tilloeva,¹ O Bobokhojaev,² A Trusov,^{1,3} A Hovsepyan,^{1,4} J Ismoilova,¹ T Alieva² ¹Project HOPE, Dushanbe,

²Republican TB Center, Tajikistan, Dushanbe, Tajikistan;

³Project HOPE, Milwood, VA, USA; ⁴Project HOPE, Yerevan, Armenia. Fax: (+992) 372 273629. e-mail:

ztilloeva@gmail.com

Background and challenges to implementation: Tajikistan is one of the 27 WHO high multidrug resistant (MDR) TB burden countries with one of the highest levels of TB prevalence in WHO Europe region. MDR cases account for 13% of new and 54% of retreatment TB cases (2011). Within this poor epidemiological situation, the lack of proper institutional capacity to adequately address TB infection control (IC) at health care facilities (HCFs) is putting health care workers (HCWs), patients, and caregivers at serious risk of TB and threatening the sustainability of TB control efforts.

Intervention or response: The Ministry of Health designated Macheton TB Hospital as the National TB IC Demonstration Site and Base for Training. A theoretical and legal assessment was conducted by reviewing existing guidelines, MoH orders and relevant documents. Training packages were developed. The program conducted TB IC risk assessments in pilot HCFs and results were discussed during the trainings. A national team of 14 trainers was established who further

rolled out 5 cascade trainings for 61 HCWs from 17 pilot sites. TB IC plans were developed during the trainings and further implemented in HCFs. A survey on TB status of HCWs was conducted by screening 3,853 HCWs for TB symptoms with further TB testing of those suspected for TB. The first regional TB IC training was conducted for 15 NTP representatives from Central Asia Republics (CAR).

Results and lessons learnt: Monitoring visits to pilot sites showed considerable improvement in TB IC practices in all areas. All 17 target HCFs have IC focal person appointed 15 had established IC committees and started implementation of TB IC plans 12 are monitoring IC plan implementation Burden of TB among HCWs was documented: 85% (3853 out of 4547) of HCWs were screened for TB 86% (122 out of 142) of HCW from those screened were identified as TB suspects were further tested for TB and 11 TB cases were detected

Conclusions and key recommendations: The program results provide evidence on the successfulness of this approach in documenting the magnitude of the TB burden at HCFs, establishing effective practices for TB IC, and building national and regional interest to propagate these advances. The program approach should be further expanded to cover the whole country to contribute to the establishment of effective TB IC control practices in Tajikistan, with high potential to be replicated in CAR.

PC-1157-06 Improving TB infection control in Odesa, Ukraine

S Yesypenko,^{1,2} A Aleksandrin,¹ M Dolynska¹ ¹USAID Strengthening Tuberculosis Control in Ukraine Project, Kyiv, ²Regional Central TB Hospital, Odesa, Ukraine. e-mail: mdolynska@stbcu.com.ua

Background and challenges to implementation: The Odesa oblast (region) of Ukraine demonstrates the country's highest tuberculosis (TB) incidence rate – almost twice as high as the national average (98.2 vs. 59.5 per 100 000). As a result, the regional health care facilities providing TB care are often overstretched. Facilities are housed in outdated buildings which make large-scale renovation to facilitate infection control (IC) challenging, and a shortfall of health service funding seriously limits environmental control and individual protection. This leads to a significant risk of occupational TB in such facilities. Between 2008 and 2012, 23 employees of the local TB services contracted TB.

Intervention or response: Since 2012, the USAID Strengthening Tuberculosis Control in Ukraine project has been providing education to health care practitioners and administrators on cost-effective TB IC interventions. Following the project's suggestions, the managers of the Odesa Central TB hospital established proper patients' flow and ensured a strict separation of smear and culture-positive patients, and patients with MDR and XDR-TB. Layouts of the premises were revised to concentrate high-risk zones and minimize patient's interaction. As mechanical ventilation was not accessible in the facility,

facility specialists, after consultations with the project experts, provided all wards and areas where aerosol-producing procedures are being performed (bronchoscopy, sputum collection etc.), waiting rooms, and X-ray departments with shielded UV-radiators. Now doctors and nurses also insist on proper use of natural ventilation and keeping windows open, as weather permits.

Results and lessons learnt: In 2014, no new TB cases were registered among employees of Odesa's central TB hospital.

Conclusions and key recommendations: Inexpensive and easy-to-implement measures are effective in the prevention of occupational TB, which is a principle indicator of proper TB IC. A safe medical environment is achievable even with limited funding.

54. TB and nutrition

PC-1158-06 Role of nutritional support in improving treatment outcomes among MDR-TB patients: experience of the Damien Foundation

S Mugudalabetta,¹ S K Muthusamy,¹ L Gujral,¹ S Satheesh¹ ¹Damien Foundation India Trust, Chennai, India. Fax: (+91) 44 2836 0496. e-mail: admin@damienfoundation.in

Background and challenges to implementation: Multi Drug Resistant Tuberculosis (MDR-TB) is closely linked with poverty and under nutrition. Many patients cannot afford to have adequate food due to loss of income and catastrophic health expenditures. There is very limited evidence available to suggest that nutritional support in addition to standard MDR-TB treatment, improves treatment adherence and outcomes.

Intervention or response: Damien Foundation is providing nutritional support worth 6 USD to poor and needy MDR-TB patients in the form of rice, wheat, cereals, egg, cooking oil etc once in two months till completion of treatment. In 2012, nutritional support was given to 51 MDR-TB patients in south west Delhi and six districts of South Andhra Pradesh in India. Treatment outcomes for those who received nutritional support along with those who didn't was retrieved from MDR-TB register and analyzed.

Results and lessons learnt: In 2012, 206 MDR-TB patients were registered for treatment in South West Delhi and six districts of South Andhra Pradesh. Among them 51 (25%) patients were identified and received nutritional support. Analysis of treatment outcomes showed higher treatment success rate of 74.5% (38/51) among those who received nutritional support along with standard MDR-TB treatment compared to 39% (61/155) among those who received only standard MDR-TB treatment. Only five patients (10%) who received nutritional support were lost to follow up compared to 48 patients (31%) among those received only standard treatment. Number of MDR-TB patients Treatment success loss to follow up other outcome Received

nutritional support with Standard MDR-TB treatment 51 38 (74.5%) 5 (10%) 8 (15.5%) Only standard MDR-TB treatment 155 61 (39%) 48 (31%) 46 (30%) Total 206 99 (48%) 53 (25.7%) 54 (26%)

Conclusions and key recommendations: Providing nutritional support in addition to standard MDR-TB treatment for patients is likely to motivate them to complete treatment and reduce the default rate.

PC-1159-06 A holistic approach to TB prevention and care: a study in Jabalpur MP, India

A Kollamparampil,¹ P Varghese,¹ M Puthenchirayil,¹ G Singh,¹ R Mathew,² B Entoor Ramachandran,³ R Babu³
¹Catholic Bishops' Conference of India-Coalition for AIDS and Related Diseases (CBCI-CARD), Delhi, ²Norbetine Social Welfare Centre (NSWC), Jabalpur, ³International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. e-mail: abhileshcbc@gmail.com

Background and challenges to implementation: Many TB patients in India are not able to complete their treatment because of lack of motivation and support system. Decentralisation of care along with counseling helps the patient to complete the treatment. Nutrition is also a very important component for successful treatment of tuberculosis. Normally TB patients in vulnerable and marginalised areas, work on daily wages. It becomes difficult for them to earn their daily living and as a consequence, having nutritious food along with TB treatment becomes impossible for them. Catholic Bishops Conference of India Coalition for AIDS and Related Diseases (CBCI CARD) a sub recipient of Global Fund is implementing a community based project for TB prevention & care with support from The Union. The project is being implemented in 29 districts across 4 states of India. Norbetine social welfare centre (NSWC) is a partner NGO with CBCI CARD Project Axshya in Jabalpur in Madhya Pradesh India.

Intervention or response: (NSWC) implementing community based activities in Jabalpur in Madhya Pradesh India. Jabalpur covering a population of 2 591 552. The major population consist of bidi workers, slum population or living in remote villages. The main interventions made by NSWC are involving motivated community members as DOT providers, nutritional supplementation to poor TB patients with food from their farms, collection from schools and other sources. NSWC offers counselling, treatment, care, and treating patients with dignity and honour. The centre describes this as a comprehensive holistic approach to TB prevention and care.

Results and lessons learnt: NSWC in the last 8 years has groomed 180 community DOT providers and has successfully treated 650 patients. Special care and attention to those families with package of TB services, minimized the lost to follow up to treatment and death due to TB

Conclusions and key recommendations: The performance of NSWC shows that when DOTS therapy is accompanied by professional counselling, nutritional

supplementation, individualized approach and dealing patients with dignity and honour, success of the treatment is enhanced significantly.

PC-1160-06 Severe malnutrition impairs treatment response among India's initial MDR-TB cohorts

M Parmar,¹ K S Sachdeva,² K Rade,^{1,2} P Darsini,³ R Pant,⁴ A Sreenivas,¹ P Dewan⁵ ¹World Health Organization Country Office for India, New Delhi, ²Central TB Division, MoH FW, Government of India, New Delhi, ³National Institute of Research in Tuberculosis, Chennai, ⁴GD Goenka World Institute, Gurgaon, ⁵Bill & Melinda Gates Foundation, New Delhi, India. e-mail: parmarm@searo.who.int

Background: Globally, India has world's highest burden of multidrug-resistant tuberculosis (MDR-TB). As rapid scale-up of Programmatic Management of Drug resistant Tuberculosis (PMDT) continues in India, initial cohort analysis revealed low body mass index and weight loss during treatment as few factors associated with non-conversion of sputum culture and poor treatment response. Further analysis was undertaken to evaluate the effect of severe malnutrition on treatment response in MDR-TB patients treated under India's PMDT programme.

Methods: Retrospective cohort analysis of MDR-TB patients diagnosed among failures of first-line treatment, registered in the national PMDT programme and treated with a standard 24-months regimen under DOT from 2007 – 2010, was done. Data on patient's height, weight, clinical and microbiological response were collected; sputum conversion and treatment outcome were defined by standard WHO definition. Logistics regression model was used to determine the risk of BMI on various treatment outcomes.

Results: Among 3713 (88%) of MDR-TB patients registered from Aug2007 – Mar2011, 2066 (56%) had some degree of malnutrition with 1314 (35%) showing severe acute malnutrition (BMI < 16). Proportion of patients with sputum culture conversion at 4th month was higher among those with BMI > 18.5 than those with BMI < 16 (69% vs.59%, $P = 0.001$) while at 6th month also this difference was statistically significant (63% vs. 56%, $P = 0.001$). Patients with BMI < 16 had two times higher risk of being sputum culture positive at end of 6 months of treatment (OR 2.21, 95%CI 1.84 – 2.74, $P < 0.0001$). Among the 1314 severely malnourished patients, treatment outcome was available for 796 patients; of whom 225 (28%) had treatment success, 239 (30%) had unfavourable response as default or failure while 332 (42%) died. Among 961 patients with BMI < 18.5, 393(41%) had treatment success 364 (38%) had unfavourable response while 204 (21%) died.

Conclusion: Severe malnutrition delays sputum culture conversion and hence risk of transmission is longer and higher compared to well-nourished MDR-TB patients. Treatment success is almost halved and death rate doubled in severe malnourished MDR-TB patients as compared to the well-nourished. Nutritional intervention to improve MDR-TB patient's response to treatment

will thus have a crucial role achieving the goals of End TB Strategy.

PC-1161-06 Role of nutrition status in multidrug-resistant tuberculosis conversion

N Librianty,¹ D Soepandi,¹ D Handayani,¹ A Fuady¹

¹Faculty of Medicine University of Indonesia, Jakarta, Indonesia. e-mail: librianty@gmail.com

Background: Recently, the burden of TB problem were emerged by MDR-TB, WHO estimate there will be 480 000 new cases of MDR-TB worldwide in 2013 and Indonesia were be in ranks tenth among high MDR-TB burden countries. The outcomes of MDR-TB was quite low with success rate was only 48%. Many factors associated with culture conversion in MDR-TB treatment including nutrition status. Nutrition was one of modifiable factor, so it was important to evaluate nutritional status among MDR-TB patients.

Design/Methods: A retrospective cohort study among patient treated with standardized MDR-TB regimen between August 2009 and December 2013 in Persahabatan Hospital. The outcomes of this study are conversion time and association of BMI and HB level with conversion time and other factors. Data were analyzed using Kaplan-Meier curves and cox regression analysis. Ethical clearance was approved by the ethical committee of Faculty of Medicine Universitas Indonesia.

Results: There are 600 patients between August 2009 and December 2013 and 436 patients included in this study. Two hundred fifty six patients (58.7%) had culture conversion at two months. Univariate analysis showed underweight patients with BMI ≤ 18.5 kg/m² [aHR 0.707; 95%CI 0.575-0.870] and anemia [aHR 0.716; 95%CI 0.587-0.847] had associated with longer culture conversion. Even in multivariate analysis, only underweight patients [aHR 0.792; 95%CI 0.637-0.983] that consistently had long time conversion. We also found obese patients with BMI ≥ 25 kg/m² [aHR 1.616; 95%CI 0.882-2.959] had shorter conversion time compared to patient with normal weight. Other factors for longer culture conversion were female [aHR 0.808; 95%CI 0.659-0.991], cavity on chest radiograph [aHR 0.781; 95%CI 0.634-0.961], high bacterial load [aHR 0.701; 95%CI 0.501-0.979], previous second line TB drugs [aHR 0.597; 95%CI 0.415-0.858], resistance with second line TB drugs [aHR 0.486; 95%CI 0.305-0.776], and lower lymphocytes count [aHR 0.681; 95%CI 0.524-0.885].

Conclusion: Nutrition status will affect culture conversion among MDR-TB patients.

PC-1162-06 Is food support for malnourished TB patients associated with treatment outcomes? TB case mortality in Kenya

J Njenga,¹ A Wairia,^{1,2} B Mungai,¹ F Ngari,² E Masini,² M Maina,³ P Agunga¹ ¹Centre for Health Solutions - Kenya, Nairobi, ²Ministry of Health, Kenya, Nairobi, ³USAID Kenya, Nairobi, Kenya. e-mail: jnjenga@chskkenya.org

Background: Malnutrition is a major cause of morbidity and mortality in many settings and nutrition therapy aims at reducing the risk of death (WHO). In Kenya, national TB program recommends nutrition support to TB patients who are severely or mildly malnourished (BMI <18.5). A number of organizations have been providing food supplements and food items to TB patients who meet the set criteria in the course of their treatment. While modality and frequency of this support varies, there is little evidence whether it improves treatment outcomes for malnourished TB patients. The aim of the study was to assess the impact of nutritional support on mortality among TB patients in Kenya.

Design/Methods: We compared the risk of death among eligible TB patients receiving food support with that of eligible patients receiving no food support. We controlled for sex, HIV status, ART uptake, TB type, patient type, facility type and severity of malnutrition (severe malnutrition, BMI <16 and mild malnutrition, BMI between 16 and 18.5). Data were abstracted from the national electronic surveillance system, TIBU, for all patients started on TB treatment between January 2012 and December 2013 and who had treatment outcome assigned and their BMI was between 12.0 and 18.5. Only patients 15 years and above were included in the analysis.

Results: Of 66 093 patients with BMI between 12.0 and 18.5, 23 816 (36.0%) received food support. Overall mortality among these patients was 7.0% with 8.7% of patients who received food support and 6.1% of those who did not receive food support dying in the course of TB treatment. Unadjusted odds of dying for patients who received food were 45% (95%CI 36.5% to 54.0%) more than those of patients who did not receive food support. Adjusting for facility type, sex, TB type, patient type, HIV status, ART status and severity of malnutrition, the odds of dying for patients on food support were 23% (95%CI 15.6% to 30.9%) more than those of patients not on food support. Severity of malnutrition was an important factor with patients severely malnourished being 73.1% (95%CI 62.7 to 84.2) more likely to die than patients mildly malnourished. Further analysis showed that 36.0% of malnourished (mild and severe) and 8.5% of patients with normal to obese BMI received food support and these proportions were statistically significantly different, $P < 0.0001$. Mortality among patients with normal to obese BMI stood at 4.6% and was statistically significantly lower than that of malnourished patients, $P < 0.0001$.

Conclusion: While there is evidence that food support is being provided to deserving patients based on BMI, the support does not translate into reduction of mortality among the targeted patients. The national TB program

needs to assess the practices associated with food support to TB patients in terms of frequency, timing, and quantity and design other complementary interventions targeted at the malnourished patients in order to reduce mortality among this group.

PC-1163-06 Does nutrition support during TB treatment improve TB treatment outcomes in Kenya?

M Mang'ut,¹ B Ulo,¹ F Ngari,² M Okoth,¹ M Mungai,¹ R Wambu,² E Masini,² T Kiptai¹ ¹AMREF Kenya, Nairobi, ²Ministry of Health, Nairobi, Kenya. e-mail: temkomangut@gmail.com

Background and challenges to implementation: Under-nutrition is a risk factor for progression from TB infection to active TB disease and is a predictor of increased risk of death and TB relapse. In turn TB can lead to undernutrition. Adequate nutrition interventions during TB treatment could improve treatment outcomes in malnourished TB patients. In Kenya, despite TB and under nutrition affecting more men than women, no specific facility based nutrition programs focus on men. Currently, Global fund TB through AMREF Kenya support 69% of severely malnourished TB patients. We sought to understand the relationship between food support and treatment outcomes.

Intervention or response: January to December 2013 data for TB patients notified in TIBU, a case based electronic system, was extracted. Analysis excluded patients with invalid Body Mass Index (BMI). Descriptive statistics were used to quantify proportions of patients by sex, patient type, BMI, TB-HIV co-infection, Anti- Retroviral Therapy (ART) and duration to TB treatment outcome against food support received or not. Logistic regression was done to determine significance of relationship between food support and death and food support and out of control.

Results and lessons learnt: Out of 89 760 patients notified from 3052 TB sites, 69.8% (62 642) had valid BMI recorded at admission. A total of 9458 (4636 females and 4822 males) patients received food support. Of the 27 870 (45.5%) with BMI <18.5, 10 391 (37.3%) had BMI ≤16.0. Among those who received food, 17.8% (1686) died and 4.5% (424) were out of control. Among those who did not receive food, 5.4% (3665) died and 5.5% (3744) were out of control. Treatment completion was at 50% in each of the two categories. Higher death rates among those who received food was observed among TB-HIV co-infected at 70.6% (1217) compared to 55.2% (2060) among those who did not. Of the 29 090 with outcome date between 0 and 4 months of TB treatment 44.9% (4505) died among those who received food and 39.3% (3584) were out of control among those who did not receive food. Those who received food were 1.5 times ($P < 0.0001$) more likely to die than those who did not, while those who did not receive food were 1.2 times ($P < 0.0001$) more likely to get out of control.

Conclusions and key recommendations: Death rate was higher among those who received food and out of control was higher among those who did not. Late initiation of nutrition interventions leads to poor treatment outcomes of out of control and death. Nutrition assessment and documentation are key for TIBU data to be useful for decision making.

PC-1164-06 Assessing the impact of nutritional support on multidrug-resistant tuberculosis patients in Kenya

R Kiplimo,¹ R Wambu,¹ H K Kipruto,² E Masini¹ ¹National Tuberculosis, Leprosy and Lung Disease Program, Nairobi, ²World Health Organization, Kenya, Nairobi, Kenya. e-mail: kiplimorichard@gmail.com

Background: Optimal nutrition is essential for achieving and preserving health for everyone. Food and nutrition thus play important roles in care and mitigation of infections and their effects. The Kenyan DR-TB management model provides both patient and nutritional supports to its MDR patients. However, treatment outcomes of Multi-Drug Tuberculosis (MDR-TB) still remain generally poorer compared to outcomes for drug sensitive disease patients. Among the risk factors associated with the poor outcome are malnutrition and HIV. This paper sought to establish the overall impact of the nutritional support provided.

Design/Methods: This was a retrospective study of MDR-TB cases notified to the National program from 2011 to 2013 had been evaluated. Descriptives of the data were obtained and later univariate analyses (χ^2) and multiple logistic regression were performed to determine the association between the food support and the outcome and effect of risk factors.

Results: A total of 371 MDR cases were included in the analysis. A cure rate of 62%, treatment success rate of 81% and death rate of 12% were obtained. While about 60% of the patients are either moderately malnourished (31%) or severely malnourished (27%), only 44% of the patients received food support. Among the HIV positives, 30% received food support. Food support is strongly associated with outcome of MDR patients ($\chi^2 = 29.793$, $P = 0.000$). In reference to out of control outcome, Patients who received food support are 3 times more likely to have an outcome of cured while HIV positive patients are 2 times more likely to have an outcome of cured.

Conclusion: Food support and HIV status are indicators that influence treatment of DR-TB patients both positively and negatively. The support provides a platform for continued communication which encourage patients to move on.

PC-1165-06 Food parcels and adherence to TB treatment

A Niyazov,¹ A Trusov,¹ E Kukhranova,¹ A Duishekeeva¹
¹Project HOPE, Bishkek, Kyrgyz Republic. e-mail: aniyazov@projecthope.org

Background and challenges to implementation: The incidence rate of tuberculosis in Kyrgyzstan in 2014 was 109.5 cases per 100 000. Factors contributing to retaining high rate of TB incidence in Kyrgyzstan are a high level of poverty, active external and internal migration of migrants with TB, and restricted access to health services for high-risk groups (ex-prisoners, drug and alcohol abusers, homeless people) as well as low level of government investments in health care. The majority of TB patients are from high-risk groups, poor and unemployed. In order to seek a better life, TB patients move to other countries and often quit TB treatment. Default rate has varied from 4% to 7% over the last few years.

Intervention or response: To ensure better adherence to TB treatment for patients in the continuation phase of treatment, it was proposed to motivate the patients by distributing free Food Parcels at places they receive their medication. The Project Hope team jointly with NTP medical staff developed the system of distribution of food parcels. TB patients sign an agreement with the medical facility to participate in the program with a commitment to continue TB treatment until their treatment is completed. Food parcels are distributed once a month. The content of food parcels include: rice-1kg, pasta- 1 kg, granulated sugar-1 kg, dry milk – 1 kg, vegetable oil – 1 liter, black leaf tea- 250 gr. Overall in 2014 the absolute number of patients participating in the food distribution program was 4916 from the 6095 patients on treatment. Selection criteria was based on the phase of treatment (continuation phase), treatment with first line drugs, New Cases, Relapses, Previously treated (Re-treatment cases) and patients with extra pulmonary TB. In order to get food parcels TB patients should not miss more than 5 doses of treatment in a month. Otherwise they will not receive food parcels.

Results and lessons learnt: The default rate between patients participating in the program (1.3%) was significantly lower than among those who didn't participate in program (26,5%) and the total default rate of 6,2%. The majority 57% of defaulters are people who migrate to another country (Russia), 23% - alcoholics, 6%- drug addicted, 2% - homeless, 2% - due to religious beliefs, 3% - due to side effects, 2% - due to stigma.

Conclusions and key recommendations: Distribution of food parcels for TB patients contributed to good adherence to TB treatment.

55. Molecular epidemiology and modelling: how can we break the cycle of transmission?**PC-1166-06 Molecular epidemiology of tuberculosis in Havana, Cuba, 2009**

A González Díaz,¹ T Battaglioli,² R Díaz,³
 R Goza Valdés,³ E Gonzalez Ochoa,¹ P Van Der Stuyft^{2,4}
¹Institute of Tropical Medicine Pedro Kourí, Havana, Cuba;
²Institute of Tropical Medicine, Antwerp, Belgium; ³Institute of Tropical Medicine Pedro Kourí, Havana, Cuba; ⁴Ghent University, Ghent, Belgium. e-mail: tbattaglioli@itg.be

Background: The objective of the study was to estimate the proportion of tuberculosis cases attributable to recent transmission and the risk factors possibly associated with tuberculosis clustering.

Design/Methods: Population-based study combining information from epidemiological investigation of tuberculosis cases notified to the national tuberculosis control program in Havana, Cuba, in 2009 with the results of genotyping of *Mycobacterium tuberculosis* isolates with variable-number tandem-repeat of mycobacterial interspersed repetitive units (MIRU-VNTR) typing.

Results: Out of 186 cases, 61 were genotyped: 33 patterns and 5 clusters with 19, 7, 3, 2 and 2 cases were found. The index of recent transmission was 45% (95% confidence interval 33%-58%). Routine contact investigation failed to identify a substantial number of epidemiological links. A history of living in a closed setting was strongly associated with clustering.

Conclusion: The index of recent transmission in Havana in 2009 is high. The existing control measures in closed settings should be strengthened. A study on a larger number of cases and for a longer time period should be carried out to get more precise estimates. Further studies on the utility and cost-effectiveness of the addition of molecular epidemiology techniques to support the progress towards tuberculosis elimination in Cuba, a low incidence resources-limited setting, are also needed.

PC-1167-06 A bacterial perspective on tuberculosis in West Africa

F Gehre,^{1,2} S Kumar,¹ L Kendall,² M E Kitata,³ E Abatih,¹
 M Antonio,² D Berkvens,¹ B De Jong¹ ¹Institute of Tropical Medicine, Antwerp, Belgium; ²Medical Research Council Unit, Fajara, Gambia; ³University of Gondar, Gondar, Ethiopia. e-mail: fgehre@itg.be

Background: West Africa, with a high burden of undetected TB, is known to harbour the greatest strain diversity worldwide, although the mycobacterial population structure has yet to be elucidated on a regional scale. Understanding TB epidemics from a bacterial point-of-view, however, is essential for a "Systems Epidemiology" approach to TB control, combining classic epidemiology with host studies and knowledge on genetic diversity of bacterial populations. Method We collated novel and published genotyping data and classified these into mycobacterial lineages and families,

followed by longitudinal and phylogeographic analyses using statistical tools and GenGIS.

Results Among 3580 isolates from 12 countries, we identified 6 lineages (L) comprising 32 families, with 91% of infections caused by *Euro-American* (L4) and *M. africanum* families (L5 and L6). We demonstrated statistically significant phylogeographic separation of families and that TB due to *M. africanum* West Africa 2 remains a persistent health concern.

Conclusion The unequal distribution of highly transmissible or resistance-prone mycobacterial families is important, as various health systems face different public health challenges. From a study design perspective, vaccine trials and bacterial geno/phenotype association studies require high strain diversity and such studies would preferably be conducted in Western West Africa, while low strain diversity is advantageous for host genetics and studies may be better suited for Eastern West Africa. Our study contributes pathogen information to systems epidemiology-based TB control, and serves as important resource for the design of future large scale clinical trials in West Africa.

PC-1168-06 A longitudinal study of the continued transmission of *Mycobacterium tuberculosis* in eastern rural China

B Xu,¹ L Wu,¹ W Jiang,¹ Q Zhao,¹ Y Hu¹ ¹School of Public Health, Fudan University, Shanghai, China. e-mail: bxu@shmu.edu.cn

Background: The present study aimed to investigate the distribution of *Mycobacterium tuberculosis* which was persistently transmitted in local population at a period of 8 years, and to explore socio-demographic and clinical factors affecting the competition and survival of *M. tuberculosis* strains.

Design/Methods: The study was carried out in two rural counties of eastern China during 2005-2012. All registered TB patients received bacteriologic-based TB diagnosis. Spoligotyping was used to define the lineage of *Mtb* isolates, and 24 loci MIRU-VNTR was applied for *M. tuberculosis* genotyping. Based on Middelkoop and her colleagues' study, persistently successful strains were defined as strains that had been present for at least 2 consecutive years and were still present in 2012 (persistence), and had ≥ 2 cases/year; transiently successful strains were strains that did not necessarily persist to 2012 but occurred for at least 2 consecutive years with a cluster density of ≥ 2 cases/year in the consecutive period; unsuccessful strains were clustered strains did not fall into these two groups, and singleton strains. Univariate and multivariate binary logistical regression analysis were applied to identify factors associated with strain success.

Results: Of the 982 *M. tuberculosis* isolates, 793 (80.8%) belonged to the Beijing family. It was found that 666 isolates (67.8%) showed a unique MIRU-VNTR genotype, while 316 isolates (32.2%) shared genotypes in 104 clusters. The size of cluster ranged from 2 to 15 isolates, and the median of cluster density was 1.4

cases/year. Of the 316 clustered isolates, 36 (11.4%) were defined as persistently successful strains, 74 (23.4%) were transiently successful and 198 (62.7%) were unsuccessful strains. Persistently successful strains were less likely to be resistant to first-line anti-TB drugs compared with transiently successful strains (27.8%.vs. 50.0%; OR=0.179, 95%CI: 0.048-0.565, $P=0.002$) and unsuccessful strains (27.8%.vs.82.3%; OR=0.068, 95%CI: 0.019-0.122, $P=0.001$). However, the Beijing family strains were more likely being persistently successful strains (83.3%.vs. 60.8%; OR=2.328, 95%CI: 1.040-5.040, $P<0.001$).

Conclusion: The present study suggests that Beijing family strains play an important role in the persistent transmission. Although drug resistant isolates have yet been dominant in the persistently successful strains, its adaption with time should be concerned and monitored longitudinally.

PC-1169-06 Spoligotype profile of *Mycobacterium tuberculosis* complex strains isolated from pulmonary tuberculosis patients in Khartoum State, Sudan

A Elegail,¹ N Y Ibrahim Mohamed,¹

E O Mohamed Nour,¹ S Hoffner,² M Haile² ¹National Public Health Laboratory, Khartoum, Sudan; ²Public Health Agency of Sweden, Solna, Sweden. Fax: (+46) 8 301 797. e-mail: melles.haile@folkhalsomyndigheten.se

Background: Aim of this study was to characterize specific genotypic lineages of *Mycobacterium tuberculosis* (MTB) strains circulating among patients with pulmonary tuberculosis (PTB) in Khartoum, Sudan. Tuberculosis is an infectious disease caused by *M. tuberculosis*. In this study DNA from a total of 120 *M. tuberculosis* strains isolated 2007 - 2009 were sent from NRL in Khartoum, Sudan for EQA to WHO SRL Stockholm. Confirmation DST results and mutation analysis for EQA were performed for all 60 MDR and 60 non-MDR strains.

Design/Methods: Data was collected consecutively from sputum smear positive patients from selected NTP diagnostic centers in Khartoum during the period 2007-2009. Species identification and drug resistance was done using biochemical tests/DNA methods and conventional culture technique respectively at NRL. Confirmation DST was done using LPA and molecular epidemiology by Spoligotyping to determine genetic diversity and susceptibility profiles of isolates circulating in Sudan.

Results: A total of 120 DNA from *M. tuberculosis* strains were studied using Spoligotyping. This revealed a total of 112 patterns from which 4 patterns represented clustered isolates with a total of 105 (88%) of the strains. In this study, the CAS1 Delhi/family was the predominant shared type detected in 61 isolates (51%), where 25 of the strains were MDR and 36 strains were susceptible. It was followed by H3/family with 19 (16%) strains, and 11 strains with LAM3/family, 14 strains with T2/T1/family type and 2 strains each with Beijing type and S

family. One isolate of these where not yet defined in the SpolDB and therefore regarded as orphan.

Conclusion: The observation obtained using spoligotyping from the Sudanese patients reflects in comparison to the global distribution highly diverse clades circulating in the country. The CAS1 Delhi/family was the predominant shared type detected in 61 isolates followed by H3/family with 19 isolates, and 11 isolates with LAM3/family, 14 isolates with T2/T1/family type and 2 isolates each with Beijing type and S family. We found 35 of the isolates were not available in the SpolDB database but was found as family in our database. These groups visually reflected some patterns similarities therefore included in the family group closely related. In general the study could not see any significant difference between MDR and non-MDR isolates within the clade types. Even though study material was limited it indicates that there exist active transmission of certain spoligotypes.

PC-1170-06 Role of stochasticity in reaching the 2025 global targets

G Huynh,¹ M Roh¹ ¹Institute for Disease Modeling, Bellevue, WA, USA. e-mail: ghuynh@intven.com

Background: Recently, the World Health Organization developed the End TB Strategy, with a milestone of 75% reduction in TB deaths and a 50% reduction in TB incidence from 2015-2025. Stochastic fluctuations in the intrinsic TB disease dynamics will affect the potential impact of new interventions and the probability of reaching the goal by 2025.

Design/Methods: We developed a stochastic model of TB transmission in China to estimate the probability that China will achieve the 2025 milestones if new interventions are introduced, including improving treatment quality and reducing the time to treatment. We consider how stochasticity affects the probability of maintaining the TB burden below the goal level beyond 2025, both at the individual community level and the aggregated country level. We also explore how the stochastic effects vary within a plausible range of community sizes.

Results: Stochastic variation increases the time needed for the incidence to stabilize after the intervention is implemented; thus, compared to deterministic estimates, more aggressive TB control is necessary to achieve the incidence goal with 50% probability. In contrast, because the mortality goal is small relative to the population size, stochastic fluctuations increase the probability of achieving the goal even with less aggressive TB control. Stochasticity decreases the probability any single community maintains the TB burden below the goal levels after 2025, but increases the probability the entire country stays below the goal.

Conclusion: Stochasticity at the community level contributes significant variability to the observed impact of new interventions. This can result in dramatic deviations from the deterministic mean when considering many communities in aggregate. In China, our model suggests that stochastic effects will increase the probability of achieving the mortality goal but decrease the probability

of achieving the incidence goal. These stochastic effects should be taken into account when estimating how new interventions might reduce overall TB burden, both in pilot studies and in the field.

PC-1171-06 A novel regression-based tool to improve estimates of the proportion of tuberculosis incidence due to recent transmission in settings of sparse data

P Kasaie,¹ B Mathema,² W D Kelton,³ A Azman¹ J Pennington,¹ D Dowdy¹ ¹Johns Hopkins University, Baltimore, MD, ²Columbia University, New York, NY, ³University of Cincinnati, Cincinnati, OH, USA. e-mail: pkasaie@jhu.edu

Background: In developing public health responses to tuberculosis (TB) epidemics, it is often important to estimate the proportion of active TB cases that result from recent infection versus reactivation ("recent transmission proportion"). This is traditionally done with molecular epidemiological data (e.g., DNA fingerprinting), but the traditional ("n-1") method for converting these data into estimates of recent transmission carries substantial bias.

Design/Methods: We developed a stochastic, individual-based simulation model of a TB epidemic that links the "true" (simulated) recent transmission proportion to the molecular clustering pattern that would be observed. We then carried out a set of controlled simulation-experiments across a variety of epidemiological settings ("derivation set") to develop an improved, user-friendly tool for estimating the recent transmission proportion as a function five inputs: underlying TB incidence, sampling coverage, study duration, clustered proportion of observed cases, and proportion of observed clusters in the sample. We compared the performance of this tool (including a simple and a more comprehensive regression model) against the traditional 'n-1' model, and validated the findings using an independent set of simulation experiments ("validation set").

Results: In the validation set, the regression tools reduced the absolute estimation bias (difference between estimated and true recent transmission proportion) in the 'n-1' technique by a median [interquartile range] of 60% [9%, 82%] and 69% [30%, 87%]. The bias in the 'n-1' model was highly sensitive to underlying levels of study coverage and duration and substantially underestimated the recent transmission proportion in settings of incomplete data coverage (Figure). By contrast, the regression models' performance was more consistent across different epidemiological settings and study characteristics. We provide one of these regression models as a user-friendly, web-based tool (<http://modeltb.org/recenttrans/>).

Conclusion: Novel tools can improve our ability to estimate the recent TB transmission proportion from data that are observable (or estimable) by public health practitioners and guide effective policies and interventions in settings where data are often incomplete and long studies are impractical.

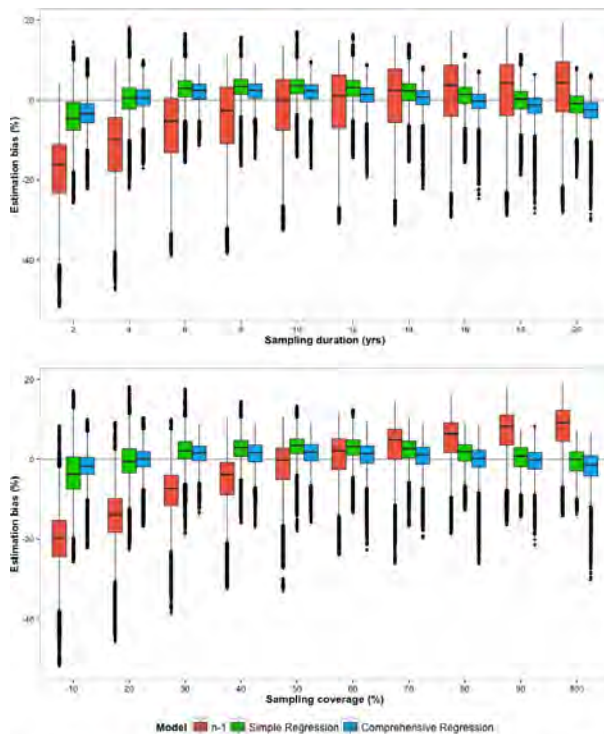


Figure: Estimation bias at different levels of study duration (top) and coverage (bottom). The y-axis presents the estimation bias [(estimated value – true value) × 100] in recent transmission proportion. The 'n-1' model tends to underestimate the recent transmission proportion at low levels of sample coverage (<50%) and study duration (<10 years), and begins to overestimate as coverage and duration are increased. The regression models are fairly robust to variation of study characteristics especially in settings of incomplete coverage and short study duration.

PC-1172-06 Individual and population-level effects of household exposure on tuberculosis transmission: a systematic review and meta-analysis

L Martinez,¹ Y Shen,¹ E Mupere,² A Ezeamama,¹ S Isaacson,³ A Kizza,¹ P Hill,⁴ C C Whalen¹ ¹University of Georgia School of Public Health, Athens, GA, USA; ²Makerere University, Kampala, Uganda; ³Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA; ⁴University of Otago School of Medicine, Centre for International Health and the Otago International Health Research Network, Dunedin, New Zealand. e-mail: leomarti@uga.edu

Background: Targeting locations where tuberculosis (TB) is likely to spread may open up entry points for interrupting transmission. Whether TB transmission is more likely to occur inside or outside the household at a population level is unclear but could assist in allocating resources in future active case finding efforts.

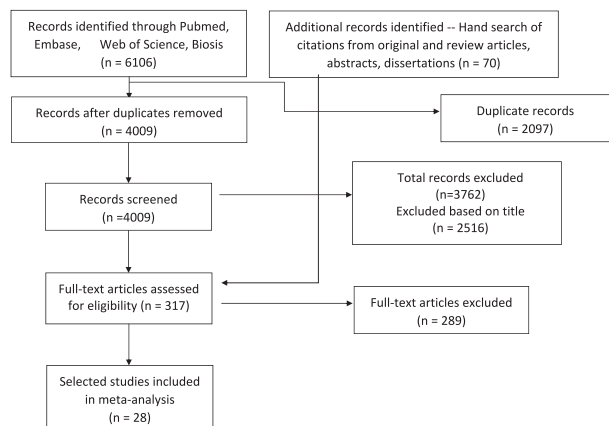
Design/Methods: We conducted a systematic review and meta-analysis on studies assessing latent TB infection in two groups: children exposed to a household member with TB and children without such exposure. Searches were conducted in multiple electronic databases. Children were used to represent recent infection and were defined as below 15 years of age. Household contacts and community controls had to be matched by age and location at a minimum. To investigate the individual impact of household exposure, we pooled odds ratios

with random-effects modeling and used stratification to investigate between-study heterogeneity. Estimating the population impact of household exposure on tuberculosis was completed by calculating prevalence ratios from randomly sampled studies and finding a population attributable fraction of household TB exposure from these studies. We used the established PAF formula, $PAF = P \text{ cases}[(RR-1) / RR]$, to calculate the population impact of household exposure.

Results: We identified 28 studies including 16 732 children exposed to TB in the household and 174 158 unexposed. Overall, children exposed to a contact with active TB in their households were 3.72 (95%CI 2.94 – 4.71) times more likely to acquire tuberculosis infection than their community counterparts. From ten studies that randomly sampled from the general population, we estimated that the PAF of transmission due to household exposure was between 11% and 15%.

Conclusion: A child exposed to tuberculosis in the household is at almost four times the risk of tuberculosis transmission compared to a child not exposed. Despite this, most TB transmission at the population level likely occurs outside the household.

Figure: Flow Diagram For Search and Selection of Included Studies



PC-1173-06 *Mycobacterium tuberculosis* transmission is associated with attendance at community gathering places in rural Malawi

P Khan,^{1,2} T Mzembe,¹ K Kranzer,² D Mulawa,¹ O Koole,^{1,2} K Fielding,² J Glynn,² A Crampin^{1,2} ¹Karonga Prevention Study/MEIRU, Karonga, Malawi; ²London School of Hygiene & Tropical Medicine, London, UK. e-mail: palwasha.khan@lshtm.ac.uk

Background: The majority of *Mycobacterium tuberculosis* transmission takes places outside the household in high burden settings. Community gathering places, including healthcare facilities, churches, funerals, markets and public transport in which crowding occurs, may be “hotspots” of *M. tuberculosis* transmission but their contribution to transmission is unclear. Identifying incident *M. tuberculosis* infection in children < 5 years can be used as a sentinel of infectious adult tuberculosis in the community.

Design/Methods: Study hypothesis: Children who attend gathering places are at increased risk of *M. tuberculosis* infection compared to children who do not. Setting: Demographic surveillance site (DSS), northern Malawi. Design and procedures: Eligible children aged < 5 years resident in the DSS were enrolled in a tuberculin skin test (TST) cohort. Children with an induration of < 10mm in the baseline TST survey were retested one year later to identify incident MTB infection. Guardians of children were interviewed to assess the child's attendance at gathering places in the preceding year. Incident infection was defined as TST conversion with an increase of at least 10mm from < 10mm to $\geq$ 10mm between rounds. **Results:** 5537 children were eligible, of whom 4967 (90%) had a baseline TST result. To date, 2267 children have had repeat TST, contributing 3334 person-years. 109 children converted from <10mm to $\geq$ 10mm with an increment of $\geq$ 10mm between rounds, giving an estimate of MTB infection incidence of 3.3 per 100 person-years. Data on attendance at gathering places is available to date for 1242 children (2238 person-years), of whom 73 TST-converted. After adjusting for age, sex, household socioeconomic status and population density, the odds of incident MTB infection were increased in children who had attended church more than 4 times in the last year compared to children attending less often (adjusted OR [aOR] 3.6, 95%CI 1.2-11.1); in those who visited a healthcare facility at least once in the year (aOR 3.1, 1.0-9.8) and in those travelling by minibus (aOR 1.8, 0.9-3.6); but not with visiting market places (aOR 0.9) or attending funerals (aOR 0.7).

Conclusion: Community gathering places that involve contact in confined spaces - church, healthcare facilities, and minibuses - but not outdoor gatherings were associated with incident MTB infection in children under-5 years in rural Malawi. These findings support the call for 'place-finding', in addition to targeted 'case-finding' in high burden settings.

Table. Crude and adjusted odds ratio for the association of attendance at various community gathering places and incident MTB infection in children aged <5 years.

Attendance at gathering place (reported no, within last year)	Incident infection n/N (row %)	Univariable ^a OR (95% CI) p value ^a	Adjusted for age, sex, household SES and population density ^b aOR (95% CI) p value ^a
Church			
<4 visits	6/207 (2.9)	1 0.07	1 0.01
≥4 visits	65/1016 (6.4)	2.5 (0.9 – 6.7)	3.6 (1.2 – 11.1)
Missing	2/20 (10.0)		
Healthcare facility			
None	8/241 (3.3)	1 0.08	1 0.02
≥1 visit	64/982 (6.5)	2.3 (0.9 – 5.9)	3.1 (1.0 – 9.8)
Missing	1/19 (5.3)		
Travel on mini-bus			
None	30/596 (5.0)	1 0.22	1 0.10
≥1 trip	42/627 (6.7)	1.5 (0.8 – 2.9)	1.8 (0.9 – 3.6)
Missing	1/19 (5.3)		
Market place			
None	43/711 (6.1)	1 0.68	1 0.80
≥1 visit	29/527 (5.5)	0.9 (0.5 – 1.6)	0.9 (0.4 – 1.8)
Missing	1/4 (25.0)		
Funeral			
None	62/983 (6.3)	1 0.16	1 0.37
≥1 visit	10/256 (3.9)	0.5 (0.2 – 1.3)	0.7 (0.3 – 1.8)
Missing	1/2 (33.0)		

^a Adjusted for household clustering

^b Likelihood ratio test

PC-1327-06 MDR-TB strains have an increased propensity to acquire PZA resistance in the context of DOTS-based chemotherapy

F Lanzas,^{1,2} P Karakousis,³ E Lopez,⁴ J Jurado,⁵ J Sacchettini,⁶ T Ioerger⁷ ¹Instituto Conmemorativo Gorgas de Estudios de la Salud, Panamá, ²Universidad de Panamá, Panamá, Panamá; ³Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁴Hospital Santo Tomás, Panamá, ⁵Hospital Manuel Amador Guerrero, Colón, Panamá; ⁶Texas A&M University, College Station, TX, USA. e-mail: flanzas11@gmail.com

Background: Drug resistance to pyrazinamide (PZA) in *Mycobacterium tuberculosis* occurs by chromosomal mutations, the most of which are SNPs or indels in the pyrazinamidase gene (*pncA*). The mutation frequency in vitro for H37Rv when selected on PZA is very similar to that in other bacteria, typically around 1×10^{-5} . But, does this represent the mutation rate in vivo? Previous studies have shown that mutations in *pncA* occur with high frequency (i.e. in a large proportion) in MDR-TB clinical isolates. This study aims to investigate the acquisition of *pncA* mutations at a microscale among a set of INH+RIF resistant strains.

Design/Methods: The genome of 97 clinical isolates (66 MDR-TB and 31 sensitive strains) were sequenced using Illumina Genome Analyzer IIx. A phylogenetic tree was constructed base on genome-wide SNP analysis. To better understand the evolution of PZA resistance in this population, we decided to develop a crude molecular clock by quantifying the number of SNPs observed between contact pairs, which are defined as strains that came from patients with a known familial relationship and are adjacent in the phylogenetic tree. We make the assumption of infection by a common strain in each contact pair, transmitted from one to the other. Thus any polymorphism observed between them can be assumed to have arisen with one host or the other. Analysis of multiple contact pairs shows an average of 10 SNPs between them, which were presumably acquired in vivo over at most only a few years of infection. This background mutation rate is consistent with what has been found in other studies (see Timothy Walker et al).

Results: In *PncA* we observed both a large number and high diversity of mutations. Among 66 isolates chosen a priori for resistance to INH and RIF, 36 had mutations in *PncA*, and these were explained by 16 distinct mutations. In contrast, none of the drug sensitive strains displayed any mutations in *pncA*. While phylogenetic analysis suggested that the mutations associated with INH and RIF resistance were shared among whole clusters, the *PncA* mutations were only shared among small subsets of strains, suggesting they arose recently and independently. **Conclusion:** MDR strains that are INH and RIF resistant are highly susceptible to acquire PZA resistance, and the probable cause for this effect is not due to increase mutation rates or reduced fitness costs in vivo, but simply to the reduction in effective drugs leading to a nearly monotherapy setting.

56. Tbilisi to Lima: a journey through TB treatment outcomes

PC-1174-06 Assessment of treatment outcome and associated factors among retreatment tuberculosis patients in selected government health facilities, Eastern Ethiopia

Y Moges,¹ K Kibret² ¹Haramaya university, Harar, Ethiopia, ²Welega university, Nekemite, Ethiopia. e-mail: mogesyoni@gmail.com

Background: Tuberculosis is the leading causes of mortality among infectious diseases worldwide. The management of previously treated tuberculosis patients (retreatment cases) is a challenge for National Tuberculosis Programmes in resource-limited settings such as Ethiopia. So the aim of this study was to determine the treatment outcomes of the different categories of retreatment tuberculosis patients in Eastern Ethiopia.

Design/Methods: A retrospective cohort study was conducted from 2002-2006 in selected health facilities in Dire Dawa town. The study included all TB cases registered as 'relapse', 'failure' or 'default' between September 2002 - March 2006 in Dilchora Referral Hospital and from September 2004 - March 2006 in Legehare Health Center. Data were sourced from TB health unit registers from the two health institutions using a structured data form. Statistical analysis was carried out using various statistical tests. Descriptive statistics were conducted using frequencies and proportions. χ^2 test was used for testing association of different characteristics.

Results: A total of 1667 TB patients were treated from September 2002 - March 2006 in Dilchora Referral Hospital and in Legehare Health Center. Of these; 103 of the patients were recorded as TB retreatment cases. The retreatment rate was 6.24. Among the 103 retreatment cases, 52 (50.5%) had a treatment outcome registered in the health unit register; 22 (21.4%) cases were transferred out and 29 (28.2%) had no record of outcome in the register. Of the 52 category II TB treated patients 29 (55.7%) were cured, 14 (26.9%) died, 5 (9.6%) retreatment failure cases and 4(7.7%) developed multidrug resistance tuberculosis (MDR-TB). Cure rate was (40.0%) and (27.4%) in the patients belonging to the default and relapse category respectively.

Conclusion: The analysis has shown that relapse cases were the most common retreatment category and treatment success rates for relapse cases were low (55%). Persistent monitoring of treatment outcomes of relapse, failure and default cases is crucial for improving TB control and to alter the incidence of MDR and XDR tuberculosis.

PC-1175-06 Treatment outcomes for multidrug-resistant tuberculosis patients under DOTS-Plus: systematic review and meta-analysis

Y Moges¹ ¹Haramaya university, Harar, Ethiopia. e-mail: mogesyoni@gmail.com

Background: Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. The WHO aims to achieve a 90% treatment success rate for TB patients by 2015 and current studies on MDR-TB treatment revealed a huge gap to this target. The aim of this study was to assess and summarize the available evidence on MDR-TB treatment outcome under DOTS-Plus.

Design/Methods: Literature based systemic review of observational studies was conducted. Original studies providing multi drug resistance tuberculosis under DOTS plus program according to WHO-defined outcomes at the end of treatment and follow-up were identified using data bases such as Medline/PubMed, Google Scholar and HINARI. The descriptions of original studies were made using frequency and forest plot. Heterogeneity across studies was checked using Cochran Q test statistic and I². Pool risk estimates of Multi-drug resistance tuberculosis treatment outcome and sub-grouping analysis were computed using a Bayesian random effects meta-analysis.

Results: Among articles identified, 13 met our inclusion criteria from 8 countries. In a pooled analysis, 55.62% [95%CI 54.34–56.89] of patients were cured and 43.48% [58.44 – 68.51] had successful outcomes, while] 14.21% [11.60–16.81] defaulted, 12.6% [8.98–16.21] died, and 7.65% [5.63–9.68] were transferred out. Individualised treatment regimens had higher treatment success than standardized regimens. HIV infection, alcohol use and previous TB treatment were significantly associated with poor multi-drug treatment outcome.

Conclusion: In general, the overall performance of DOTS-Plus was acceptable but still it is far from WHO treatment success target. In addition, we have identified high rates of default, which likely contributes to the development and spread of MDR-TB.

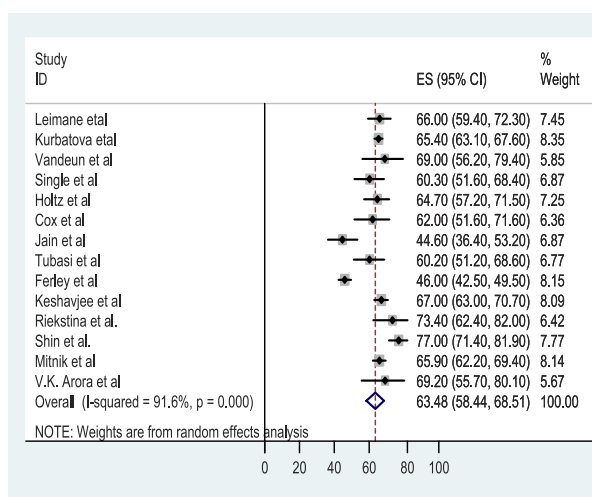


Fig: Forest Plot of the 13 observational Studies that quantitatively assessed the multi- drug resistance tuberculosis treatment outcome under DOTS plus approach.

PC-1176-06 Adverse reactions associated with injectable second-line anti-tuberculosis drugs among patients with M/XDR-TB in Tbilisi, Georgia

M Buziashvili,^{1,2} V Mirtskhulava,¹ M Kipiani,² N Tukvadze,² J Furin,³ M Magee,⁴ R Kempker,⁵ H Blumberg⁵ ¹Tbilisi State Medical University, Tbilisi, ²National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; ³Case Western Reserve University, Cleveland, OH, ⁴Georgia State University, Atlanta, GA, ⁵Emory University, Atlanta, GA, USA. e-mail: mari.buziashvili@yahoo.com

Background: The country of Georgia has high rates of MDR- and XDR-TB (11% of new and 38% of retreatment cases) which require the use of second-line anti-TB drugs; these regimens are frequently accompanied with severe adverse drug reactions (ADRs). The aim of our study was to determine the rates of and risk factors for ADRs associated with injectable drug use among M/XDR-TB patients.

Design/Methods: Consecutive patients, who initiated treatment for M/XDR-TB at the National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia in 2011, were enrolled in a retrospective cohort study. All patients received kanamycin or capreomycin. Data was abstracted from medical and laboratory records and the national surveillance database using a standardized form. Ototoxicity was defined as self-reported tinnitus and/or impaired hearing by a patient. Creatinine clearance (CrCL) was calculated using the Cockcroft-Gault formula and nephrotoxicity was defined according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification of acute kidney injury (AKI). Bivariate analysis was performed to assess the association between patients' clinical characteristics and ADRs.

Results: Among 67 patients treated for M/XDR-TB the median age was 35 years (range 17-73) and 68% were male. Rates of HIV co-infection were 5%, HCV 15%, and 9% had diabetes. Median baseline CrCL was 88.9 ml/mi (IQR 68-103). Any AKI (CrCL decrease >25% compared to baseline) was developed in 36 (54%) patients (30 received kanamycin and 6 received capreomycin). Renal injury (CrCL decrease >50%) occurred in 8 (12%) patients. Most AKI (76%) occurred in the first 6 months of treatment. Ototoxicity was reported by 36% including 18 (27%) patients with tinnitus and 22 (33%) with impaired hearing. Compared to those without AKI, patients with AKI were significantly more likely to have an incarceration history (23% vs 3%, $P < 0.05$). Patients with AKI had a higher rate of developing ototoxicity (44% vs. 26%, $P 0.11$) and higher prevalence of diabetes at baseline (14% vs. 3%, $P 0.13$) but the differences did not reach statistical significance.

Conclusion: AKI and ototoxicity were very common among patients with M/XDR-TB who received an injectable drug. A history of prior incarceration was found to be associated with increased risk for development of AKI. Further defining risk factors for AKI and ototoxicity will help guide ADR prevention efforts.

PC-1177-06 Poor tuberculosis treatment outcomes in the district of Manhica, Mozambique, 2011-2012

A L Garcia-Basteiro,^{1,2} D Respeito,¹ O Joaquim Augusto,¹ E Lopez Varela,^{1,2} C Sacoar,¹ I Manhica,³ F Cobelens,⁴ P Alonso^{1,2} ¹Centro de Investigação em Saude de Manhica (CISM), Manhica, Mozambique; ²Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain; ³National Tuberculosis Control Program, Ministry of Health, Maputo, Mozambique; ⁴Amsterdam Institute for Global Health and Development, Academic Medical Centre, Amsterdam, Netherlands. e-mail: alberto.garcia-basteiro@manhica.net

Background: In Mozambique, there is limited data regarding the monitoring of tuberculosis (TB) treatment results and determinants of adverse outcomes under routine surveillance conditions. The main objective of this study was to evaluate the treatment outcomes among TB patients and analyze factors associated with a fatal outcome. As a secondary objective, we estimated the proportion of deaths attributable to TB in a very high HIV- and TB-burden area in southern Mozambique.

Design/Methods: This is a retrospective observational study based on TB patients diagnosed in the period 2011-2012 in the district of Manhica, Mozambique. We used three different data sources: a) TB related variables collected by the NTP in the district of Manhica for all TB cases starting treatment in the period 2011-2012. b) Population estimates for the district were obtained through the Mozambican National Statistics Institute. c) Estimates on population growth, number of deaths and other relevant demographic variables were collected from the Demographic Surveillance System (DSS) at CISM. From 2012 onwards, the DSS records the cause of death in all deaths belonging to the study area. WHO guidelines were used to define TB cases and treatment outcomes.

Results: Of the 1957 cases starting TB treatment in the period 2011-2012, 294 patients (15.1%) died during anti-tuberculous treatment. Ten per cent of patients defaulted treatment. The proportion of patients considered to have treatment failure was 1.1%. HIV infection (OR 2.73; 95%CI: 1.70-4.38), being female (OR: 1.39; 95%CI: 1.31-1.91) and lack of laboratory confirmation (OR 1.51; 95%CI: 1.10-2.08) were associated with dying during the course of TB treatment ($P < 0.05$). Among HIV positive patients, those who were not on ART were more likely to die during treatment (uOR: 1.78 95%CI 1.31-2.42). The contribution of TB to the overall death burden of the district for natural reasons was 6.5% (95%CI: 5.5-7.6) in the year 2012, higher for males than for females (7.8%; 95%CI: 6.1-9.5 versus 5.4%; 95%CI: 4.1-6.8 respectively). The age group within which TB was responsible for the highest proportion of deaths was 30-34 among males and 20-24 among females (20% of all deaths in both cases).

Conclusion: This study shows a very high proportion of fatal outcomes among TB cases starting treatment. There is a high contribution of TB to the overall causes of mortality. These results call for action in order to

improve TB (and TB-HIV) management and thus treatment outcomes of TB patients.

PC-1178-06 Investigating gender differences in the profile and treatment outcomes of tuberculosis in Ebonyi State, Nigeria: implications for tuberculosis control

S Oshi,¹ I Alobu,² K Ukwaja,³ D Oshi¹ ¹Centre for Development and Reproductive Health, Enugu, Enugu State, ²National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, ³Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, Nigeria. e-mail: ukwajakingsley@yahoo.co.uk

Background: Globally, twice as many men as women are being diagnosed with tuberculosis (TB) annually. Little is known about gender differentials in TB in Africa. The aim of this study was to describe gender differences in the epidemiological characteristics and treatment outcomes of TB in Nigeria.

Design/Methods: A retrospective cohort analysis of routine data was carried out among adult TB patients treated between 2011 and 2012 in two large health facilities in Nigeria. Gender differences in their demographic characteristics and treatment outcomes were analyzed accordingly.

Results: Of 1668 TB patients enrolled, the male to female ratio was 1.4:1. The mean ages of males and females were 40.2 ± 14.7 and 36.1 ± 14.6 years respectively (t -test 6.62, $P < 0.001$). Male gender was associated with a higher failure to smear convert after 2 (21.8% vs. 17.5%; $P = 0.06$) and 5 months (4.3% vs. 1.5%; $P = 0.02$) of treatment for smear-positive TB patients. Also, men were more likely than women to fail treatment (2.2% vs. 0.7%; $P = 0.01$). No significant differences exist in the treatment success rates between women and men (78.2% vs. 74.5%; $P = 0.08$). Adjusted analyses showed significant association between being an urban-male and a HIV-infected female with unsuccessful outcome adjusted by socio-demographic and clinical factors.

Conclusion: We found that gender disparities exist in TB profile and treatment outcome in Nigeria and gender-specific strategies are needed to optimize TB management. We recommend that: (1) urgent strategies to reduce treatment default and mortality in men and women with TB need to be implemented; (2) TB case finding in older women should be improved; (3) specific measures to reduce unsuccessful outcomes for patients in the high-risk groups should be implemented; (4) socioeconomic interventions to improve treatment success for rural TB patients, especially women, should be implemented; and (5) further studies on the impact of biological factors on TB treatment outcomes in men and women need to be carried out and the influence of HIV co-infection, sex hormones and poverty assessed.

PC-1179-06 Agbami tuberculosis control and management initiative in Nigeria

S Kashim,¹ H Deji,¹ O Sam,¹ A Thomas,¹ O Pitan,¹ C Onwurah,¹ O Sunday,¹ E Egbochukwu¹ ¹Star Deep - a Chevron Company, Lagos, Nigeria. e-mail: gidadomansu@yahoo.com.au

Background: For over 50 years Chevron has operated in areas of Nigeria where weakened health systems have contributed to the prevalence of the triad of HIV, Malaria and TB. These diseases pose challenges which are faced by our employees, their families, the communities in which we operate, and ultimately, the business. We recognize that supporting public health is core to the success of our business in the society. **Methodology:** The strategy is to achieve early detection and proper management of tuberculosis, chest and lung diseases in Nigeria which aligns with the national strategy. The objectives are to provide infrastructural support; medical equipment and supplies; capacity building targeting health workers; and advocacy on TB disease in 25 States over 8 years. Activities already undertaken include the conduct of a needs assessment, building and equipping of 23 chest clinics in state-owned health institutions across the country, provision of medical supplies and training of health workers. The clinics have consulting rooms, wards, and fully-equipped laboratories with mobile X-ray units and molecular diagnostic (GeneXpert) machines. In addition to delivering health benefits, the program has generated more than 1000 jobs and opportunities for people and local firms.

Results and lessons learnt: A practical training on molecular-genetic diagnostics of tuberculosis was organized for over 100 laboratory attendants and supervisors in collaboration with the National TB Program as at 2014. The training focused on providing participants with basic computer skills, equipment operation, turn-around maintenance competency and record keeping; this training targeted health workers from the chest clinics and neighboring hospitals. The program has provided 18 GeneXpert machines representing 19 % of the National donor contributions. From which a total of 31 571 sputum were tested. In 2014 a total of 14 352 presumptive TB cases were registered in the chest clinics; with 1124 smear positive cases examined. 701 smear positive TB cases were traced and identified while 321 TB contacts were confirmed positive. A total of 506 MDR suspects were traced and identified with 92 drug resistant cases identified and 53 enrolled for care.

Conclusion: The above best practice summarises the contribution of the Agbami Coventurers towards control and management of TB in Nigeria.

PC-1180-06 Characteristics of patients with active TB and their relation to treatment outcomes in patients previously treated in two DISAS of Metropolitan Lima

C C Contreras,¹ M Lindeborg,² D Chen,¹ M F Franke,³ S Shin³ ¹Socios En Salud Sucursal Peru, Lima, Peru; ²Harvard College, Boston, MA, ³Harvard Medical School, Boston, MA, USA. e-mail: ccontreras_ses@pih.org

Background: Tuberculosis (TB) is a product of socioeconomic, political, and medical factors. This study identifies characteristics, in patients who have already been treated, that influence the risk of having an unfavorable treatment outcome in Lima, Peru. It focuses on differences between patients from the public sector (PS) and patients who auto-administered treatment (AA), or obtained treatment from outside of the PS.

Design/Methods: 1545 patients older than 18 years of age, with a past treatment and current diagnosis of active TB, of 145 establishments in Lima Metropolitana, were included between January 2005 and May 2008. Information was taken from clinical histories, treatment cards, and laboratory registries. A statistical analysis was carried out through Epi Info 3.4.3.

Results: Within the cohort of 1545, 1404 were from the public sector (PS) and 141 were auto-administered (AA). Following univariate analysis, AA patients had better outcomes than SP patients (OR 1.85 [1.25, 2.74], $P = 0.002$). For example, non-adherence to TB treatment (more than 20% of days without treatment, $n = 1530$) was greater in the SP group than in the AA group (26.0% vs. 16.7%, $P = 0.02$). However, the correlation decreased upon multivariate analysis (OR 1.46, [0.94 2.26] $P = 0.10$). With respect to demographics, multivariate analysis revealed that finishing secondary school (OR 1.85 [1.45, 2.36], $P < 0.0001$) and having a higher body mass (OR 1.12 [1.08, 1.16], $P < 0.0001$) increase the probability of favorable results. On the other hand, the consumption of alcohol (OR 0.59 [0.44, 0.81], $P = 0.001$) and drugs (OR 0.49 [0.35, 0.70], $P = 0.0001$); coinfection with HIV (OR 0.67 [0.45, 0.98], $P = 0.04$); and having resistance to H or R (OR 0.45 [0.30, 0.69], $P = 0.0002$) and to H and R (OR 0.29 [0.21, 0.40], $P < 0.0001$), are all negatively associated with treatment outcomes.

Conclusion: The recurrence of TB should be attended by state health services and the public sector, taking into account the diverse social factors that influence clinical results of patients. There should be greater communication between the public and private sectors, in order to achieve effective management, monitoring, and reporting of cases following national guidelines.

PC-1181-06 Prevalence, risk factors, and treatment outcomes of isoniazid- and rifampicin-mono-resistant pulmonary tuberculosis in Lima, Peru

L Villegas,¹ L Otero,² T Sterling,¹ E Gotuzzo,² C Seas² ¹Vanderbilt University School of Medicine, Nashville, TN, USA; ²Universidad Peruana Cayetano Heredia, Lima, Peru. e-mail: leonela.a.villegas@vanderbilt.edu

Background: Isoniazid (H) and rifampicin (R) are the two most efficacious first-line agents for tuberculosis (TB) treatment. Peru has had stable rates of multidrug resistant (MDR) TB, accounting for 3.9% of new cases and 35% of retreatment cases in 2013; however, there are limited data on H and R monoresistance. We assessed the prevalence of H and R monoresistance, associated factors, and the effect on treatment outcomes.

Methods: A prospective observational cohort study actively enrolled adults with a first episode of smear-positive pulmonary TB from 34 health facilities in North Lima, Peru, from March 2010 through December 2011. A structured questionnaire was administered at enrollment. A sputum sample at diagnosis was cultured on Löwenstein-Jensen (LJ) media and drug susceptibility testing (DST) was performed using the LJ proportion method at the following concentrations: H at 0.2 µg/ml and 1 µg/ml and R at 40 µg/ml. Patients were followed up at the end of each treatment. We determined the patients' characteristics associated with H and R monoresistance and evaluated the effect of resistance on treatment outcomes (lost to follow up, death, transfer, and failure were considered poor outcomes).

Results: Of 1292 patients enrolled, 1039 (80%) were culture-confirmed. H monoresistance was present in 85 (8%) patients, of whom 45 (53%) were resistant to 1 µg/ml of H. R monoresistance was present in 24 (2%) patients. The best prediction models for H monoresistance (compared to H susceptible) and for R monoresistance (compared to R susceptible) are shown in the Table. Variables that were not predictors of monoresistance included prior H prophylaxis, history of tobacco use, and age. H monoresistant patients had a higher risk of poor treatment outcomes (OR = 2.46; 95%CI: 1.40-4.30) after adjusting for prior imprisonment (OR = .25; 95%CI: .03-1.88) and alcohol abuse (OR = .57; 95%CI: .29-1.11). In addition, R monoresistant patients had a higher risk of poor treatment outcomes (OR = 2.53; 95%CI: 1.02-6.27) with no measured confounders.

Conclusion: H and R monoresistance were associated with a significantly increased risk of poor outcomes, after controlling for potentially confounding variables. This underscores the importance of early case detection and initiating appropriate TB treatment regimens in these patients.

57. When the tail wags the dog: drug resistance in TB programmes

PC-1182-06 Sputum bacterial load predicts multidrug-resistant tuberculosis in retreatment patients: a case-control study

M Sander,¹ C Vuchas,¹ H Numfor,¹ A Nsimen,¹

J-L Abena Foe,² J Noeske,³ A Van Deun,^{4,5} K Morgan⁶

¹Tuberculosis Reference Laboratory Bamenda, Bamenda,

²National TB Program, Yaounde, ³Independent Consultant, Yaounde, Cameroon; ⁴Institute of Tropical Medicine,

Antwerp, Belgium; ⁵International Union Against Tuberculosis and Lung Disease, Paris, France; ⁶University of Liverpool,

Leahurst, UK. e-mail: melissa.sander@gmail.com

Background: Rapid and effective diagnosis of multidrug-resistant tuberculosis (MDR-TB) is an essential component of global tuberculosis control, but most MDR-TB cases are still not diagnosed. Our objective was to assess if patient sputum bacterial load can be used to identify patients that are at higher risk of multidrug resistance.

Design/Methods: We used a case-control study and multivariable logistic regression models to investigate associations between MDR-TB and sputum bacterial load among retreatment TB patients at a reference laboratory in Cameroon.

Results: MDR-TB was associated with a smear microscopy grade of 3+ (odds ratio, 21.9; 95% confidence interval [CI] 6.2-76.8) or 2+ (odds ratio, 10.8; 95%CI 2.9-40.7), as compared to a result of 1+, scanty or smear-negative, among 80 MDR-TB cases and 521 controls. MDR-TB was associated with automated time to detection of ≤ 160 hours (odds ratio, 2.2; 95%CI, 1.1-4.7) as compared to >160 hours among a sub-population of 47 cases and 350 controls.

Conclusion: A higher sputum bacterial load is associated with MDR-TB in retreatment patients in Cameroon. If this association proves generalizable to other populations, prioritizing more highly smear positive patients for laboratory screening could provide a simple and effective approach to improve the detection of MDR-TB in resource-limited settings.

PC-1183-06 Is 'initial loss to follow-up' overestimated in India's TB programme?

S Shastri,¹ S Burugina Nagaraja,² S Katakoti¹

¹Lady Willingdon State TB Centre, Bangalore, ²ESIC Medical

College and PGIMS, Bangalore, India. e-mail:

susha007@gmail.com

Background: In India, despite the efforts from national TB control programme, tuberculosis remains the major public health problem. As a policy in the programme, all those patients diagnosed as smear positive tuberculosis are initiated on treatment within seven days of diagnosis. Those smear-positive pulmonary tuberculosis (PTB) patients not confirmed as starting treatment are reported as 'initial loss to follow-up'; irrespective of whether the patients die, migrate or access to private treatment. We

conducted the study to determine the reasons for initial loss to follow-up under programmatic settings.

Methods: The study was conducted in Karnataka, a southern state in India with a population of 63 million. A validated data collection format was used to gather the information from the available programmatic records and reports. The data was collected from 31 districts for the period October to December 2014. The field level program managers were trained to collect the information by making home visits; if the patients were not available during the visits information was gathered from the patient's relatives or neighbours. The data collection forms were entered in microsoft excel formats and were compiled at state level for analysis.

Results: A total of 12 159 new sputum smear positive cases were diagnosed during the study period and 8318 (68%) patients were registered for TB treatment. Out of the 3841 that were initial loss to follow up as per the definition, 264(7%) patients died before start of the treatment, 204(5%) patients migrated/provided wrong address, 149(5%) patients referred outside the state but no feedback was received about starting the treatment and 547(14%) patients registered for the treatment in the subsequent 3 months.

Conclusion: The study findings suggest that the current recording and reporting system in the programme is inflating the "initial loss to follow-up" with inclusion of deaths. Policy change in the recording and reporting has to be made to ascertain the cause of "initial loss to follow-up" routinely. Provision of electronic technologies at the microscopy centre level to track the patients will strengthen the timely initiation of treatment.

PC-1184-06 Why the current TB performance in Nigeria? Obvious but hidden deterrent factors

M Gidado,¹ S Useni,¹ J Onazi,¹ N Peter,¹ E Mitchell,¹

C Fischer,² G Akang,³ R Eneogu³

¹KNCV TB Foundation, Abuja, ²USAID, Abuja, ³Federal Ministry of Health, Abuja,

Nigeria. e-mail: gidadomansu@yahoo.com.au

Introduction: Nigeria is ranked 3rd among high TB burden countries in the world. Despite its existing service coverage for microscopy labs of 1:109 000, and 79% DOTS coverage by population; the case notification rate for 2013 was 57.3/100 000 population which is 17% of the estimated incidence (338/100 000 population). The aim of the assessment was to unveil the hidden deterrents on case notification to guideline specific interventions.

Methods: An assessment tool was developed which includes TB disease burden; HIV burden; service coverage and distribution by population, LGA, and among all existing health care facilities in the states; functionality of existing DOTS and laboratory facilities; and health system related factors. Teams of assessors were trained on the tool and subsequently the tool was pre-tested and adjusted. The assessment was conducted within two weeks in 12 selected states representing each of the six zones in Nigeria. This involved desk review of 2014 program data at state & LGA levels, in-depth interview/focused group discussions and health facility

visits. Data was analyzed using simple descriptive statistics of all the indicators disaggregated by LGAs. Among all the states there was very low TB CNR an average of 52/100 000 population (range 31-77/100 000 popn); proportion of childhood TB among notified cases varied by states from 1.5% to 13%; HIV prevalence varied significantly by state (range 1% to 15.2%); DOTS and AFB microscopy coverage by population was 0.8/25,000 popn and 0.5/50 000 popn, with huge variation by state and LGAs respectively; proportion of existing DOTS clinics not reporting a case within a period of two quarters was 29.5% (range 4.3% to 54%); proportion of microscopy centers not reporting within a quarter was 24.5% (range 2.6% to 64.%); the coverage of TB services within total health care facilities was 20% (range 7.6% to 39%).

Conclusion and recommendations: TB program interventions should be state and LGA specific; emphasis should be on fixing not reporting sites rather than expansion; focus on community and health care staff awareness on TB and TB service delivery points; and develop a mechanism for partner's coordination at state level using state specific operational plans.

PC-1185-06 Prevalence of pre-XDR-TB and XDR-TB among MDR-TB patients registered at the Ojha Institute of Chest Diseases, Karachi

N Rao,¹ S Baig,¹ N Ahmed,¹ D Rao² ¹Ojha Institute of Chest Diseases, Karachi, Hamdard College of Medicine & Dentistry, Karachi, Pakistan. Fax: (+92) 219 926 1470. e-mail: nisar.rao@aku.edu

Background: Drug resistant tuberculosis is a major public health problem. Surveillance of sensitivity pattern of MTB against anti-tuberculosis drugs is crucial for the successful management of tuberculosis. Pre-XDR and XDR-TB are threats for the successful control of tuberculosis. Data on this issue will help us to determine success of our already running TB control program.

Design/Methods: We reviewed the record of all patients registered in MDR clinic of Ojha Institute of Chest Diseases between January 2010 and December 2014. Data was collected about clinical details and resistance pattern.

Results: A total of 919 patients were enrolled during the period. 465(51%) were male. Most of the patients (718/919) were young i.e. from 15-44 age group. The pre-XDR-TB and XDR-TB prevalence rate among MDR-TB patients were 363/919 (39.5%) and 18/919 (02%) respectively. Out of 18 XDR-TB patients 05 were resistant to Km (Kanamycin) Am (Amikacin) Cm (Capreomycin) FQ (Fluoroquinolone), 04 were resistant to Km + FQ, 03 against Am + FQ and 06 against Cm + FQ. Out of 363 Pre-XDR-TB patients 332 were resistant to FQ, 04 to Km, 07 to Cm, 02 were resistant to Km + Am and 18 were resistant to Km Am Cm.

Conclusion: There is high prevalence of pre-XDR tuberculosis in patients registered at Ojha Institute of Chest Diseases, Karachi, Pakistan. The XDR- TB cases are also reported and registered. There is a need to closely

follow the new TB patients registered in chest clinics for proper treatment and compliance to prevent drug resistant tuberculosis. There is also a need to ban over the counter sale of ATT and specifically quinolones.

PC-1186-06 Description of new pulmonary tuberculosis cases in southern India

G Roy,¹ R Kubiak,² A Sivaprakasam,¹ N Hochberg,² S Govindarajan,³ P Salgame,⁴ J Ellner,² S Sarkar¹

¹Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; ²Boston University Medical Center, Boston, MA, USA; ⁴Government of Puducherry, Puducherry, India; ⁵Rutgers New Jersey Medical School, Newark, NJ, USA. e-mail: rachkubiak@gmail.com

Background: India has the largest tuberculosis (TB) burden with an estimated 2 million cases annually accounting for over 20% of the world's cases. Recent data are lacking about the demographic characteristics of TB cases in southern India. Understanding the epidemiology of TB in India is critical for the development of effective TB control measures.

Design/Methods: Data were collected through the Regional Prospective Observational Research for TB (RePORT)-India collaboration. New sputum smear-positive pulmonary TB cases diagnosed by the Revised National TB Control Programme (RNTCP) in Puducherry and the Cuddalore district of Tamil Nadu, India were enrolled within one week of treatment initiation starting in May 2014. Standardized questionnaires including the Alcohol Use Disorder Identification Test (AUDIT-C) were used to collect a medical history and socio-demographic data. Sputum was collected to document culture positivity. We compared our findings to 2011 Indian census data and the existing literature and used the binomial test for significance testing.

Results: Of the 232 smear-positive patients diagnosed through RNTCP, 210 were culture-confirmed and included in this analysis. A greater proportion of cases were male than in the general populations in both Puducherry (72.6% vs. 49.1%, $P < 0.0001$) and Cuddalore (74.3% vs. 50.1%, $P = 0.0058$) and 15-59 years old; 140 (80%) in Puducherry and 30 (85.7%) in Cuddalore, compared to 66.0% ($P < 0.0001$, 0.0160, respectively) in the general populations. Among cases, the mean reported household size in Pondicherry was 3.8 people (range 2-7) and 3.1 in Cuddalore (range 2-4) compared to 4.1 in both states. Most cases were lower castes (206, 98.1%) and reported low monthly household incomes of 3000-5000 rupees (48-80 USD; 102, 45%). The World Health Organization estimates 27.1% of south Indians currently or formerly smoke compared with 102 (48.6%) of cases. Harmful or hazardous alcohol use was reported by 76 (36.2%) cases, which is markedly higher than the prevalence rates of 3.7% and 14.9% found in recent studies in rural Tamil Nadu. Previous studies found diabetes prevalence rates in southern Indian populations in the range of 6-14%, while among TB cases in this study, 62 (29.7%) reported a previous diagnosis of diabetes. Only one (0.05%) case

was HIV positive suggesting a prevalence similar to the national rate of 0.27%.

Conclusion: New sputum-positive pulmonary TB cases were more commonly male, of lower socioeconomic status, and had a higher prevalence of diabetes and alcoholism (but not HIV) compared to the general population.

PC-1187-06 Role of exogenous reinfection in patients with recurrent tuberculosis in the United States

J Interrante,^{1,2} M Haddad,^{1,2} L Kim,¹ N Gandhi² ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, ²Emory University, Atlanta, GA, USA. e-mail: jdi5w@virginia.edu

Background: Although substantial gains in reducing tuberculosis incidence in the United States have occurred over the past 2 decades, progress toward the national goal of tuberculosis elimination is slowing. One area to target interventions in order to achieve elimination is in reducing the proportion of tuberculosis cases that recur. The etiology of recurrent tuberculosis is typically thought to be reactivation of residual *Mycobacterium tuberculosis* infection; however, recent studies suggest that reinfection with new strains may account for a greater proportion of recurrent tuberculosis in the United States than previously recognized. The objective of this study was to characterize the etiology of recurrent tuberculosis in the United States using genotyping of initial and recurrent *M. tuberculosis* isolates.

Design/Methods: The study population for this retrospective national population-based cohort in the United States was drawn from all persons reported to the National Tuberculosis Surveillance System as having 2 episodes of tuberculosis during 1993–2011. Genotyping results were available from both tuberculosis episodes for 194 cases. We analyzed the proportion of recurrent tuberculosis attributable to reinfection and the risk factors associated with reinfection.

Results: Among 136 recurrences meeting the inclusion criteria for this study, 20 (15%) had differing genotypes between the initial and recurrent *M. tuberculosis* isolates, and thus, were likely attributable to reinfection; genotypes were the same for 116 (85%) cases and were categorized as reactivation. Using exact logistic regression, factors associated with reinfection included Mexican birth with immigration to the United States within 12 years of the second episode (adjusted odds ratio, 10.7; 95% confidence interval, 1.7–86.3), and treatment of the first episode exclusively by directly observed therapy (adjusted odds ratio, 4.5; 95% confidence interval, 1.0–29.2).

Conclusion: Reinfection with a new *M. tuberculosis* strain was the cause for approximately 15% of recurrent tuberculosis cases in this US cohort. The proportion caused by reinfection increased to as high as 60% in certain subpopulations, such as recent immigrants from Mexico. Public health initiatives should focus on these populations and their areas of residence, work, and

recreation to stop further transmission of *M. tuberculosis*.

PC-1188-06 Risk factors associated with tuberculosis in Kazakhstan: implications for disease prevention and control

A Davis,¹ A Aifah,¹ A Terlikbayeva,² Z Zhumadilov,² T Abildaev,² M Darisheva,² N Schluger,¹ N El-Bassel¹
¹Columbia University, New York, NY, USA; ²Columbia University Global Health Research Center of Central Asia, Almaty, Kazakhstan. e-mail: alissad22@gmail.com

Background: Kazakhstan has experienced an increase in tuberculosis (TB) infections. Identifying key populations and the social determinants of TB is essential for controlling the spread of the disease. Studies in other regions have indicated that smoking, alcohol and substance use are risk factors for TB and decrease the effectiveness of TB control efforts. Furthermore, other studies have found that HIV positive individuals and individuals with a history of incarceration have an elevated risk for TB. This study examines the relationship between TB, criminal history, tobacco, alcohol and substance use, and HIV in Kazakhstan.

Design/Methods: A case-control study included 1590 participants recruited from four regions in Kazakhstan. We defined index cases as those who had a positive culture, confirmation by positive smear and nucleic acid testing or X-ray confirmation and response to anti-tuberculosis drugs. Of the total sample, 598 (37.6%) met the criteria as index cases (e.g. diagnosed with TB). Participants completed a survey containing items on sociodemographics, history with the criminal justice system, tobacco, alcohol and drug use, and HIV diagnosis. Multivariate regression was used to examine associations between a TB diagnosis and a number of risk factors: criminal history, tobacco, alcohol and drug use and injection. Fisher's exact tests were used to calculate significant differences in HIV positivity between individuals with TB and without TB.

Results: After controlling for demographic variables (sex, age, ethnicity and education), participants who had ever been charged with a criminal offense (adjusted odds ratio (AOR) 3.51, 95%CI [1.93-6.37]), spent time in jail (AOR 6.26, 95%CI [2.66-14.70]), ever used non-smoking tobacco (AOR 1.99, 95%CI [1.26-3.14]), ever smoked tobacco (AOR 1.59, 95%CI [1.21-2.08]), ever used alcohol (AOR 1.54, 95%CI [1.22-1.95]), and ever used marijuana (AOR 1.99 [1.04-3.82]) were more likely to have a TB diagnosis. No significant associations were found between TB and injecting drug use. Individuals with TB had higher rates of HIV positivity than individuals without TB (1.2% vs. 0.1%, $P \leq 0.05$).

Conclusion: The findings about risk of TB are consistent with previous studies. The association between TB and criminal history and tobacco, alcohol and drug use in Kazakhstan suggests a need for targeted intervention and prevention approaches for individuals in the criminal justice system and for those who use substances.

PC-1189-06 Projecting the impact of alternative drug susceptibility testing strategies on future TB drug resistance

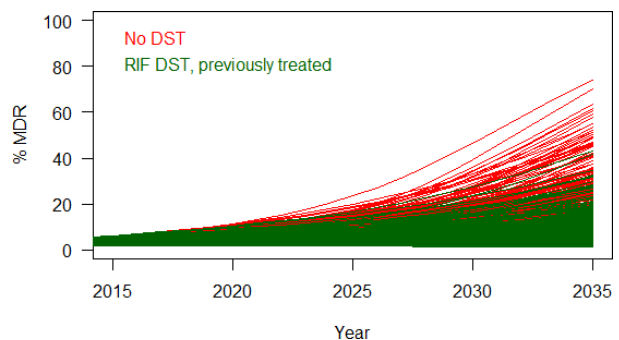
M Fofana,¹ S Shrestha,¹ G Knight,² T Cohen,³ R White,² F Cobelens,⁴ D Dowdy¹ ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ²London School of Hygiene & Tropical Medicine, London, UK; ³Yale School of Public Health, New Haven, Connecticut, USA; ⁴KNCV Tuberculosis Foundation, The Hague, Netherlands. e-mail: mariam.fofana@gmail.com

Background: Drug resistance presents a major obstacle to tuberculosis (TB) control efforts. Although the incidence of TB is decreasing in most settings, many areas have seen an increase in multidrug-resistant (MDR) and extensively drug-resistant forms of TB. Understanding the potential future trajectories of drug resistance and the impact of interventions such as drug susceptibility testing (DST) can help improve TB control policies.

Methods: We used a multi-strain dynamic transmission model of TB calibrated to the Southeast Asia region to project trajectories of resistance to rifampin, moxifloxacin, and pyrazinamide from 2015 to 2035. We randomly sampled values of key parameters for which data are unavailable or of poor quality, including probabilities of acquiring drug resistance during treatment, relative transmission fitness of drug-resistant strains, and treatment outcomes for different drug resistance profiles. We then selected only those parameter sets that were consistent with current data on TB incidence, prevalence and drug resistance in Southeast Asia ($n = 1190$), and used them to evaluate a range of possible future epidemics of MDR-TB under different algorithms for the implementation of DST.

Results: Initial MDR prevalence in 2015 was calibrated to a median of 3.1% (interquartile range [IQR] 2.5-3.8%). Under the assumption of no DST, the proportion of MDR among all TB cases by 2035 varied widely (median 7.5%, IQR 5.2-12.4%), and was consistently higher among previously treated (median 30%) than treatment-naïve cases (median 5%). A focused strategy, in which TB patients receive DST for rifampin only if they experience treatment failure, substantially reduced projected MDR prevalence among all TB cases in 2035 (median 5.0%, IQR 3.7-7.4%). Testing for rifampin resistance among all patients who were previously treated for TB provided an additional but small incremental benefit (median proportion MDR in 2035 4.6%, IQR 3.4-6.6%).

Conclusions: Given current epidemiologic data, the future trajectory of TB drug resistance in Southeast Asia remains highly uncertain; future trends depend on the transmission fitness of resistant strains which may vary over time, adding further uncertainty. Nevertheless, implementation of DST can have an important population-level impact, by reducing the probability of epidemiologic scenarios in which a large proportion of TB cases are MDR. Scale-up of DST should prioritize patients with a previous history of treatment failure.



58. Advancing the END TB strategy and other policy issues

PC-1191-06 Impact of social support in all forms of TB case detection and in MDR-TB treatment outcome

S Islam,¹ M Rana,¹ M Siddiqui,¹ M Akramul Islam,¹ S Reza,¹ S Alam,¹ M Haque² ¹BRAC, Dhaka, ²NTP, Dhaka, Bangladesh. Fax: (+88) 2988 8026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: BRAC has been implementing TB control programme in Bangladesh in collaboration with the National TB control Programme for about 20 years. Since its inception, the programme has evolved to its current stage through identifying implementation gaps and adapting the best solution in country settings. The social support is one of those initiatives that were adopted recently to overcome the economic, geographical, socio-cultural and health system barriers for TB patients, especially for the poor and protect them from increasing socio-economic vulnerability due to more out of pocket expenditure for TB diagnostic purpose.

Intervention or response: In a country like Bangladesh the diagnosis of smear negative and extra pulmonary TB is expensive. To mitigate this issue, BRAC began providing financial support for the poor presumptive TB patients from January 2013 as a social protection initiative. Poor TB symptomatic with smear negative, receive investigation and transportation costs to attend diagnostic facilities, and consultation fees in case they visited private sector and diagnosed as TB (USD 13). Poor people with extra pulmonary TB symptoms and child presumptive cases receive same supports (USD 33) for diagnosis. In addition, drug resistant (DR) TB patients are getting nutritional support during treatment period for treatment adherence.

Results and lessons learnt: Among 1 73 568 presumptive TB patients who received social support in 2013, the number of TB patients identification was 48 322 (28%). Similarly of 1 52 063 presumptive TB patients who received social support in 2014, the number of TB case identified 49,888 (33%). Considering total patient identified in 2012, 2013 and 2014 was respectively 1

02 716, 1 21 239 and 1 24 286 which showed an increasing pattern. Treatment outcome of DR TB cases was 71% in 2012 cohort.

Conclusions and key recommendations: Introducing social support effectively by providing diagnostic support to poor TB presumptive increased all types of case notification and improved DR TB treatment success rate which finally facilitate in reducing TB burden in the community.

PC-1192-06 School-based TB prevention activities in Georgia

G Bakhturidze,^{1,2} Nana Peikrishvili^{1,2} ¹Georgian Health Promotion and Education Foundation, Tbilisi, ²Georgian Health Promotion and Education Foundation, Tbilisi, Georgia. e-mail: iayd@yahoo.com

Background and challenges to implementation: While adults are more locked into existing stereotypes regarding TB, youth are more open to the new information and have joined information activities with great enthusiasm. This experience we earned in 2013, when implemented project related information and communication campaigns in Universities and in some public schools supported by USAID.

Intervention or response: Considering above needs, we organized school based TB prevention actions targeted youth from all regions of Georgia during 2014. We worked very actively with the teachers of public schools in target towns. The special trainings of teachers were organized by participation of 130 teachers. Also indirectly we approached about 400 other teachers and school administration members, who were involved in information meetings and other events in target schools. The second main targets for our activities were pupils of public schools. We selected 130 schools throughout Georgia and totally directly involve about 3000 pupils in the age of 13-17 years through information meetings and presentations. Indirectly, we approached about 20 000 pupils and 10 000 adults through different activities organized by schools and distribution of information materials.

Results and lessons learnt: Methodical guideline for teachers regarding TB created. 130 teachers have received ToT regarding TB issues and raised their capacity. Information flier for youth regarding TB issues distributed (20 000 copies). T-shirts with slogans and logos (500 pieces) were used during school activities. Information meetings in 120 schools organized and about 3000 pupils attended. At least 20.000 pupils and 10.000 adults (parents, teachers, etc.) reached through teachers' trainings, pupils' activities, distribution of printed materials and received information about TB. At least 80 different activities/events organized by schools. 3 articles appeared in regional newspapers and 2 reportages in regional TV/radio reaching totally about 300 000 population. 5 talk-shows organized in internet TV and radio covering all issues of TB reaching about 500 000 people.

Conclusions and key recommendations: School based TB prevention programs are essential to raise awareness among new generation. Appropriate curricula's and trained teachers will sustain the process and prevent TB among youth and their rounding communities.

PC-1193-06 Understanding the effectiveness of engaging pharmacists in TB care and control from the TB patient's perspective

V Panibatla,¹ S Prasad² ¹TB Alert India, Hyderabad, ²Eli Lilly and Company (India) Ltd., New Delhi, India. e-mail: vikas@tbalertindia.org

Background: Pharmacists are important community stakeholders in India. They also are the first contact point for consultation for any sort of illnesses. In a project, with aim of engaging pharmacists in National TB Program (NTP), supported by UWW & Lilly MDR-TB Partnership and implemented by TB Alert India results are encouraging. Pharmacists from Feb '13 to Feb '15 referred 2175 people with TB symptoms for testing. Around 92% (1989/2175) got tested and 11% (225/1989) are diagnosed with TB. To understand how much time people diagnosed with TB would have taken for TB testing if pharmacist would have not referred, a study was taken up. Study also focused on how satisfied are they with pharmacists service.

Intervention: An independent external consultant interviewed 19% (42/225) of people who were diagnosed with TB due referral by pharmacists in two districts among four implementing districts in Telangana state, India. Line listing of all such in two districts was prepared. People diagnosed with TB listed at even serial number in the line listing were contacted for willingness to participate in the study. Based on the response TB patients were either interviewed over phone or through personal interview.

Results: Around 81% (34/42) male and 19% (8/42) female were interviewed. Majority (32 /42) were in age group of 19-59 years. About 52% (22/42) reported that they reached pharmacy shop within 7 days of onset of symptoms. Around 26 out of 42 interviewed (62%) reported that it was their first visit to pharmacy shop after onset of symptoms. About 61% (26/42) of referred people reached for TB testing next day of the referral and with no out of pocket expenditure. Near about 3/4th (34 /42) were referred for testing in the first visit to pharmacy. About 25% (11) shifted to NTP treatment from private hospitals after visiting Pharmacist. Major chunk (70%) reported that they would have waited for another 7-10 days before going to any doctor if pharmacist did not refer them. About 86% (36/42) expressed satisfaction with information given and way pharmacist behaved with them. Referrals made by pharmacists reached 10-15 days earlier for testing than other TB patients at NTP clinic.

Conclusion: Engaging pharmacists proved very useful in early identification and early treatment initiation. Pharmacists were able to give correct information and convince people to go for testing. Effective training,

frequent follow up and reiteration of motivation are key factors for success.

PC-1194-06 Increasing TB case detection in small-scale private facilities through sputum sample networking in Nyanza, Kenya

P Izulla,¹ J H Ochieng,¹ G Cheruiyot,¹ J Marwanga¹

¹Population Services Kenya, Nairobi, Kenya. e-mail:

Plzulla@gmail.com

Background and challenges to implementation: Kenya is among the 22 countries that account for 80% of TB cases in the world. Close to 20% of TB cases in Kenya are in Nyanza region in part due to the higher HIV prevalence. Despite close to 50% of Kenyans seeking health services in private facilities, their involvement in TB detection and management has been limited. With funding from TB Reach, Population Services Kenya (PS Kenya) in partnership with Kisumu Medical and Education Trust (K-MET) are carrying out a one year pilot project whose aim is to increase case detection and treatment of TB in 48 franchised private facilities in Nyanza. At baseline only 12 facilities could offer sputum microscopy and 12 were offering treatment. Service providers were trained in TB case management and sputum microscopy where applicable. 92 community health volunteers (CHVs) were trained to conduct community screening and mapped to the facilities for referral of TB suspects. Screening only sites were linked to facilities with microscopy and treatment services for referral of TB suspects. Despite increase of sputum microscopy services from 12 to 24 facilities and treatment services to 18 facilities in first 2 quarters, many TB suspects were lost to follow up through double referrals from community to screening only sites and then to microscopy sites.

Intervention or response: Sputum sample networking system for non-diagnostic facilities was introduced in Q3. Screening only facilities were provided with sputum containers for collection of sputum and cooler boxes for transportation to the nearest diagnostic center. CHVs transported the cooler boxes from one site to the next and followed up on the results. Sputum was collected on designated days and transport costs to the referral sites catered for by the program to minimize delays in specimen movement. Data was captured on a paper based data collection tool, verified and subsequently fed into the program HMIS. Service quality was assured by field based demand creation and clinical coordinators that work closely with the providers and CHVs.

Results and lessons learnt: There was a four-fold increase in the numbers who tested sputum positive by microscopy from 79 in Q2 to 328 in Q3.

Conclusions and key recommendations: Sputum sample networking improved TB case detection among patients seeking TB services in small scale private facilities with inadequate infrastructure by minimizing movement of patients from one facility to another.

PC-1195-06 Measuring the effect of two community-based intervention strategies on diagnostic delay in Southern Ethiopia

L Blok,¹ G Asnake,² D Gemechu,^{2,3} M Bakker⁴ ¹Royal Tropical Institute (KIT), Amsterdam, Netherlands;

²REACH-Ethiopia, Hawasa, Ethiopia; ³London School of Tropical Medicine, Liverpool, UK; ⁴Royal Tropical Institute (KIT), Amsterdam, Netherlands. Fax: (+31) 20 568 8444. e-mail: l.blok@kit.nl

Background: In Ethiopia health extension workers (HEW) as first line cadres have been involved in identifying and referring people at risk of tuberculosis. REACH Ethiopia has implemented an innovative package of community based enhanced TB case finding expanding the role of HEW from referral of symptomatic people to include sputum collection, smear preparation, and treatment follow up once diagnosis is confirmed. This approach led to a marked increase in case notification in Sidama zone. Since 2013 the program successfully extended into 4 additional zones trying slightly less intensive packages of support in three of these zones. This study aims at measuring the effect of the full package (FP) and the targeted package (TP) on diagnostic delay.

Design/Methods: Diagnostic delay was defined as time between onset of symptoms and date of diagnosis, and further broken down in health seeking delay (time from symptoms till first visit to a health provider) and health system (HS) delay (from first visit till diagnosis). Data were collected through systematic interviews with SS+ patients and validated against suspect and treatment registers during baseline and intervention. Seventy seven patients were included, 40 baseline and 37 intervention (21 FP and 16 TP). Median number of days were calculated and compared using a non-parametric test (Kruskal Wallis).

Results: The overall diagnostic delay reduced from a median of 77.0 days (IQR 31.5-122.5) at baseline to 31 days (IQR 28.0-62), $P = 0.0795$, due to a significant reduction in HS delay (from median 27.5 days (IQR 2.5-63.5) to 7 days (IQR 0-31), $P = 0.0366$). The median HS delay under the FP was slightly shorter than under TP (4 and 7.5 days respectively), but this difference was not significant $P = 0.893$. No change was observed in the delay in seeking care.

Conclusion: Our study shows that community based case finding efforts can accomplish significant reductions in time till diagnosis in particular reducing health systems delay and referral time. The seemingly little influence on delay in seeking care is however worrisome given its relative importance in total delay. Recall bias may have affected the accuracy of time estimates, but was partially compensated by triangulation of data for the health system period. The difference in diagnostic delay between the two intervention packages was non-significant and will need to be further evaluated against cost implications.

PC-1196-06 Engaging commercial transporters (Keke NAPEP) in mobilizing community members for TB services: experiences from Imo state, Nigeria

A F Omoniyi,¹ A Awe,¹ G Akang,² G Madu,³ E Ubochioma,² M Gidado,⁴ C Orji,³ R Eneogu² ¹World Health Organization, Abuja, ²NTBLCP, Abuja, ³Imo State TBL Control Programme, Owerri, ⁴KNCV, Abuja, Nigeria. e-mail: omoniyifadare@yahoo.com

Background and challenges to implementation: Tuberculosis is major public health problem in Imo state, a state with a population of about 3.9million inhabitants. The National KAP survey conducted in 2012 revealed that only 27% of the populace have correct knowledge of the cause of TB, early symptoms and signs of TB. This low knowledge is one of the major factors responsible for low TB case finding in all the states in Nigeria, Imo state not exempted. Only 8% of the estimated TB cases in Imo state were notified in 2013. The programme in order to address this conducted an outreach campaign in Imo state during which commercial transporters popularly referred to as “Keke NAPEP” were used to mobilized members of the community for TB services for one week. The aim of this study is to assess what worked and the lessons learnt in the use of commercial transporters (Keke NAPEP) in mobilizing community members for TB services.

Intervention or response: Amakohia/Akauma community in Owerri North LGA of Imo state was selected for the outreach after analysis of state TB programme data. Advocacy visits was conducted to the community leaders during which the use of commercial transporters was agreed upon for community mobilization during the outreach. A total of 20 commercial transporters were selected, the transporters were sensitized for about 1 hour on the content of information to be passed to the community. They were also given IEC materials in local languages. Health workers were also trained and necessary commodities provided.

Results and lessons learnt: An increased average daily out patient load was observed in the PHC in the community from an average of about 5 patients per day to about 50 patients daily. A total of 308 presumptive TB cases (125 males & 183 females) were sent for TB diagnosis during the one week outreach campaign, 5% (15) of the presumptive TB cases were diagnosed with TB and were treated.

Conclusions and key recommendations: The use of commercial transporters for active community mobilization resulted in massive turnout of TB suspects for TB screening during the outreach. These transporters are well known in the community and therefore present an opportunity for continuous community mobilization and raising awareness about TB in the community.

PC-1197-06 Engaging commercial motorbike riders in creating TB awareness in the communities in Oyo State, Nigeria

O Lawal,¹ O Oladimeji,^{2,3} O Eltayeb,⁴ O Daniel,⁵ A Awe,⁵ M Gidado⁶ ¹Oyo state Ministry of Health, Ibadan, ²Center for Community Health Care, Research and Development, Abuja, Nigeria; ³Liverpool School of Tropical Medicine, Liverpool, UK; ⁴Damien Foundation, Ibadan, ⁵World Health Organization, Abuja, ⁶KNCV Nigeria, Abuja, Nigeria. e-mail: droladfb@gmail.com

Background: Poor awareness of free screening and treatment of TB is one of the major factors responsible for missed TB cases and delayed diagnosis in Oyo state, which is one of the thirteen high burden states in Nigeria. It is therefore necessary to evolve ways of improving the situation of TB screening and diagnosis. Motorbikes are major means of transportation in most streets in cities, towns and villages either commercially or privately owned. The objective is to highlight the contribution of this innovative approach to improve TB case notification in the communities.

Design/Methods: Advocacy meetings with members of the association of commercial motorcyclists in four LGAs to facilitate awareness building on TB and contract engagement to carry the TB banners. Capacity building on TB and referral linkages involving the 2 DOTS officers per LGA on data collection tools and 80 members of the association selected on the basis of 20 motorbikes per LGA from 4 LGAS.

Results: A total of 24 DOTS officers and 80 motorcyclists were involved in the project resulting in 3945 presumptive TB referral and 2562 phone calls and text messages received in the 4th Q 2014 compared to 2341 screened in 3rd Q 2014. The case notification also increased by 12% from 1623 in Q4 2013. HIV positivity rate was 7%. Eight percent of those referred were new smear +ve TB cases.

Conclusion: The results indicated that engaging the motor bikers to carry the banners in their rears have positive and cost effective impacts for creating awareness to also compliment the efforts of CBO and CV. We suggest a bigger try of this strategy.

PC-1198-06 Tuberculosis contact investigation: perspectives of TB contacts in Kampala, Uganda

I Ayakaka,¹ S Ackerman,² L Davis,³ A Katamba,⁴ E Fair,⁵ A Cattamanchi,³ M Handley,⁵ J Ggita⁴ ¹Infectious Diseases Research Collaboration, Kampala, Uganda; ²University California San Francisco, San Francisco, CA, ³Curry International TB Center, San Francisco, CA, USA; ⁴Makerere University, College of Health Sciences, Kampala, Uganda; ⁵San Francisco General Hospital, San Francisco, CA, USA. e-mail: ayakaka@gmail.com

Background and challenges to implementation: The WHO recommended TB contact investigation (CI) be routinely implemented in high-burden countries like Uganda. Many national guidelines recommend CI, but data on how to implement this in routine practice is

limited. We conducted focus group discussions (FGDs) and in-depth interviews (IDIs) with household TB contacts to describe their knowledge and attitudes towards contact investigation and identify barriers to and enablers of CI in Kampala, Uganda.

Intervention or response: We developed a theory-informed discussion guide based on the Behavior Change Wheel, a synthesis of 19 behavior-change frameworks to assess how contacts described their capabilities, opportunities and motivations (COM) in regard to CI. We explored acceptability of potential interventions, like home sputum collection and HIV testing and use of technology to collect clinical information and communicate results, to address identified barriers. A Ugandan social scientist and TB epidemiologist led the discussions. Thematic analysis of de-identified FGDs and interview transcripts was performed to identify barriers related to COM.

Results and lessons learnt: We held 1 FGD and 13 IDIs with 36 TB household contacts from 14 households. Of the 14, 7 had been visited by a community health worker (CHW) to monitor treatment adherence and the other 7 had not. The main barrier related to capability was limited TB knowledge especially in households not visited by a CHW. Barriers to physical opportunity included clinic travel costs and inconvenient clinic hours. Barriers to motivation included fear of community stigma from identification of CHWs in uniform. Most prevalent in households not yet visited by a CHW, contacts described lack of confidence in health centers due to long queues, inattentive medical workers and drug stock outs in government facilities. Main enablers of CI cited were CHWs, valued for the ability to provide much needed information about TB and direct linkage to providers, reducing clinic waiting times. Communication with CHWs through home visits or phone contact were both acceptable and desirable.

Conclusions and key recommendations: Cited barriers to CI were lack of knowledge, belief that health units provide poor, challenging to access services. Our analysis suggests improved education, convenient access to TB diagnostics, streamlined clinic visits and improved communication may overcome identified barriers. Homebased sputum is acceptable.

59. Basic science: host

PC-1199-06 Quantitative membrane proteomics reveals new functions of CD13 in *Mycobacterium tuberculosis* infection

C-P Kuo,¹ R Lin¹ ¹MacKay Memorial Hospital, Taipei, Taiwan. e-mail: pongow@gmail.com

Background: The cellular immune response for *Mycobacterium tuberculosis* infection remains incompletely understood. To uncover membrane proteins involved in this infection mechanism, an integrated approach consisting of an organic solvent-assisted membrane protein digestion, stable-isotope dimethyl labeling and LC-MS/

MS (chromatography-mass spectrometry/mass spectrometry) analysis was used to comparatively profile the membrane protein expression of human dendritic cells upon heat-killed *M. tuberculosis* treatment.

Design/Methods: Organic solvent-assisted trypsin digestion coupled with stable-isotope labeling and LC-MS/MS analysis was applied to quantitatively analyze the membrane protein expression of THP-1 derived dendritic cells. We evaluated proteins that were up-regulated in response to heat-killed *M. tuberculosis* treatment, and applied STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) website database to analyze the correlations between these proteins.

Results: By using confocal microscopy and flow cytometry, we found that membranous CD13 expression was upregulated and was capable of binding to mycobacteria. Treatment dendritic cell with anti-CD13 antibody during *M. tuberculosis* infection enhanced the ability of T cell activation.

Conclusion: Increasing expression of CD13 on dendritic cells while *M. tuberculosis* infection and enhancement of T cell activation after CD13 treated with anti-CD13 antibody indicates CD13 positively involved in the pathogenesis of *M. tuberculosis*.

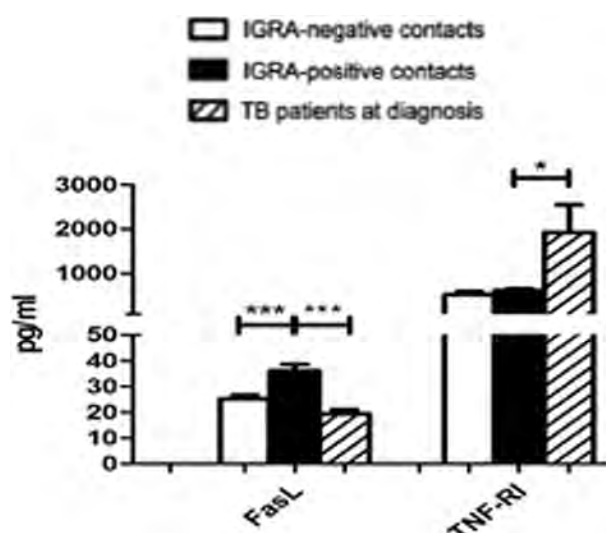
PC-1200-06 T-lymphocyte dysfunction is responsible for immunosuppression in active tuberculosis

C-C Shu,¹ J-Y Wang,¹ C-J Yu¹ ¹National Taiwan University Hospital, Taipei, Taiwan. e-mail: stree139@yahoo.com.tw

Background: Tuberculosis (TB) remains one of the most common infectious diseases and leading causes for mortality. During active tuberculosis, immunosuppression happens but the nature is unclear. Design: We enrolled 133 patients with TB and 193 IGRA-screening TB contacts (95 of them IGRA positive) to compare the cytotoxic ability by serum level of Fas ligand (FasL) and tumor necrosis factor receptor 1 (TNFR1). T-SPOT was used as IGRA method to screen latent TB infection. Furthermore, we enrolled 3 healthy subjects and 3 patients with TB to check the expression of programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) over CD4 lymphocyte.

Results: Serum FasL level was higher in IGRA-positive contacts than IGRA-negative contacts and TB patients whereas TNFR1 was higher in TB patients than IGRA-positive group (Figure 1). Further check in 3 healthy subjects and TB patients, PD-1 and CTLA-4 were higher in TB patient's CD4 lymphocyte than control group (Figure 2). Th1 lymphocyte by double positive stain of CD4 and interferon-gamma was lower in TB group but the PD-1 expression was higher. By contrast, Foxp3 positive CD4 lymphocyte was higher in TB patients, who's PD-1 was also higher than healthy control.

Conclusion: In TB infection, extrinsic pathway of apoptosis was down-regulated in active infection than latent status. In cellular pathway, PD-1 and CTLA-4 may play the important role in the down-regulation mechanism.



PC-1201-06 Recruitment of antigen specific T-cells in pulmonary tuberculosis

B Kalsdorf,^{1,2} T Schmidt,³ E Petruccioli,⁴ J Hofmeister,¹ M Sester,³ D Goletti,⁴ C Lange^{1,2} ¹Research Center Borstel, Borstel, ²German Center for Infection Research, Borstel, ³University of the Saarland, Homburg, Germany; ⁴National Institute for Infectious Diseases, Rome, Italy. Fax: (+49) 4537188 3130. e-mail: kalsdorf@yahoo.de

Background: T-cell mediated immunity is critical for immune control of tuberculosis. To investigate how antigen-specific T-cells are attained to the lungs, cells from peripheral blood and bronchoalveolar lavage (BAL) of individuals with pulmonary tuberculosis and LTBI were compared.

Design/Methods: In three centers in Europe, peripheral blood was drawn and a bronchoscopy was performed on patients who were suspected of having pulmonary tuberculosis with negative acid-fast bacilli sputum smears, who underwent regular bronchoscopy as part of the diagnostic workflow. Healthy persons with LTBI (defined by the positive interferon gamma (IFN γ) immune response to *M. tuberculosis*-specific antigens in the blood but not in the BAL) served as a control group. Cells were left unstimulated or stimulated with aCD3, PPD, ESAT-6 / CFP-10 and CMV for 18 hours. Immunophenotype was characterized by effector/ memory (CD3, CD4, CD8, CD27, CD45RO), homing receptor expression (CCR7) and functionality by antigen-specific IFN γ and IL-2 production. Statistical analysis for paired data was performed by Wilcoxon Signed Rank test and comparative analysis between groups by the Mann-Whitney U-test for nonparametric data.

Results: Fourteen out of 69 patients, in whom the diagnosis of tuberculosis was confirmed by culture positivity, were compared with ten healthy participants. Irrespective of tuberculosis status, BAL T-cells had significant higher percentages of CD4+ CD27- CCR7-intermediate differentiated effector T-cells ($P < 0.01$) and CD4+ CD45RO- CD27- CCR7- terminally differentiated

T-cells ($P = 0.016$) than blood. Comparing patients with tuberculosis and LTBI, the proportion of CD4+ CD45RO+ CD27+ CCR7- effector-memory T-cells in blood trended to be reduced. After antigen-specific stimulation of in BAL cells, interleukin (IL)-2 and IFN γ were mainly produced from a CD4+ CD45RO+ CD27- CCR7- subpopulation.

Conclusion: Effector T-cells in BAL of patients with pulmonary tuberculosis are specifically recruited into the lungs and produce antigen-specific cytokines. Due to the loss of the CCR7 homing receptor, the intermediate differentiated T-cells will persist at the focus of infection and not move back to the lymphnodes. Results from this study may have implications for vaccine development or therapeutic interventions.

PC-1202-06 Smoking and interleukin-4 gene C-589T polymorphism in patients with chemoresistant pulmonary tuberculosis

D Butov,¹ M Kuzhko,² N I Makeeva,¹ T Butova,¹ A Stepanenko,¹ N N Pitenko¹ ¹Kharkiv National Medical University, Kharkiv, ²National Institute on Phthisiatry & Pulmonology, F.G. Yanovsky NAMS of Ukraine, Kiev, Ukraine. e-mail: dddimad@yandex.ru

Background and objective: Determine IL-4 gene C-589T polymorphism in smokers with multi-drug-resistant tuberculosis (MDR-TB) in lungs on the background of the respective cytokine production of blood.

Methods: The study included 170 people in Kharkiv region of Ukraine including 60 patients with MDR-TB and smoking (1st group), 36 - without MDR-TB and smoking (2nd group), 14-with MDR-TB and non-smoking (3rd group) 30-without MDR-TB and non-smoking (4th group) and 30 healthy donors (5th group). Serum levels of IL-4 were evaluated by ELISA. Investigations of gene polymorphisms of this cytokine were performed using restriction analysis of the amplification products of specific regions of the genome, i.e., promoter region C-589T of IL-4 gene. Statistical evaluation: the obtained data were evaluated by standard Student t-test and probability relative frequency deviation from a constant probability of independent trials. The difference was considered to be significant at $P < 0.05$.

Results: In the 1st group the levels of IL-4 were (7.35 ± 0.27) pg/L, 2nd - (10.19 ± 0.42) pg/L, 3rd - (10.58 ± 0.66) pg/L, 4th- (12.61 ± 0.50) and 5th - (29.99 ± 1.27) pg/L. Differences between the 1st and 3rd, 2nd and 4th, TB patients and 5th groups were significant ($P < 0.001$). Normal homozygote genotype IL-4 predominated in healthy donors was $56.67 \pm 9.05\%$ ($n = 17$) compared to patients with TB: 1st group- $11.67 \pm 4.14\%$ ($n = 7$), 2nd- $8.33 \pm 4.61\%$ ($n = 3$), 3rd- $21.43 \pm 11.38\%$ ($n = 3$) and 4th- $26.67 \pm 8.07\%$ ($n = 9$). Heterozygous genotype IL-4 was observed in $83.33 \pm 4.81\%$ ($n = 50$) in 1st, $22.22 \pm 6.93\%$ ($n = 8$) in 2nd, $21.43 \pm 11.38\%$ ($n = 3$) in the 3rd, $3.33 \pm 3.28\%$ ($n = 1$) in 4th and $23.33 \pm 7.72\%$ ($n = 7$) in 5th groups. Mutation homozygous genotype IL-4 was $5.00 \pm 2.81\%$ ($n = 3$) in the 1st group, in 2nd- $69.44 \pm 7.68\%$ ($n = 25$),

3rd–57.14±13.73% ($n=8$), 4th–66.67±8.61% ($n=20$) and 5th–20.00±7.30% ($n=6$). Differences between the 1st and 3rd, 2nd and 4th, TB patients and 5th groups were significant ($P < 0.05$).

Conclusion. Smoking contributes to significant activation polymorphism C-589T gene IL-4 heterozygous type that may lead to changes in the immune system making susceptible to MDR-TB. Compared to healthy controls patients with TB had significantly decreases levels of serum IL-4. This coincided with greater frequency of heterozygous and heterozygous genotype polymorphism C-589T of IL-4 gene. In addition, these studies revealed a significant influence of the polymorphism C-589T gene IL-4 (with polymorphism IL-2 and IL-10 genes, which we also studied) on the changes in the population of Th-lymphocytes, clinical symptoms, relapse of tuberculosis, formation destructions in the lung, which may treatment outcomes in patients with MDR-TB.

PC-1204-06 Epigenomic effects of hookah tobacco smoke in normal human respiratory epithelia and lung cancer cells

D Schrupp,¹ Y Xiong,¹ S Xi,¹ S Azoury,¹ M Zhang,¹ J Shan,² J Hong¹ ¹National Cancer Institute, Bethesda, MD, ²National Cancer Institute, Frederick, MD USA. e-mail: David_Schrump@nih.gov

Background: Although perceived by many to be a safe alternative to cigarettes, hookah smoke contains a number of carcinogens present in cigarette smoke. To date, epidemiologic associations between hookah tobacco exposure and lung cancer risk have not been firmly established. In the present study, a well-established in-vitro model system was used to directly compare the epigenomic effects of hookah smoke relative to cigarette smoke in normal human respiratory epithelia and lung cancer cells.

Design/Methods: Waterpipe condensates (WPC) and cigarette smoke condensates (CSC) were prepared from commercial Al Fakher tobacco and 3R4F cigarettes (University of Kentucky Research Labs), respectively, using Borgwaldt precision smoking machines. Normal human small airway epithelial cells (SAEC), and cdk-4/hTERT-immortalized human bronchial epithelial cells (HBEC), as well as Calu-6 (p53 -/-) and A549 (p53 wt) NSCLC lines were cultured in the presence or absence of varying concentrations of WPC or CSC. MTT assays were used to evaluate effects of condensates on cell proliferation; qRT-PCR, and immunoblot techniques were used to examine mRNA, microRNA and histone alterations mediated by WPC relative to CSC.

Results: Five day WPC exposures mediated variable effects in cultured respiratory epithelia and lung cancer cells. In SAEC and HBEC, WPC exposure mediated dose-dependent growth inhibition. At lower doses (0.1mg/ml and 0.5mg/ml), WPC enhanced, whereas at higher concentrations (1.0mg/ml and 2.0mg/ml), WPC inhibited proliferation of Calu-6 cells. WPC had minimal effects on growth of A549 cells except at high concentrations (2.0mg/ml), which inhibited proliferation of these cells.

Similar to CSC, WPC decreased H4K16Ac and H4K20Me3 levels in SAEC and HBEC. In addition, like CSC, WPC increased miR-31 and decreased miR-487b expression in SAEC, HBEC and lung cancer cells. Furthermore, in a dose-dependent manner, WPC increased expression of Cyp1a1, Cyp1b1, ABCG2, Lin28B, Myc, SALL4, CTCF, and JARID2 in SAEC and/or HBEC cells, and up-regulated Cyp1a1, Cyp1b1, and ABCG2 in lung cancer cells. WPC (2mg/ml) exposure significantly decreased expression of Dkk-1 in HBEC and Calu-6 cells. Cigarette smoke induced similar changes in these cells.

Conclusion: These preliminary findings support more comprehensive array-based analysis of this in-vitro model system to further delineate epigenomic mechanisms by which hookah smoke may contribute to initiation and progression of human lung cancers.

60. Imaging and prediction rules for TB diagnosis

PC-1206-06 An improved hardware neutral computer aided detection platform for tuberculosis interpretation from chest X-rays with advanced false-positive reduction

M Acharyya¹ ¹Advenio TecnoSys, Chandigarh, India. e-mail: mausumi.acharyya@adventecnosys.com

Background: An automated CADx tool for consistent high performance interpretation of pulmonary tuberculosis (PTB) in dCXRs with a focus on reducing false-positives (FPs) is proposed.

Design/Methods: A two-layered coarse-to-fine cascade framework under supervised learning is proposed. The first step is candidate generation module on a training data set. A true candidate is a localized region within the lung which exhibits TB patterns. Candidate generation step involves extracting several descriptive features within annotated localized patches corresponding to normal and TB infected and subsequently training the first level classifier (random tree) with these features. At this stage we achieve high sensitivity but also with a high false positive level. The candidates classified as TB infected are positive examples are then described by regions of interest (ROI) and are used as input for the second level classifier. In the second level each candidate is resampled via scaling, translations, and rotations to increase the variation of the training data and to avoid overfitting. These multiple views of candidates are used to train a deep Convolutional Neural Network (CNN) classifier. The CNN provides probability for each ROI view which are averaged and a single probability measure is obtained for each ROI or candidate. For an unknown test dCXR image, candidates are similarly generated and the CNN classifier is applied to produce the probability measures for each ROI averaging which gives the single probability of each candidate and classifies it to be normal or abnormal based on a threshold value of the probability measure. This second

level classifier behaves as a highly discriminating process to discard challenging false positives while still achieving high sensitivity. The training dataset is representative of clinical and community settings. Around 1000 digital X-ray of chest – dCXR (posterior-anterior view) would be obtained in partnership with The National Institute for Research in Tuberculosis (WHO Supranational Reference Laboratory), Chennai & Asian Institute of Public Health (grantee StopTB REACH programs in East India), Bhubaneswar. The data represents the spectrum of PTB radiological markers with confirmatory clinical annotations (microbiology culture as gold standard).

Results: ROC and AUC are calculated. 90% sensitivity with 80% specificity is achieved

Conclusion: Proposed tool consistently interprets dCXRs with high sensitivity and specificity.

PC-1207-06 Imaging characterization of cavitary lesion of lungs and histopathological correlation: a hospital-based prospective observational study

S Dahal¹ ¹National Academy of Medical Sciences, Kathmandu, Nepal. e-mail: shishir15@mail.ru

Background: Pulmonary tuberculosis is an important cause of lung cavity along with bronchogenic carcinoma. Imaging characterization of cavitary lesion in chest radiograph and/or in computed tomography has great importance in identifying benign versus malignant lesion where suspicious malignant lesion requires further invasive investigation. Differentiating benign cavity from malignant one is crucial in further investigations and management.

Design/Methods: This cross sectional, hospital based, observational study was conducted at National Academy of Medical Sciences. A total of 54 patients with cavitary lung lesion were evaluated in contrast enhanced computed tomography and computed tomography guided biopsy were taken from the cavitary wall for histopathological diagnosis. In computed tomography pulmonary cavities were characterized by size, wall thickness, and smoothness of inner wall, content of cavity and enhancement of cavitary wall. Each of these parameters are correlated with the Fine Needle Aspiration Cytology findings of malignant and inflammatory (tubercular and non tubercular) cavity. Univariate analysis is presented as Spearman correlation coefficient.

Results: Malignant cavity showed the strongest correlation with larger cavity with mean diameter more than 20 mm ($r=0.6$) and irregularity of inner cavitary wall ($r=0.7$). While significance enhancement of cavitary wall has weakly correlated with malignancy ($r=0.35$). Correlation between malignant cavity and content is of no statistical significance. All non malignant cavities are tubercular in histopathology. Fluid content in the cavity has stronger negative correlation with non malignant cavity ($r=2$). There is no statistical significant correlation between non malignant cavities rest of other characteristics of cavity.

Conclusion: Irregularity of inner wall of pulmonary cavity and larger size cavities correlates best with malignancy while fluid content in the cavities show strong negative correlation with non malignant cavities.

PC-1208-06 Objective computerized chest radiography screening to detect tuberculosis in the Philippines

R Philipsen,¹ C Sánchez,¹ P Maduskar,¹ J Melendez,¹ B Van Ginneken,¹ W J Lew² ¹Radboud University Medical Center, Nijmegen, Netherlands; ²World Health Organization, Philippine Country Office, Manila, Philippines. e-mail: rphilipsen@gmail.com

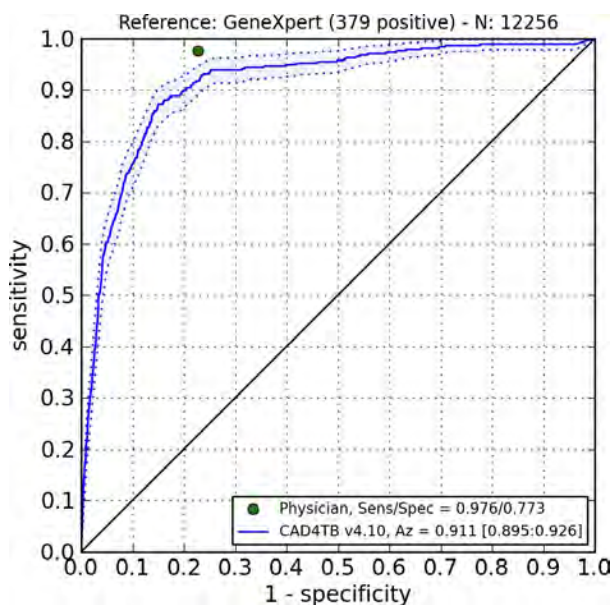
Background: In the Palawan provincial areas of the Philippines, screening for pulmonary tuberculosis (TB) is performed in a WHO project by symptom screening combined with chest radiography; if at least one of these is positive, subjects undergo molecular Xpert testing. However, interpreting chest radiographs (CXRs) requires skilled personnel whose availability is limited and training is expensive and logistically challenging. Computerized reading is a potential solution: CXRs are objectively interpreted by software for the presence of TB related abnormalities. Operational costs are minimal and a result is available within one minute. We retrospectively engaged computerized reading in the DetectTB (Diagnostic Enhanced Tools for Extra Cases of TB) project, an intensified case finding program targeting prison settings and high-risk communities on Palawan Island in the Philippines.

Methods: A retrospective study was carried out on all cases in the DetectTB program available mid 2014. We compared the performance of CAD4TB v4.10, a commercially available software package, against the performance of the physician's readings. CAD4TB scores a posterior-anterior CXR for TB related abnormalities on a scale from 0 (normal) to 100 (abnormal). We performed Receiver Operator Characteristic (ROC) curve analysis to compare the computerized and human reading and visually inspected CXRs marked as normal by the physician but as highly suspicious by the software.

Results: In total, 12 256 radiographs were available for analysis. The number of cases positively read by the physicians was 3068 (25.0%). 379 subjects (3.1%) tested positive on Xpert. Defining these cases as positive, and the remaining cases as negative, the area under the ROC curve (Az) achieved by CAD4TB v4.10 was 0.911 [CI: 0.895-0.926]. The software achieved 90.0% sensitivity at 80.0% specificity. The physician had a sensitivity of 97.6% and a specificity of 77.3%, which is slightly better than the software. However, this reading is biased as cases that were considered normal by the physician were considered negative by definition in our study design. An independent human observer considered 78 out of the 100 cases read as normal by the physician with the highest CAD4TB scores to be abnormal.

Conclusion: Computerized reading provides high sensitivity and specificity and may be used to assist or possibly

replace a human reader in active case finding programs, and thus improve screening throughput.



PC-1209-06 Computerized reading of chest radiographs in The Gambia National Tuberculosis Prevalence Survey: retrospective comparison with human experts

P Maduskar,¹ I Adetifa,^{2,3} E Leroy Terquem,⁴ J Van Den Hombergh,⁵ A Fasan-Odunsi,⁶ C Sánchez,¹ U D'alessandro,² B Van Ginneken¹ ¹Radboud University Medical Center, Nijmegen, Netherlands; ²Medical Research Council Unit, Fajara, Gambia; ³London School of Hygiene & Tropical Medicine, London, UK; ⁴Centre Hospitalier de Meulan les Mureaux, Meulan-en-yvelines, France; ⁵PharmAccess International, Dar Es Salaam, Tanzania; ⁶Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria. e-mail: pragnya.m@gmail.com

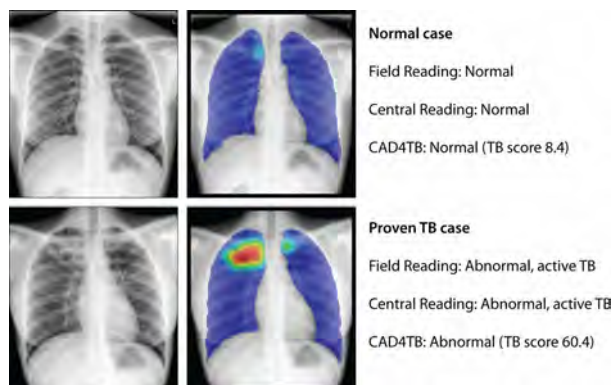
Rationale: Tuberculosis (TB) prevalence surveys require recruitment of trained personnel for reading chest radiographs (CXRs), which is scarce in high TB burden countries. Computerized CXR reading could replace human readers in such a scenario and we retrospectively investigate this possibility on data from the 2011-2013 TB prevalence survey in The Gambia.

Methods: Computerized readings were compared with field and central readings on 4552 CXRs. The survey participants were screened based on symptoms and CXR findings. Field readers judged CXRs on radiological findings as: "Normal", "Abnormal, suggestive of TB" or "Other abnormalities"; the latter two were considered abnormal. In case of symptoms and/or abnormal CXR, sputum samples were collected and bacteriological tests (fluorescence microscopy and BACTEC MGIT[™] culture) were performed for confirmatory TB diagnosis. Following the analysis, 73 subjects with proven TB were considered "Abnormal" and the remainder as "Normal". The CXRs were centrally audited by an expert reader and one of the following categories was assigned to each

CXR: "Normal", "Active TB", "Abnormal, healed TB", or "Other pathology". The software (CAD4TB, Radboud University Medical Center, Nijmegen, The Netherlands) computed a TB score between 0-100 (0-Normal, 100-Abnormal) for each CXR. The area under receiver operating characteristic curve (AUC) was calculated for CAD4TB and various cut-off points were chosen on the TB score to compare specificities at the sensitivities of the field and central readings.

Results: The field reading achieved a sensitivity of 86.3% at 72.8% specificity. The central reading had a sensitivity of 67.1% at 93.3% specificity, and when the "healed TB" category was considered abnormal, sensitivity increased to 87.7% with a decrease in specificity to 65.2%. CAD4TB attained an AUC of 0.90 and at all three sensitivity levels of human readers, specificity was nearly identical and not significantly different ($P > 0.05$): at field sensitivity, CAD4TB had a specificity of 72.2%, and for central sensitivity levels, specificities of 93.7% and 66.0% ("healed TB" as abnormal) were obtained.

Conclusions: When selecting subjects in a prevalence survey on the basis of chest radiography to undergo confirmatory testing for TB, the performance of computerized reading is not significantly different from field and central readings by human experts. The software has potential to improve the efficiency of TB prevalence surveys.



PC-1210-06 Development of a clinical prediction rule for the diagnosis of pleural tuberculosis in Peru

A Soto,^{1,2} L Solari,¹ J Agapito,³ P Van Der Stuyft^{1,4}

¹Institute of Tropical Medicine of Antwerp, Antwerp, Belgium;

²Hospital Nacional Hipolito Unanue, Lima,

³Universidad Peruana Cayetano Heredia, Lima, Peru; ⁴Ghent University, Ghent, Belgium. e-mail: lelysol@hotmail.com

Background: Pleural tuberculosis is one of the most common forms of extra-pulmonary tuberculosis and is still a diagnostic challenge. Some Clinical Prediction Rules (CPRs) are available for pleural tuberculosis, but their external validity is uncertain. The aim of this study was to develop a CPR for diagnosis of pleural tuberculosis in Peru.

Design/Methods: Adult patients with pleural exudates of unknown origin attending 2 reference hospitals in Lima, Peru, from 2009 to 2011 were evaluated through basic laboratory tests on pleural fluid and microbiologic tests (smears for Acid-fast bacilli (AFB), cultures and Real Time PCR). Closed pleural biopsy was performed for diagnosis of tuberculosis, which was defined as a positive smear for AFB, a positive culture or positive PCR in pleural fluid or biopsy OR presence of caseating granulomas in histopathology OR suggestive histopathological results with resolution of clinical symptoms at the third month of treatment initiation. Logistic regression defined the parameters significantly associated with pleural tuberculosis and a score was developed on this basis. The required sample size was 259.

Table Results of the logistic regression model for pleural tuberculosis and number of points assigned to each predictive finding in the developed Clinical Prediction Rule.

Predictive findings	Odds Ratio (95% confidence interval)	p value	Number of points assigned
Clinical predictors			
Gender (male)	2.85 (1.23-6.56)	0.01	+11
Contact with a tuberculosis case	3.03 (1.26-7.24)	0.01	+14
Disease duration in weeks	0.93 (0.87-1.00)	0.05	-(duration of disease/2)
Haemoptysis	0.15 (0.04-0.66)	0.01	-15
Lymphadenopathy	0.21 (0.08-0.57)	<0.001	-17
Age	0.97 (0.94-0.99)	<0.001	-(Age in years/2)
Pleural fluid analysis			
Proteins in g/dL	1.75 (1.18-2.62)	<0.001	+8*(proteins)
Adenosine deaminase (ADA) in U/L	1.04 (1.03-1.06)	<0.001	+(ADA)/2

Results: We included 268 patients with complete data available. 181 (67%) had pleural tuberculosis according to our criteria. The parameters associated to tuberculosis were age, gender, contact with a case of tuberculosis, duration of disease, haemoptysis, lymphadenopathy, pleural fluid proteins and ADA. Night sweats, fever, blood cell count, lymphocyte predominance in pleural fluid and pleural LDH were not associated to tuberculosis. According to the results of the logistic regression model, a CPR was proposed. Table 1 shows these results and the CPR. Its area under the ROC curve was 0.94. At a cutoff of 38 points, the CPR attained a sensitivity of 90%, a specificity of 91%, a positive likelihood ratio (PLR) of 9.72 and a negative likelihood ratio (NLR) of 0.11. If 2 cutoffs instead of one were used at 30 and 50 points, where patients with <30 points were taken as low probability and patients with >50 as high probability of pleural tuberculosis, the PLR would be >10 and the NLR <0.10 and decisions could be taken on 92% of patients.

Conclusion: The developed CPR can be used as a tool for diagnostic evaluation of patients with clinical suspicion of pleural tuberculosis. Its diagnostic performance in this population was high. Prospective validation is needed before widespread implementation in Peruvian hospitals.

PC-1211-06 A systematic review of prediction models for estimating the probability of pulmonary tuberculosis in adults

S Van Wyk,¹ H-H Lin,² M Claassens¹ ¹Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; ²Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan. e-mail: susansvanwyk@gmail.com

Background: Current symptom screening for tuberculosis (TB) has sub-optimal sensitivity and TB cases are missed. A prediction model combining socio-demographic characteristics and medical history to estimate an adult's absolute probability of having active pulmonary TB (PTB) could be useful in identifying presumptive TB cases at an early stage, leading to early diagnosis and treatment. A systematic review was conducted to describe the characteristics of prediction models for estimating the probability of having PTB in adults.

Design/Methods: A prediction model was defined as the combination of two or more clinical predictors designed to estimate the probability of having TB. Studies using culture confirmed PTB as reference standard were included. Models for inpatients, children or specific patient populations (e.g. dialysis patients) were excluded. PubMed, Scopus and the Cochrane Library and abstracts from the Union, American Thoracic Society and European Respiratory Society conferences were searched. Reference lists from identified studies were checked. The TRIPOD statement was used to assess completeness of reports and model classification. The CHARMS checklist guided risk of bias assessment.

Results: From 13 671 identified records, 10 were included for data extraction; 9 were from high burden countries; 5 assessed only smear negative PTB as outcome and 7 focused on human immunodeficiency virus (HIV) infected individuals only. Full appraisal of models was difficult due to lack of clarity and incomplete reports. Eight studies were type 1a prediction model studies where predictive performance was evaluated using exactly the same data set as was used for development (apparent performance); one study was a type 1b model where internal validation was done using bootstrapping techniques and one was a type 4 study, where predictive performance of a published prediction model in inpatients was assessed on outpatient data. The type 4 model included hemoptysis, age >45, weight loss, expectoration and apical infiltrates on chest radiography as predictors and might be useful for ruling out PTB in smear negative presumptive TB cases without previous history of TB in hospital outpatient settings (score<0: NPV 94.9% [95%CI: 86-99]). Results could not be pooled due to heterogeneity.

Conclusion: Existing prediction models for estimating the probability of having PTB in adults at primary care level are poorly reported and validated and therefore not useful for TB screening. WHO symptom screening is still recommended.

61. Alternative diagnostics for drug resistance

PC-1214-06 Multicenter evaluation of high resolution melting curve for detection of extensively drug-resistant *Mycobacterium tuberculosis*

Y Pang,¹ X Hui,¹ H Dong,² Z Zhang,² S Huan,³ J Zhang,²
D Chin,³ Y Zhao¹

¹Chinese Center for Disease Control and Prevention, Beijing, ²PATH, Beijing, ³Bill and Melinda Gates Foundation, Beijing, China. e-mail: pangyu@chinatb.org

Drug-resistant tuberculosis (TB), especially multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), is still one of the most serious threats to TB control worldwide. Early diagnosis of drug-resistant is essential for generating the effective chemotherapy regimen. High resolution melting curve (HRM) is a rapid method for detecting XDR-TB. Several preliminary data have demonstrated that HRM shows excellent performance to detect the rifampicin- and isoniazid-resistant TB, while it has not been effectively evaluated among large clinical samples. In this study, we evaluated the performance of HRM for XDR-TB in 772 TB smear-positive patients in two TB laboratory of China. When setting the MGIT 960 drug susceptibility testing (DST) as golden standard, our results revealed that the sensitivity and specificity of HRM were 90.1% and 96.3% for rifampin (RIF) resistance, and 81.5% and 98.3% for isoniazid (INH) resistance, respectively. For second-line anti-TB drugs, the sensitivity and specificity of HRM were 76.3% and 98.3% for ofloxacin (OFLX) resistance, and 50.0% and 98.4% for kanamycin (KAN) resistance, respectively. In conclusion, our research demonstrates that HRM can be used as an alternative for detecting RIF, INH and OFLX resistance. The low cost of HRM makes it available to be broadened in limited-resource laboratories in China. The unsatisfactory performance of HRM to detect KAN resistance highlight the urgent need for explore the potential KAN resistant mechanism of *Mycobacterium tuberculosis*.

PC-1215-06 Revisiting the microbial diagnosis of drug-resistant tuberculosis

E Cambau¹ ¹Assistance Publique Hôpitaux de Paris, Paris, France. Fax: (+33) 1 4995 8537. e-mail: emmanuelle.cambau@lrp.aphp.fr

Background: Detection of drug-resistance and reliable detection of susceptibility are both required in order to design an efficient individualized treatment regimen for multidrug resistant tuberculosis. While genotypic detection of resistance can be done for some drugs only, phenotypic drug susceptibility testing is difficult to standardize for second line antituberculous drugs.

Design/Methods: We aim to combine phenotypic drug susceptibility testing and genotypic detection of resistance to first line and second line drugs for the microbial diagnosis of drug-resistant *Mycobacterium tuberculosis* strains. We performed first a new protocol of DST, using the TBeXiST-Epicenter software in MGIT 960. This protocol includes a first phase of resistance screening with one critical concentration. In case of resistance, TBeXiST DST has a second phase of quantitative determination of resistance by testing growth at increasing drug concentrations, complemented by genetic assessment of resistant mutations.

Results: Combining phenotypic and genotypic assessment of resistance provided highly reliable results for resistance. Screening at critical concentration closed to epidemiological cut-off (ECOFF) provided highly reliable results for susceptibility. In case of MDR or XDR-TB, the determination of the resistance level helps in setting a 4 to 5 drugs regimen affordable for these cases. The final results are obtained rapidly (median 10 days) since the growth is observed in a real-time manner and not endpoint of 28-42 days. Resistance can be observed even shorter, after 4-5 days. Finally, heterogeneous resistance is easily detected since 10-fold diluted growth controls are run in parallel

Conclusion: Microbial diagnosis of drug resistance in TB was revisited by combining a new phenotypic DST protocol and extensive genotypic characterization providing a reliable and rapid protocol for assessment of susceptibility and resistance.

PC-1216-06 Mutations associated with second-line tuberculosis drug resistance in Georgia

N Bablishvili,¹ N Tukvadze,¹ E Shashkina,² B Mathema,³ Z Avaliani,¹ N Gandhi,⁴ H Blumberg,⁴ R Kempker⁴

¹National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; ²Public Health Research Institute TB Center in Newark, Newark, NJ, ³Department of Epidemiology, Columbia University, New York, NY, ⁴Division of Infectious Diseases Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA. e-mail: nino_bablishvili@yahoo.com

Background: Rapid detection of multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) is an essential component of TB-control. In prior work, we found the MTBDRsl assay, a commercially available molecular test, to have suboptimal performance in the detection of fluoroquinolone and injectable drug resistance. To better understand the genetic determinants of resistance we conducted targeted genetic sequencing of *Mycobacterium tuberculosis* (MTB).

Design/Methods: We performed a cross sectional study at the National Reference Laboratory (NRL) of the National Center for Tuberculosis and Lung Diseases (NCTLD) in Tbilisi, Georgia and the Public Health Research Institute (PHRI) TB Center in Newark, New Jersey. MTB isolates were stored samples obtained from a previous prospective study evaluating the performance of the MTBDRsl assay. DNA extraction was performed using the QIAamp DNA-kit for all positive subcultures

of MTB. Targeted DNA sequencing was performed for *gyrA*, *gyrB*, *rrs* and *eis* genes and compared to phenotypic drug susceptibility results.

Results: Among 112 MDR-TB isolates examined by phenotypic testing, 16(14%) were resistant to ofloxacin (OFX), 17(15%) to capreomycin (CAP), and 63 (56%) to kanamycin (KAN). Sequencing was successfully performed for each gene as follows: 111(99%) *gyrA*, 107(96%) *gyrB*, 104(93%) *rrs*, and 103(92%) *eis*. DNA sequencing identified mutations in *gyrA* and *gyrB* genes in 9(56%) of 16 and 5(31%) of 16 MTB isolates phenotypically resistant to OFX, respectively. The addition of *gyrB* mutations increased the sensitivity of OFX resistance detection by 13%. No *gyrA/B* mutations were found in 95 susceptible isolates. The A1401G *rrs* mutation was detected among 7 of 15(47%) and 7(12%) of 60 available MTB isolates resistant to CAP and KAN, respectively. No *rrs* mutations were found in susceptible isolates. Any *eis* mutations were found in 14(24%) of 59 and 7(14%) of 49 available isolates resistant and susceptible to KAN, respectively. In contrast, the C-14T mutation was found in 6(10%) of 59 KAN resistant isolates and in none of the KAM susceptible isolates. The addition of the C-14T mutations increased the sensitivity of KAN resistance detection by 10%.

Conclusion: The inclusion of C-14T *eis* and *gyrB* gene mutations would improve the sensitivity of rapid detection assays for KAN and fluoroquinolone resistance, respectively. In many MTB isolates, CAP and KAN resistance is not associated with known drug resistance mutations in *rrs* and *eis* genes.

PC-1217-06 Changes in mutations: a closer look at GenoType MTBDRplus assay results for the molecular diagnosis of drug-resistant *M. tuberculosis* in Lima, Peru

R Calderon,¹ C Pantoja,¹ K Tintaya,¹ L Lecca,¹ J Coit,² D Coleman,³ G R Davies,⁴ C Mitnick² ¹Socios En Salud Sucursal Peru, Lima, Peru; ²Harvard Medical School, Boston, MA, USA; ³Saint Georges University of London, London, ⁴University of Liverpool, Liverpool, UK. Fax: (+51) 1 547 2121. e-mail: rcalderon_ses@pib.org

Background: Multi-drug resistant tuberculosis (MDR) seriously threatens TB control and prevention programs. Effective control requires rapid diagnosis to facilitate prompt implementation of adequate therapy. The GenoType MTBDR assay is an effective diagnostic tool for MDR but it also provides key information on gene mutations involved in drug resistance. Here, we report resistance prevalence and mutation frequency in the context of a clinical trial in Lima, Peru

Design/Methods: Drug susceptibility testing (DST) for first-line anti-TB drugs was performed on sputum samples from patients newly diagnosed with TB and who consented to participate in a trial between 2013-2015 in Lima. DST for isoniazid (INH) and rifampin (RIF) was performed using BD BACTEC MGIT 960 system and GenoType MTBDR assay at the Socios En Salud Laboratory (SES-Lab).

Results: Among the 351 patients who consented, 328 were tested with the GenoType. Of those, 60 (20.1%) were drug-resistant; 28 (8.5%) were INH monoresistant, 32 (9.8%) were MDR and 5 were RIF monoresistant. GenoType and DST results are currently available for 197 patients; of these, 5 of were MDR on both methods (100% concordance) and mutations involved were *rpoB* S531L & D516V, *katG* S315T and *inhA* C15T. In all resistant specimens *rpoB* S531L, codon 533 & D516V, *katG* S315T and *inhA* C15T & T8C were involved. In the group resistant detected by GenoType, the frequency of mutations for *rpoB* D516V: 11 (28.9%); *rpoB* 526 codon: 0 (0%) and *rpoB* S531L: 27 (71.1%); for *katG* S315T: 36 (59.0%) and; for *inhA* C15T: 14 (23.0%). Moreover, mixed infections were detected in 15 (22.4%) of the patients. No discordant results between the two methods were found for RIF susceptibility, but discordance with INH was detected in 5; 3 without mutations and 1 with *inhA* T8C and 1 with *inhA* C15T

Conclusion: In Peru, TB control requires rapid DSTs for RIF as well as INH due to the high prevalence of INH monoresistance. This work also shows a possible change in the frequency of mutations. Therefore, given the high prevalence of MDR found in this group of newly diagnosed TB patients, continuous monitoring and deep evaluation on existing molecular DST will become important in the coming years in order to retain accuracy in results reporting. Genomic analysis may be necessary in order to further dissect these findings. Lastly, the application of the GenoType MTBDR assay is important and shows excellent concordance with standard drug susceptibility testing done in Peru.

PC-1218-06 Predictive value of the new GenoType MTBDRsl V2 for the baseline detection of drug resistance mutations among multidrug resistant tuberculosis patients

A W Dreyer,^{1,2} S Omar,¹ N Ismail^{1,3} ¹National Institute for Communicable Diseases, Johannesburg, ²University of Witwatersrand, Johannesburg, ³University of Pretoria, Pretoria, South Africa. e-mail: aw.dreyer@gmail.com

Background: The management of multidrug resistant tuberculosis (MDR-TB) patients in most cases consists of empiric second line drug regimens with subsequent long turnaround times for phenotypic results and potentially suboptimal therapy and associated drug resistance with poor outcomes. Molecular diagnostics assays have decreased turnaround times for the rapid detection of both *Mycobacterium tuberculosis* (MTB) and associated drug resistance significantly. The GenoType MTBDRsl V2 (Hain Lifesciences, Germany) is a commercially available assay for the detection of secondline drug resistance and utilize hybridization technology to assess both intact wildtype and associated mutations for fluoroquinolones (FQ) and second line injectables (SLI). The improved version includes detection associated with mutations in both *gyrA*, *gyrB*, *rrs* and *eis*.

Design/Methods: Baseline sputum samples were collected from MDR-TB patients initiating treatment. MTB

was isolated using liquid culture (Bactec MGIT960 system) and sequencing performed for secondline drug resistance mutations targeting *gyrA*, *gyrB* (FQ) and *rrs* (SLI) regions. The frequency of the resistance mutations were determined and expressed as a percentage. The performance of the assay to predict secondline resistance was assessed.

Results: Of the 254 MTB isolates available for sequencing a total of 49(19.29%) showed mutations in the *gyrA* region and 11(4.33%) mutations in the *gyrB* region. For the fluoroquinolones A90V (42.86%) and D49G (46.94%) were the most common mutations detected within *gyrA*. Among the 11 mutations within *gyrB* and K537Q (36.36) and L566F (18.18) were more frequent. Mutations within the *rrs* region was detected among 65(25.6%) of isolates and showed great variability with 11 different mutations detected of which A514C (17.65%) and C517T (23.53%) were the most frequent. The predictive value of the Genotype MTBDRsl assay was calculated at 97.96% for *gyrA* when considering probing for both absence of wildtype and mutations and 45.45% of *gyrB* mutations. The mutation missed in *gyrA* was a double mutation, L105R_G112A, with corresponding phenotypic resistance. Only 14.71% of the *rrs* mutations would have been detected with the assay.

Conclusion: The Genotype MTBDRsl assay V2 is a useful tool for the rapid baseline assessment for second line drug resistance pending phenotypic drug susceptibility results and could potentially improve patient outcome by early initiation of appropriate therapy.

PC-1219-06 Preliminary analytical performance of the BD MAX MDR-TB assay for the detection of *M. tuberculosis* complex and rifampicin and isoniazid resistance

I Ashman,¹ M Porter¹ ¹Becton Dickinson, Sparks, MD, USA. e-mail: iramarc_ashman@bd.com

Background: Tuberculosis is a deadly infectious disease and continues to remain one of the world's top health challenges. Rapid and accurate detection of *Mycobacterium tuberculosis* and drug resistance is of paramount importance to appropriately identify and treat patients suffering with the disease, reduce the death rate and stop the spread of TB. The BD MAXTM MDR-TB assay is an automated, qualitative test that allows for the direct detection of *M. tuberculosis* complex and identification of genetic mutations correlated with rifampicin (RIF) and isoniazid (INH) resistance from raw (unprocessed) and NALC/NaOH-treated (processed) clinical sputum samples. The assay is designed for use on the BD MAXTM System, which offers true walk-away automation by incorporating sample lysis, extraction, amplification and detection all in one system.

Design/Methods: Analytical sensitivity of the assay for both *M. tuberculosis* complex detection and mutant discrimination was determined using spiked negative sputum. BD MAXTM MDR-TB analytical sensitivity for the detection of *M. tuberculosis* complex was evaluated

using the H37Rv strain. Mutant discrimination was assessed using five clinical isolates. Mutant genotypes were determined by Sanger sequencing and drug-resistant phenotypes were determined by BACTEC MGIT 960 culture. Analytical sensitivity for the identification of a RIF mono-resistant strain was evaluated using a clinical isolate with a His526Tyr substitution in *rpoB*, while analytical sensitivity for the identification of an INH mono-resistant strain was evaluated using a clinical isolate with a Ser315Thr substitution in *katG*. Analytical sensitivity for detection of multi-drug resistant strains was evaluated using three isolates with mutations in both *rpoB* and *katG* genes; namely, Ser531Leu/Ser315Thr, His526Asp/Ser315Thr and Gln513Lys/Ser315 *rpoB*/*katG* mutants.

Results: Analytical inclusivity, specificity, and cross-reactivity were verified for five *M. tuberculosis* complex organisms and five nontuberculous mycobacteria (NTMs). Analytical sensitivity of the assay was found to be less than 50 cfu/mL-sputum for *M. tuberculosis* detection and less than 250 cfu/mL-sputum for rifampicin and isoniazid resistance detection. The assay successfully detected all five *M. tuberculosis* complex organisms tested. There was no detectable cross-reactivity with any of the five NTMs. The BD MAXTM MDR-TB assay is currently under development and not available for sale or use.

62. Insights into drug-resistant tuberculosis from Ghana to Peru

PC-1221-06 Discordant rifampicin resistance results on MGIT960 and Xpert® MTB/RIF in the TB Control in Prisons Programme of Azerbaijan

E Gurbanova,¹ K Blondal,² F Mirzayev,³ R Tahirli,⁴ V Popova,⁴ R Mekhdiyev,¹ A Ismayilov,⁵ A Altraja⁶ ¹Main Medical Department of the Ministry of Justice, Baku, Azerbaijan; ²Department of Communicable Disease Prevention and Control, Reykjavik Health Care Services, Reykjavik, Iceland; ³Laboratories, Diagnostics & Drug Resistance Unit, World Health Organization, Geneva, Switzerland; ⁴Reference Laboratory, Specialized Treatment Institution for Detainees with Tuberculosis, Baku, Azerbaijan; ⁵Project HOPE, Dushanbe, Tajikistan; ⁶University of Tartu, Tartu, Estonia. e-mail: e.gurbanova@prisonhealth.az

Background: The Main Medical Department of Azerbaijan Ministry of Justice implements a comprehensive TB Control programme in the penitentiary system (PS). This programme practices active tuberculosis (TB) case finding among inmates and provides effective treatment for all identified cases of both susceptible and drug-resistant TB in the Special Treatment Institution (STI). The STI also houses a modern reference laboratory that is quality-assured by the Supra-national Reference Laboratory in Borstel, Germany and performs all WHO-recommended diagnostics including Xpert MTB/RIF and culture with following drug-susceptibility testing (DST) on MGIT960. As soon as susceptibility result on R is available from either Xpert MTB/RIF or MGIT960, the

patient starts adequate treatment with regimen adjustment after full DST is available. Since 2010, frozen cultures of all culture-positive samples processed in this laboratory are maintained.

Objectives: To assess the proportion of discordant R resistance results on Xpert MTB/RIF and MGIT960 among patients identified in Azerbaijan PS during 2011-2015.

Design and methods: All pulmonary TB cases undergoing testing for TB in STI were included into this retrospective study. TB cases under treatment monitoring were excluded. Sputum samples from admitted patients were investigated both with Xpert MTB/RIF and MGIT960 culture and DST. To increase the number of strains evaluated, additional strains were revived from culture archive.

Results: Overall 532 strains were included, 286 consecutive sputum samples from admitted patients and 246 frozen strains. Out of the 532 strains, 33 (6.2%) had discordant results, where 21 (3.9%) were R-resistant according to Xpert MTB/RIF, but R-sensitive according to MGIT960 and 12 (2.3%) were R-sensitive on Xpert MTB/RIF but R-resistant according to MGIT960 (Table 1). Both tests, however, were in a good agreement with each other (Cohen's kappa 0.825, $P < 0.001$). If MGIT results were taken as reference, then sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and test accuracy of Xpert MTB/RIF were 90.8%, 95.2%, 84.9%, 97.2% and 94.2% respectively. Table 1. Rifampicin susceptibility results by Xpert MTB/RIF and MGIT960. Xpert MTB/RIF Sensitive Resistant Total MGIT 960 Sensitive 393 21 414 Resistant 12 106 118 Total 405 127 532

Conclusions: Despite the 6.2% discordance between the methods, the results by Xpert MTB/RIF had acceptable sensitivity, specificity, PPV, NPV and accuracy and were in a good agreement with those obtained with MGIT960. Further research and sequencing will be necessary to better understand the genetic profile of strains that exhibit discordance in Rif susceptibility results between these two diagnostic techniques. 97.2% and 94.2% respectively.

PC-1222-06 Feasibility of multidrug-resistant tuberculosis treatment with improved regimens based on drug resistance profiles

M H Wu,¹ R Jou^{1,2} ¹Centers for Disease Control, Taipei, ²National Yang-Ming University, Taipei, Taiwan. Fax: (+886) 2 2653 1387. e-mail: rwj@cdc.gov.tw

Background: Since multidrug-resistant tuberculosis (MDR-TB) cases with additional resistance to a fluoroquinolone or a second-line injectable drugs might be qualified for treatment with bedaquiline and cases with no resistance to fluoroquinolones and second-line injectable drugs could be treated with a short-course regimen, we analyzed drug-resistant profiles of MDR *Mycobacterium tuberculosis* to assess possible use of improved regimens for MDR-TB treatment.

Methods: This is a prospective laboratory-based study. *M. tuberculosis* isolates were subsequently collected from 196 MDR-TB cases during 2013-2014. Drug susceptibility testing was performed using the Middlebrook 7H11 agar proportion method. In addition, the resazurin microtiter assay was used to determine the minimum inhibitory concentrations (MICs) of clofazimine and linezolid. The susceptibility breakpoints for clofazimine and linezolid are suggested to be 1.0 µg/mL and 1.0 µg/mL, respectively. Extensively drug-resistant (XDR) TB was defined as MDR-TB plus resistance to any fluoroquinolone and at least one second-line injectable drugs.

Results: Of the 196 isolates, ratios of resistance were 34.2% (67/196) to pyrazinamide, 15.8% (31/196) to ofloxacin, 16.3% (32/196) to moxifloxacin, 12.8% (25/196) to levofloxacin, 5.6% (11/196) to gatifloxacin, 3.6% (7/196) to kanamycin, 2.6% (5/196) to amikacin, 1.5% (3/196) to capreomycin, 24.0% (47/196) to ethionamide, 8.7% (17/196) to para-aminosalicylate, 89.8% (176/196) to rifabutin, 0% to cycloserine. No XDR-TB case was found. The range of MIC against tested clinical strains was 0.06 to 4 µg/mL for clofazimine and 0.06 to 1 µg/mL for linezolid. Furthermore, only 5.6% (11/196) of MDR-TB cases were resistant to clofazimine (MIC > 1 µg/mL) and no isolates resistance to linezolid (MIC > 1 µg/mL). We found that MDR *M. tuberculosis* isolates resistant to clofazimine were not associated with ofloxacin and moxifloxacin resistance with $P = 0.1344$ and 0.1525 , respectively.

Conclusion: Of 196 MDR-TB cases, 157 (80.1%) cases susceptible to fluoroquinolones and second-line injectable drugs might be qualified to be treated with a short-course regimen. Whereas, of 185 clofazimine susceptible cases, 28 (15.1%) cases with resistance to any fluoroquinolone or 7 (3.8%) cases with resistance to any second-line injectable drug might be qualified to be treated with bedaquiline-containing regimen.

PC-1223-06 First- and second-line *Mycobacterium tuberculosis* drug resistance at a tertiary hospital chest clinic in Ghana

S Kudzawu,¹ M Omari,¹ A Forson,¹ A Badoo,¹ H Ganu,¹ B C De Jong,² J Otu,³ A Kwara,⁴ M Antonio³ ¹Korle-Bu Teaching Hospital, Accra, Ghana; ²International Tropical Institute, Antwerp, Belgium; ³Medical Research Council Unit, Fajara, Gambia; ⁴Brown University, Providence, RI, USA. e-mail: skudzay@yahoo.com

Background: *Mycobacterium tuberculosis* drug resistance is a major challenge to the use of standardized regimens for tuberculosis (TB) therapy, especially among previously treated patients. To inform drug selection for previously treated TB patients at Korle-Bu Teaching Hospital, we investigated the frequency and pattern of drug resistance among predominantly previously treated patients with smear-positive pulmonary tuberculosis.

Design/Methods: A cross-sectional survey was carried out from 2010-2013 of patients with AFB smear positive pulmonary TB who were previously treated or were

smear positive at month 2 or 5 of first-line therapy. *M. tuberculosis* cultured isolates were shipped to the TB diagnostics Laboratory at The MRC Unit, The Gambia for confirmatory testing and phenotypic Drug Susceptibility Testing (DST), for isoniazid, rifampin, streptomycin and ethambutol. Multi-drug resistant (MDR) *M. tuberculosis* isolates were additionally subjected to second-line DST including ofloxacin, capreomycin, kanamycin and ethionamide.

Results: 170 *M. tuberculosis* isolates were submitted for DST, of which 29 were not viable and 21 were considered contaminants. Of the 120 evaluable samples, 107 (89.2%) were from previously treated TB cases and 13 from newly-diagnosed TB patients. Ninety patients (75%) were males, and median age (IQR) was 37 (28.0 – 48.0) years. Overall 62 isolates (51.6%) were susceptible to the first-line drugs tested, 28 (23.3%) were MDR, 42 (35.0%) were resistant to streptomycin and 22 (18.3%) were mono resistant. Of the MDR isolates, 26 (92.8%) were from previously treated patients, 20 (71.4%) were also resistant to streptomycin and 6 (21.4%) were pre-XDR. Among the 13 newly diagnosed cases, 2 (15.4%) had MDR-TB and 3 (23.1%) had streptomycin resistance. Both cases of MDR-TB had a history of contact with a previously treated case that had MDR-TB.

Conclusion: There is an urgent need for routine DST and the early use of individualized regimens in previously treated TB patients in Ghana given the high prevalence of MDR-TB and streptomycin resistance among these patients. The high prevalence of pre-XDR among the MDR-TB isolates requires that new cases of TB with known MDR-TB exposure should be prioritized for culture and DST for both first and second-line drugs. This is necessary to optimize outcomes among patients with high risk for MDR-TB, and minimize the risk of transmission of MDR/XDR-TB to their contacts.

PC-1224-06 Stable anti-tuberculosis drug resistance prevalence in Bamako, Mali, 2006-2014

B Diarra,^{1,2} M Sanogo,² B Baya,² A Togo,² S Tounkara,² S Dao,² B De Jong,¹ S Diallo² ¹Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; ²SEREFO, University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali. Fax: (+223) 202 27 513. e-mail: bdiarra@icermali.org

Background: Drug resistant tuberculosis (DR-TB) continues to threaten global tuberculosis control, resulting from either primary infection with resistant bacteria or from acquired resistance. Mali, a large country with limited resources, reported 9,000 new TB cases, including 12 cases of MDR-TB in 2013. In Mali, individual patient drug susceptibility testing (DST) is not universally accessible, however, at SEREFO, DST has been conducted since 2006 for each patient enrolled in research protocols. Given the absence of a nationwide drug resistance survey, we present here the evolution of TB drug resistance among new and retreatment cases over the 9-year period.

Design/Methods: Between 2006 and 2014, we conducted a descriptive cross-sectional study by enrolling pulmonary TB cases from local reference centers and the University Teaching Hospital at Point G, in Bamako, Mali. The study protocols were approved by the Ethics Committee of the FMPOS-Mali and IRB of the NIAID/NIH, USA. Confirmed *Mycobacterium tuberculosis* complex (MTBc) isolates underwent indirect first line DST using BD-MGIT AST/SIRE System, and in the context of a regional collaboration, subcultures had DST repeated for first line drugs, plus second line DST by agar proportion method for MDR isolates, at the Medical Research Council (MRC), the Gambia.

Results: A total of 1186 mycobacterial cultures were performed on samples from 522 patients, including 1105 sputum and 81 blood samples. Of these patients, 120 (23%) had a negative culture, 43 (8.2%) grew NTM, and 343 (65.7%) grew MTBc. Phenotypic DST was performed on 337 (98.3%) of the MTBc isolates. Among the 337 patients, 127 (37.7%) had resistance to at least one drug, including 75 (22.3%) multidrug resistant (MDR) cases. The overall prevalence of MDR-TB was 3.4% among new cases and 66.3% among retreatment cases. The rates of resistance, both MDR and other resistances, remained stable during the study period, with a small increase observed in 2009, and 2010. Second line DST was available for 35 (46.7%) of MDR cases, and no XDR-TB was identified.

Conclusion: The drug resistance levels, including MDR, found in this study are relatively high, likely related to the selected referral population. While worrisome, the numbers remained stable over the study period. As culture and DST are only available in Bamako, the nationwide surveillance of retreatment cases will provide more accurate results on countrywide drug resistance rates.

PC-1225-06 From facility to finding drug resistance mutations: drug resistance survey in Nigeria

V Sebastian,^{1,2} I Uko,² G Akang,³ T Abiola,³ S Ogiri,⁴ Denn Onotu,² N. Nwokoye,⁵ M Zignol⁶ ¹NTBLCP, Nigeria National DR-TB Survey Consultant, Abuja, ²US-Centers for Disease Control and Prevention (US-CDC) Nigeria, Abuja, ³Federal Ministry of Health Nigeria (FMOH), Abuja, ⁴World Health Organization Country Office Nigeria, Abuja, ⁵Nigeria Institute of Medical Research (NIMR), Lagos, Nigeria; ⁶World Health Organization, Geneva, Switzerland. e-mail: vsebastian@cdc.gov

Background: Nigeria notifies about 100 000 sputum smear positive (SS+) tuberculosis (TB) cases annually and is listed among the 22 high TB Burden (HTB) countries. We determined the prevalence and pattern of resistance to anti-tuberculosis drugs: rifampicin (RIF) and isoniazid (INH) using Line Probe Assay (LPA) and compared with culture drug sensitivity testing (DST).

Design/Methods: By cluster sampling we systematically randomly sampled 30 clusters of DOTS facilities from a national sampling frame of all DOTS facilities. Each cluster was proportionate to size of new sputum smear

positive (SS+) TB cases reported. In each survey cluster, consenting SS+ TB patients (>15yrs old) were enrolled consecutively as patients visit these facilities till a required national total sample size of 1,723 respondents – new and re-treatment cases - were enrolled. Two most positive sputum samples per respondent were transported under cold-chain in triple layered-packaging to in-country TB reference laboratories for LPA (using Genotype MTBDR plus) testing and cultured (LJ slopes) to obtain isolates. Isolates of all resistant and 10% of sensitive samples were transferred under cold chain to Supra-national Reference Laboratory at CDC Atlanta and retested by LPA, solid and liquid culture DST to determine (and compare) resistance to RIF and INH and other anti-TB drugs.

Results: Of 1723 patients enrolled, 1449 had samples successfully subjected to LPA, 70 were found to be MDR-TB strains, giving a general prevalence of 4.8% (95%CI: 3.8 – 6.1 %), comprising a prevalence of 2.9% (weighted) among new TB cases (95%CI: 2.1 – 4.0%) and 14.3% (95%CI: 10.2–19.3%) among retreatment TB cases. We found resistance to other anti-TB drugs and the strongest predictor of MDR-TB was previous anti-TB treatment ($P < 0.000$). The results of LPA done directly on smear-positive sputum concurred highly with culture DST performed on isolates using 'MGIT 960'. Sensitivity, specificity, positive and negative predictive values of Genotype MTBDR plus relative to conventional DST using MGIT 960 and agar proportion method for detection of resistance were 96.8, 92.1, 81.1 and 98.8 percent respectively for RIF and 73.8; 98.7; 96.9 and 87.5 percent respectively for INH. No XDR-TB strain was found.

Conclusion: Line Probe assay (Genotype MTBDR plus assay) was found to be feasible, rapid, sensitive and specific test for routine DST for diagnosis of RIF resistance. There is a notable prevalence MDR-TB in Nigeria and potential for XDR-TB, history of prior anti-TB treatment a very strong predictor of MDR-TB.

PC-1226-06 Scaling up of a commercial line probe assay for diagnosis of drug resistance and evaluation against an agar proportion method in Peru

Z Puyen,¹ J R Acosta Barriga,¹ L Solari¹ ¹Instituto Nacional de Salud, Lima, Peru. e-mail: zpuyeng@gmail.com

Background: In Peru, a commercial line probe assay (LPA), Genotype MTBDRplus®, was introduced by the National Tuberculosis Control Program (NTCP) to detect resistance to Isoniazid (H) and/or Rifampin (R). Sputum samples or cultured strains in Lowenstein-Jensen media, (L-J) from patients entering treatment were sent to the National Institute of Health (NIH) to be tested. Genotype MTBDRplus is used as a screening test: if patients are found to have resistance to H or R, it must be checked using the agar proportion (AP) method, which includes other first and second line drugs. These results define the final regimen to be given. The aim of this study is to describe the process of scaling up of the LPA test and

to compare its results with those obtained through AP for evaluation of resistance to H and R.

Design/Methods: This is a descriptive cross-sectional study. All results from sputum samples/ cultured strains of patients with smear-positive pulmonary tuberculosis in Peru that were sent to the NIH for LPA during 2011-2014 were included. The number of tests done was compared with the number of cases according to the NTCP for each year to calculate the coverage. Comparison between LPA and APP for resistance to H and R was calculated using the positive predictive value, the agreement and Cohen's κ coefficient for resistance to H, R, and MDR.

Results: From 2011 to 2014, the total number of Genotype MTBDRplus tests performed was 1075, 5472, 9621, and 11 954. This represents a coverage of 6% 31%, 57% and 71% respectively. 15%-43% of these patients had previous episodes of tuberculosis. The Figure shows the proportion of patients showing resistance to H and R in each of the studied groups. The positive predictive values of Genotype MTBDRplus were 98%, 92% and 94% for resistance to H, R and MDR respectively. The agreement and κ coefficients for resistance to isoniazid were 94.9% and 0.85, for resistance to rifampin were 91.9% and 0.84 and for MDR were 91.9% and 0.84.

Conclusion: The LPA Genotype MTBDRplus is a suitable screening test for resistance to H, R and MDR, allowing early diagnosis of resistance. Since 2011, it has been scaled up in Peru by 15-25% per year, increasing its coverage to 71% of cases with positive sputum smears in 2014. The concordance found between LPA and AP is very good for resistance to H, R and MDR. The universalization of this test in all the country is strongly recommended.

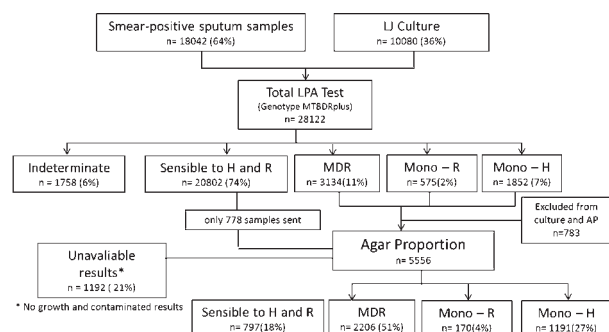


Fig. 1: Flow of LPA samples in the Laboratorio de Referencia Nacional de Micobacterias, Peru, 2011-2014.

PC-1227-06 Evaluation of *Mycobacterium tuberculosis* resistance levels and cross-resistance to isoniazid and rifampin with their respective structural analogues

I Rukasha,^{1,2} H Said,^{1,2} S Omar,¹ A W Dreyer,¹ A Hoosen,² N Ismail¹ ¹National Institute for Communicable Diseases, Johannesburg, ²University of Free State, Bloemfontein, South Africa. Fax: (+27) 71 477 8978. e-mail: irukasha@yahoo.co.uk

Background: Studies have shown that some second-line structural analogues of first-line drugs may have equivalent or greater potency for MDR treatment. In developing countries, second-line analogues are initiated on failure of first line drugs without confirming their efficacy. Structural analogue drugs such as Rifampicin (RIF) and rifabutin (RFB) resistance to *Mycobacterium tuberculosis* is mutually associated with mutations within the rifampicin resistance determining region (RRDR) of the *rpoB* gene. Similarly, Isoniazid (INH) and ethionamide (ETH) resistance is mediated by the shared target *inhA*. Thus cross-resistance between structural analogues is common. Particular genes in *rpoB* mutations and in promoter of the *inhA* gene have been shown to be likely associated with high levels of resistance while, others may be found in phenotypically susceptible isolates. Correlating specific mutation to MICs allow for prompt detection of resistance.

Design/Methods: The aims of the present study were to analyze the MICs data to determine whether cross-resistance occurs between the structural analogues and to correlate the MICs of RIF and RFB to the *rpoB* mutation as well as MICs of ETH and INH to *inhA* and *katG* mutations in order to determine levels of MICs in relation to each mutation. The Sensititre MYCOTB assay was used to determine the MIC levels. Sanger sequencing was used to determine mutation. Kruskal-Wallis was used to determine correlation between the MICs and different mutations.

Results: Cross-resistance between the analogues RIF and RFB was 89% while for INH and ETH 75%. Isolates with mutations S531L, H526Y, H526R, S531Q in the RRDR were associated with RIF/RFB resistance while, mutations D516V and L533P were RIF resistance/RFB susceptibility. All mutations in the *inhA* promoter and *katG* were associated with high-level of resistance to both INH and ETH.

Conclusion: There was a high level of cross resistance between the analogues. Isolates with high INH and RIF resistance levels also displayed high MIC values for their structural analogs. These findings stress the need to test the effectiveness of second-line structural analogues before their incorporation in the therapeutic schemes. The study has shown that the usefulness correlating MICs to specific mutations which can allow rapid detection of cross-resistance.

PC-1228-06 Routine surveillance for anti-tuberculosis drug resistance in two districts of Botswana, 2012–2014

A Finlay,¹ J Basotli,¹ C Modongo,² E Click,³ J Oeltmann,³ R Boyd,¹ N Zetola,² P Moonan³ ¹Centers for Disease Control and Prevention, Gaborone, ²Botswana University of Pennsylvania Partnership, Gaborone, Botswana; ³U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: afinlay@cdc.gov

Background: Previous nationwide antituberculosis (TB) drug resistance (DR) surveys demonstrated an increasing trend of multidrug-resistant (MDR) TB from 1995 – 2008 in Botswana, a country with the second highest prevalence of HIV in the world. The World Health Organization recommends routine DR surveillance through universal drug susceptibility testing (DST) to monitor control efforts. We describe the performance of routine DR surveillance among patients enrolled in a TB transmission study in Gaborone – an urban setting with moderate TB incidence and high HIV prevalence and Ghanzi – a rural setting with high TB incidence and moderate HIV prevalence.

Methods: From Aug 2012 – Dec 2014, extra sputum samples were collected from patients within two weeks of initiating TB treatment in Gaborone and Ghanzi districts. All *Mycobacterium tuberculosis* isolates underwent liquid or solid based DST for isoniazid, rifampin, ethambutol and streptomycin. HIV status was collected through patient history or rapid testing. District-wide resistance prevalence estimates and 95% confidence intervals (95%CI) were calculated. Differences in proportions for each anti-TB drug were compared to previous survey data.

Results: During the study period, 3159 patients were registered for TB treatment, among whom 2717 (86%) were enrolled. Of these, 2499 (92%) submitted ≥ 1 sample for testing, 1423 (52%) had a culture positive for *M. tuberculosis* and 1225 had complete DST results. Resistance to isoniazid and rifampin (i.e., MDR-TB) was detected among 37 (3.0 %) patients: 1.9% ($n = 15$) among those with new smear positive disease; 1.4% ($n = 3$) among those with new smear negative disease; 9.5% ($n = 19$) among previously treated (Table). The prevalence of MDR-TB was 2.7% (95%CI 1.7–3.7) in Gaborone and 4.3% (95%CI 1.7–6.9) in Ghanzi. MDR-TB prevalence did not differ when stratified by HIV status. The proportion of resistance for each anti-TB drug was similar to previous surveys, except for any ethambutol resistance, which was slightly higher 4.4% (95%CI 3.0 – 5.9) vs. 1.8% (95%CI 1.1–2.9) in 2008.

Conclusions: Results of routine DR surveillance from two districts show anti-TB drug resistance patterns consistent with the 2008 national survey suggesting current control efforts have not reduced the prevalence of drug-resistant TB. Routine anti-TB DR surveillance is feasible if efforts to collect initial diagnostic specimens are improved and a modest increase in laboratory capacity can be supported.

Table: Comparison of Antituberculosis Drug Desistance Between the 2008 National Antituberculosis Drug Resistance Survey and Routine surveillance in Two Districts in Botswana, 2014–2015

Resistance Pattern*	National Survey, 2008 Prevalence (95% CI, n)	Routine Surveillance 2014 – 2015 Prevalence (95% CI, n)
Newly diagnosed, smear positive	n = 924	n = 810
Any drug resistance	16.9% (14.6–19.4, 156)	20.3% (17.5–23.0, 164)
Any INH, RIF, EMB	8.9% (7.2–10.8, 82)	10.4% (8.8–12.5, 84)
Any isoniazid	7.6% (6.0–9.4, 70)	7.2% (5.4–8.9, 58)
Any rifampicin	3.6% (2.5–4.9, 33)	3.2% (2.0–4.4, 26)
Any ethambutol	1.8% (1.1–2.9, 17)	4.4% (3.0–5.9, 36)
Any streptomycin	10.6% (8.7–12.8, 96)	13.2% (10.8–15.6, 107)
Any monodrug resistance	13.0% (10.9–15.3, 120)	15.7% (13.2–18.2, 127)
Isoniazid monodrug resistance	3.8% (2.7–5.2, 35)	2.7% (1.6–3.8, 22)
Rifampicin monodrug resistance	1.1% (0.6–1.9, 10)	0.7% (0.2–1.9, 3)
Multidrug resistance	2.5% (1.6–3.7, 23)	1.9% (0.9–2.8, 15)
Previously treated patients	n = 137	n = 200
Any drug resistance	23.4% (16.8–31.0, 32)	30.5% (24.0–36.9, 61)
Any INH, RIF, EMB	23 (16.8% (11.2–23.8, 23)	18.5% (13.1–23.9, 37)
Any isoniazid	10.2% (5.9–16.2, 14)	14.5% (9.6–19.4, 29)
Any rifampicin	13.1% (8.2–19.6, 18)	13.5% (8.7–18.3, 27)
Any ethambutol	6.6% (3.3–11.7, 9)	5.5% (2.3–8.7, 11)
Any streptomycin	11.8% (7.1–18.0, 16)	23.5% (17.6–29.4, 47)
Any monodrug resistance	14.6% (9.4–21.3, 20)	17% (11.7–22.3, 34)
Isoniazid monodrug resistance	2.2% (0.6–5.8, 3)	2.0% (0.0–4.0, 4)
Rifampicin monodrug resistance	5.8% (2.7–10.8, 8)	3.0% (0.6–5.4, 6)
Multidrug resistance	6.6% (3.3–11.7, 9)	9.5% (5.4–13.6, 19)

63. MDR-TB: detection, prevalence and drivers

PC-1229-06 Why MDR-TB patients do not accept treatment

Z Xu,¹ L Bai¹ ¹TB Control Institution of Hunan province, Changsha, China. e-mail: evan.xu21@gmail.com

Background: There were 1091 MDR-TB patients detected through drug sensitive test (DST) in designated MDR-TB hospital of Hunan province, China, from January 1, 2012 to December 31, 2013. According to the provincial MDR-TB control guideline, all patients have to accept a 24 months treatment regime including first 4-6 weeks hospitalization. However, only 419 cases started the treatment to the end of March 2014, the other 672

(61.6%) patients did not receive any proper treatment although following up and tracing efforts were made by all level TB control personnel. This study intends to identify the reasons of patients who did not receive MDR-TB treatment.

Design/Methods: The designated MDR-TB hospital would inform the county CDC staff about MDR-TB patients' information once the diagnosis was confirmed. CDC's personnel and/or the village doctors were due to trace patients to the designated hospital for treatment, and feedback the tracing results to hospital; then hospitals would record patients' treatment information and feedback to the county CDC every month. The patients not receiving treatment would be traced by county CDC as well as newly diagnosed MDR-TB patients, until all MDR-TB patients started treatment. The information feedback was done mainly through e-mail, QQ, MSN and telephone and the tracing procedure and results were recorded, collected and analyzed.

Results: Among the 672 cases who did not started MDR-TB treatment, the identified causes were the economic hardship (386, 57.4%), moving to other city for work (126, 18.8%), lacking of detailed address and telephone number (47, 7%), refusing treatment (32, 4.8%), with other severe illness or too weak to be hospitalized (28, 4.2%), and death (14, 2.1%).

Conclusion: The leading causing of patients not accepting MDR-TB treatment was economic hardship in Hunan province. In addition, moving to other city for work, unknown contact information, refusing treatment, too weak or with other severe diseases and death were other important reasons. Therefore, reducing treatment expense and increasing the coverage of health insurance, improving the MDR-TB treatment affordability and availability need to be addressed to enhance the proportion of patients of accepting MDR-TB treatment.

PC-1230-06 RNTCP experience in rolling out base-line second-line drug susceptibility testing among MDR-TB cases

M Ghedia,¹ K S Sachdeva,^{1,2} A Amar Shah,¹ S Anand,¹ P Parmar,¹ R Ramachandran,¹ A Sreenivas,¹ F Sayyed Imran¹ ¹World Health Organization – Country Office for India, Delhi, ²Central TB Division, Delhi, India. Fax: (+91) 112 306 3226. e-mail: drmayank381981@gmail.com

Background and challenges to implementation: India is highest MDR-TB burden country with approximately 61 000 MDR-TB cases among notified pulmonary TB cases. The precise prevalence of XDR-TB among MDR-TB is not known with only few survey have captured data that is also very limited. RNTCP has well-articulated PMDT services available across country with rapid diagnosis of MDR-TB with CB-NAAT or LPA. The second line Drug Susceptibility testing for MDR-TB was available to very selected patients whose follow-up culture positive at fifth month. The performing base line Second line DST in MDR-TB was limited because of lack of adequate number of SLD certified laboratories and no guideline on SLD certification for laboratories.

Intervention or response: To address these challenges the Central Tuberculosis Division in coordination with National Reference laboratory developed guidelines for certifying the laboratory on second line DST in January 2013 with participation of all NRLs, finalized of Standard Operative Procedure for Second Line Drug susceptibility testing in liquid Culture (MGIT). Training schedule for Laboratory Personal and proficiency testing methods conducted the training of identified laboratory, expedited the proficiency testing among identified laboratories. All the document was duly approved by technical committee and ministry of health. Training of laboratory personal was conducted in NRL and on-site in liquid culture (MGIT).

Results and lessons learnt: RTNCP has only three laboratory (National Reference Laboratory) certified for Second Line DST in 2013 and in March 2015 has 16 laboratory certified for SLD (2013-1, 2014- 6 2015- 6). Development of guidance document for certification, involvement of all NRLs for formulating guidelines and training method will help to achieve rapid scale-up of SLD certified laboratories.

Conclusions and key recommendations: Based upon our experience well-coordinated and step-wise approach involving all stake holders e.g. National Programme, Technical Committee, National Reference Laboratory and Intermediate Laboratory generated notable result and with a short time. With one year RNTCP reached 16 SLD certified laboratories which is currently providing services for base line Second line DST among MDR-TB patient in selected states.

PC-1231-06 Genetic characterization of multidrug-resistant *Mycobacterium tuberculosis* strains from various regions of Delhi

J Arora,¹ Z Sidiq,¹ M Bhalla,¹ P Visalakshi,¹ V Myneedu,¹ U Singh,² D Behera,^{2,3} R Sarin¹ ¹National Institute of Tuberculosis and Respiratory Diseases, New Delhi, ²AIIMS, New Delhi, ³PGIMER, Chandigarh, India. e-mail: arojjyoti@gmail.com

Background: Multi drug-resistant (MDR) tuberculosis is a potential threat to tuberculosis (TB) control programs throughout the world. The present study was aimed to evaluate the population structure among multidrug resistant *Mycobacterium tuberculosis* (*M. tuberculosis*) strains isolated from MDR suspects registered at 6 DOTS centers located in South, West and South-West zones using spoligotyping.

Design/Methods: Sputum samples obtained were processed and inoculated on to Lowenstein Jensen slants. Positive cultures were subjected to drug susceptibility testing against four first line drugs- streptomycin (4µg/ml), isoniazid, (0.1 µg/ml), rifampicin (40 µg/ml) and ethambutol (1 µg/ml). Spoligotyping was performed according to the standard protocol on 200 MDR isolates.

Results: Spoligotyping yielded 81 different patterns, 67 of these patterns were unique (1 isolate only) whereas 14 patterns containing 133 isolates were clustered (2 or

more isolates) with a clustering rate of 66.5%. SIT 26 predominated in this study with 49/200 (24.5%) isolates, followed by SIT 1 with 45/200 (22.5%) isolates. The predominant spoligotyping families in this study were found to be Central Asian (CAS) family (43.0%), followed by Beijing Family (23.0%), the East African-Indian family (8.0%) and the ill defined T family (5.0%). The LAM, X and MANU were present as minor families. The study showed an intriguing, marked distribution of two strain families (CAS and Beijing) in all the regions. **Conclusion:** The data obtained shows an almost similar population structure of MDR strains in different regions of Delhi. SIT 26 and SIT 1 were responsible for approximately 50% of burden of MDR-TB in Delhi, suggesting an enhanced ability of these strains to transmit.

PC-1232-06 Multidrug-resistant tuberculosis among foreign-born persons in Japan

N Kobayashi,¹ T Hattori,² T Kirikae,³ S Kato,⁴ J Suzuki,¹ K Ohta¹ ¹NHO Tokyo National Hospital, Kiyose, ²Tohoku University, Sendai, ³National Center for Global Health and Medicine, Tokyo, ⁴The Research Institute of Tuberculosis, Kiyose, Japan. e-mail: kobayashin@tokyo-hosp.jp

Background: Although the rates of tuberculosis (TB) in Japan have been decreasing, the proportion of TB cases in the foreign-born has been steadily increasing from 2.1% to 5.2% of the national total during 1998-2013. Recently, we demonstrated that multidrug-resistant TB (MDR-TB) in Tokyo was more prevalent in foreign-born patients compared with Japanese patients, and indicated, by genotypic analysis of *M. tuberculosis* isolates, that foreign-born patients most coming from high/relatively high TB burden countries would have the potential risk of spreading to other residents in Japan. The purpose of this study is to clarify the current epidemiological status of MDR-TB and contribution of foreign-born cases to MDR-TB in Japan.

Design/Methods: We conducted a questionnaire survey among MDR-TB patients registered from January 2011 to December 2013 in Japan. We analyzed the clinical and microbiological differences between foreign- and Japanese-born MDR-TB patients.

Results: In the three-year period under study, a total of 184 TB cases were reported as MDR: mean age was 52.7 years, 65.2% were male. Ninety nine (53.8%) patients were new cases and 84 (45.6%) were previously treated cases. Among the MDR-TB, 20 (10.9%) cases showed resistance to LVFX and KM. Japanese patients were 132 (71.7%) and foreign-born were 52 (28.3%). The foreign-born MDR-TB patients were female dominant and markedly younger than native Japanese patients. Of the 52 foreign-born patients, 23 (44.2%) originated from China. Other countries of origin were the Philippines (*n* = 9), Myanmar (*n* = 5), Mongolia (*n* = 2), other Asian countries (*n* = 12) and Ukraine (*n* = 1). Eight (20%) of 52 foreign-born patients with MDR-TB had organisms resistant to LVFX, 3 (8%) to KM and 1 (3%) to EVM. There was a higher prevalence of extensively drug-resistant tuberculosis (XDR-TB) among Japanese MDR-

TB than among foreigner MDR-TB (14% vs.4%). Treatment outcomes of foreign-born MDR-TB: 33 (65.3%) patients underwent successful treatment, 11 (23.1%) patients returned to their home countries during treatment, 2 (3.8%) patients failed and 1 (1.9%) patient died (3 patients unknown).

Conclusion: Among recently registered MDR-TB in Japan, foreign-born patients accounted for about 30%, who were mainly from Asian high burden TB countries. Treatment outcome of foreigner MDR-TB was more successful than Japanese MDR-TB. The return to their home countries before completion of treatment might be a problem.

PC-1233-06 Drug-resistant tuberculosis and risk factors of multidrug resistance in Ukraine: results of the first nationwide survey

E Pavlenko,¹ A Barbova,² A Hovhannesian,³ Z Tsenilova,⁴ A Slavuckij,⁴ A Dean,⁵ M Dara,⁶ A Dadu⁷ ¹Temporary adviser of the Ministry of Health of Ukraine, Kyiv, ²Central Reference Laboratory on TB Microbiological Diagnostics of the Ministry of Health, Kyiv, Ukraine; ³World Health Organization Temporary Adviser, Yerevan, Armenia; ⁴World Health Organization, Country Office, Kyiv, Ukraine; ⁵World Health Organization, Geneva, Switzerland; ⁶World Health Organization Office at the European Union, Brussels, Belgium; ⁷World Health Organization, Regional Office for Europe, Copenhagen, Denmark. e-mail: dad@euro.who.int

Background: Ukraine belongs to the world's 27 countries with high burden of multidrug resistant tuberculosis (MDR-TB) was one of the few without sufficiently representative data on level of drug-resistance.

Design/Methods: To investigate the levels and patterns of resistance to first-line anti-TB drugs among new and previously treated pulmonary TB cases and explore the risk factors for multidrug-resistant (MDR) TB. Weighted cluster sampling approach was used to select the study participants. Patients enrolled between November 2013 and May 2014. Microscopy, culture and isolation of *M. tuberculosis* were performed at regional level, while drug-sensitivity tests (DST) were performed at five selected inter-regional TB laboratories. Internal and external quality assurance was performed correspondingly at National Reference Laboratory in Kiev and Supranational Reference Laboratory in Riga.

Results: Of the 1590 patients enrolled into study, 1266 were newly-diagnosed and 324 previously treated TB patients. MDR-TB was detected in 22.7% (95% Confidence Interval (CI): 19.6-25.9) among the new patients and 58.3% (95%CI: 52.1-64.6) among the previously treated patients. Human immunodeficiency virus (HIV) was found in 249 (15.7%) patients. Independent risk factors for MDR-TB among new patients were HIV (Odd Ratio (OR): 1.44; 95%CI: 1.02-2.03), poor socio-economic status (OR: 1.55; 95%CI: 1.16-2.05), and living in South-East oblasts (OR: 2.37; 95%CI: 1.51-3.72). Age was inversely associated with MDR-TB in linear pattern: every 10 years increase in age reduced Odd of MDR in new cases

by 19% (OR: 0.81; 95%CI 0.72-0.91). Among the previously treated patients the risk factors associated with MDR-TB were the setting and outcome of previous treatment: previously treated patients living in large cities had 72% lower Odd of MDR-TB compared to those that live in towns (OR: 0.24; 95%CI: 0.11-0.51), while patients that were lost to follow-up had lower Odd of MDR-TB compared to those relapsed (OR: 0.42; 95%CI: 0.21-0.83).

Conclusion: The prevalence of MDR among new TB patients in Ukraine is higher compared to WHO estimates and routine drug resistance surveillance data. Findings suggest that there is urgent need to for better HIV-TB collaborative activities, addressing social determinant of TB and accelerating the MDR-TB detection, treatment and improve treatment adherence. Further operational research are needed for full understanding of DR TB in Ukraine.

PC-1234-06 Prevalence of MDR-TB and drug resistance patterns in retreatment cases in Punjab, Pakistan

A Majeed,¹ M Awais Arif,¹ H Javed,¹ S Kanwal¹ ¹Provincial TB Control Program, Punjab, Lahore, Pakistan. e-mail: hasnain_javed@hotmail.com

Background: Tuberculosis has emerged a serious public health problem in recent years. In 2013, 9 million people fell ill with TB and 1.5 million died from the disease while an estimated 480 000 people developed multidrug-resistant TB (MDR-TB). Pakistan ranks 4th in 22 high burden TB countries and ranks 4th in 27 high burden MDR-TB countries. However little or no data exists on prevalence and/or drug resistance pattern amongst high risk MDR-TB groups from Punjab, the most populous province of the country. Previously treated cases are considered at high priority for drug susceptibility testing to identify cases with multi-drug resistance (MDR-TB).

Design/Methods: A total of 1250 retreatment cases were included in this study from January 2010 to December 2014. This cross sectional study was carried out in 9 tertiary care hospitals implementing Programmatic Management of Drug Resistance TB (PMDT) in Punjab. TB culture and drug resistance pattern study was performed at National TB Reference Lab Islamabad, Agha Khan diagnostic and research Laboratories and Provincial TB Reference Lab, Lahore. Data was collected from the Electronic Nominal Review System (ENRS) and analysis was done with SPSS version 17.

Results: Among 1250 retreatment cases, 861 (69%) were MDR-TB while 31% of the remaining showed mono resistance. The mean age was 32 years; amongst them 53% were males and 97% resided urban area of Punjab. Our study showed that MDR-TB is more prevalent in the most productive age group 15-45 years (57%; $P = 0.000$), in the urban area of the Punjab (97%, $P = 0.040$) and in the pulmonary site (68%; $P = 0.041$). Overall 41% of retreatment cases showed resistance to all first line anti-TB drugs (RHZES) while 28% showed resistance to oral first line anti-TB drugs (RHZE). Five

hundred and twenty six retreatment cases also have the resistance to FQs and SLD, amongst them 420 (81%, $P=0.000$) patients showed highly significant resistance to (FQs) and 5% had Ethionamide resistance.

Conclusion: Prevalence of MDR-TB among enrolled retreatment cases is alarmingly high. Drug-resistant tuberculosis including MDR-TB has emerged as a serious public health problem in Pakistan and will greatly impact TB control strategies. This study may have important implications for TB control as it highlights the need to fully implement National Tuberculosis guidelines with main focus on expansion and effective implementation of DOTS in order to prevent further emergence of drug resistance.

PC-1235-06 Estimating true MDR prevalence rates using routinely collected data

Z McLaren,¹ R Burger² ¹University of Michigan, Ann Arbor, MI, USA; ²Stellenbosch University, Stellenbosch, South Africa. e-mail: zmclaren@umich.edu

Background: In the case of the tuberculosis epidemic in South Africa, where TB has been the leading cause of death for over a decade, the lack of reliable estimates of local tuberculosis prevalence leads to inefficient allocation of government resources. Surveillance studies can provide an unbiased estimate of prevalence, but are costly and therefore infrequent. In the absence of inexpensive, accurate diagnostic tests accessible to the majority of the patient population, statistical methods can produce an unbiased estimate of prevalence from routinely collected data.

Design/Methods: In this context, we use high-quality tuberculosis test result data from South Africa's National Health Laboratory Service (NHLS) to estimate the prevalence of MDR-TB. The data set spans 2004-2011 and includes 32 058 877 test records from over 12 445 000 patients at health facilities around the country. We develop a theoretical model of the clinician's decision to perform drug susceptibility testing on a patient with suspected TB based on the patient's risk factor profile and subject to clinical guidelines and limited resources. Our identification strategy employs a simulated maximum likelihood estimation (SMLE) method and a generalized method of moments (GMM) to generate estimates. We rely on exogenous variation in drug resistance testing rates induced by time period, national health policy changes, and local resource allocation to estimate our parameters.

Results: We estimate that the MDR rate in South Africa could be as high as 3.63%. This is likely to be an upper bound because there is information that the clinicians have access to that we, as statisticians, do not. The subgroup analysis demonstrates that the estimated MDR-TB rates are higher in health clinics and health centers, for women, those between ages 30-60, and for Northern Cape, Mpumalanga, North West and Eastern Cape (KZN omitted from analysis due to data limitations).

Conclusion: Our results suggest that resource allocations for tuberculosis diagnosis and treatment should be revised upwards. Resources should be targeted towards provinces that have the lowest index of suspicion for DR or that have the highest MDR rates. More frequent surveillance of MDR-TB is needed to track the evolution of MDR-TB prevalence over time. Between surveillance studies, modeling of disease prevalence rates are an inexpensive and efficient way to guide the allocation of TB resources.

PC-1236-06 Drug resistance patterns in MDR-TB patients: challenges for future regimen design

H Stagg,¹ J Brown,^{1,2} E Ibraim,³ V Riekstina,^{4,5} P Viiklepp,⁶ G Dravniece,^{7,8} C Jackson,¹ P White^{9,10}

¹University College London, London, ²Royal Free London NHS Foundation Trust, London, UK; ³Marius Nasta Institute of Pulmonology, Bucharest, Romania; ⁴Riga East University Hospital, Riga, ⁵Centre of TB and Lung Diseases, Riga East University Hospital, Riga, Latvia; ⁶Estonian Tuberculosis Registry, National Institute for Health Development, Tallinn, Estonia; ⁷KNCV Tuberculosis Foundation, The Hague, Netherlands; ⁸Otsuka Pharmaceutical, Geneva, Switzerland; ⁹Imperial College School of Public Health, London, ¹⁰Public Health England, London, UK. e-mail: h.stagg@ucl.ac.uk

Background: Globally, numbers of multi-drug resistant tuberculosis (MDR-TB) cases are growing, with many concerns about the challenges of treating what may be increasingly complex drug resistance patterns. We sought to inform future regimen selection by examining additional drug resistance in MDR-TB cases over time in three epidemiologically differing nations of the WHO European region: Estonia, Latvia and Romania.

Methods: Analysis of demographic (vulnerable groups) and microbiological (drug sensitivity testing (DST)) surveillance data for Estonian, Latvian and Romanian MDR-TB cases, 2004-13.

Results: In 2013 Estonia, Latvia and Romania had 50, 76 and 575 MDR-TB cases, respectively. The percentage of cases undergoing DST to second line drugs was high (98-100%) for Latvian and Estonian cases, but only 67% in Romania. The percentage of MDR-TB cases resistant to fluoroquinolones and/or injectables was concerning in all three countries (Estonia 50%, Latvia 47%, Romania 25%). In Romania more MDR-TB cases are resistant to second-line injectables than fluoroquinolones; the reverse is true in Estonia. Since 2004 absolute numbers of MDR-TB cases have decreased in all countries (27-59% decrease). Although the proportion of MDR-TB cases with resistance to injectables has decreased during the study period, there has been an increase in cases with additional resistance to fluoroquinolones. The proportion of MDR-TB cases with XDR-TB was 1.7-fold higher in Latvia in 2013 (17%) vs. 2004 (10%). The percentage of cases resistant to pyrazinamide in 2013, where tested, was high for both retreatment and new cases (69-75%). The percentage of MDR-TB cases resistant to ofloxacin was high in Estonia and for retreatment cases in Latvia and Romania. Prothionamide resistance was common (43-73%) in Estonian retreatment cases and both new

and retreatment cases in Latvia. Latvia had the highest percentage of MDR-TB cases known to be co-infected with HIV (24%).

Conclusions: High levels of additional resistance to currently recommended second line drugs was seen in all countries, with important variations between countries in drug sensitivity profiles. Accurate DST and DST data for second line drugs from a variety of countries is vital for comparison to WHO treatment recommendations in order to inform the development of future MDR-TB treatment regimens that meet the needs of all regions and patient groups.

64. Patient-centered care and methods to improve treatment adherence

PC-1237-06 Health-related quality of life assessment using EQ-5D in newly diagnosed pulmonary tuberculosis patients

S Mcallister,¹ S Imaculata,² Y Laurence,³ S Kerry,⁴ J Critchley,⁴ P Hill,¹ R Ruslami,² B Alisjahbana² ¹University of Otago, Dunedin, New Zealand; ²Padjadjaran University, Bandung, Indonesia; ³London School of Hygiene & Tropical Medicine, London; ⁴St George's University of London, London, UK. e-mail: sue.mcallister@otago.ac.nz

Background: Tuberculosis (TB) remains a major public health problem worldwide. TB studies have focussed mainly on severity and clinical outcomes but TB can have an impact on patient health-related quality of life (HRQOL). However, there is limited information available on this, particularly in TB endemic countries. Our study evaluated HRQOL and associated characteristics in pulmonary TB patients in Bandung, Indonesia.

Design/Methods: As part of the TANDEM program on TB and diabetes in different countries, we conducted a cross-sectional study of newly diagnosed pulmonary TB patients aged >18 years recruited from Community Health Clinics and DOTS clinic. In-person interviews were conducted to ask about socio-demographic characteristics and HRQOL using the EuroQol Group EQ-5D-5L Indonesian validated measure (dichotomised to 2-levels for analysis – 'No problems'; 'Any problems'), and Visual Analogue Scale (VAS: a scale from 0 to 100). The Karnofsky score was clinician-assessed. Odds ratios (OR), 95% confidence intervals (CI), coefficients and *P* s were generated using logistic regression and ordered logistic regression.

Results: A total of 275 TB patients were recruited from February 2014 to January 2015. The proportion reporting 'Any problems' was highest for EQ-5D Pain/discomfort (75%), followed by Anxiety/depression (59%), Usual activities (45%), Mobility (28%), and Self-care (13%). The mean VAS score was 70.4 (SD 17.8). People with a bank account had significantly reduced risk of reporting 'Any problems' on four EQ-5D variables: Mobility (OR 0.41, 95%CI 0.19-0.83), Usual activities (OR 0.44, 95%CI 0.25-0.78), Pain/discomfort (OR 0.39, 95%CI 0.22-0.73) and Anxiety/depression

(OR 0.52, 95%CI 0.29-0.90). People with higher education had a substantially reduced risk of 'Any problems' for two EQ-5D variables: Usual activities (OR 0.13, 95%CI 0.03-0.52) and Pain/discomfort (OR 0.19, 95%CI 0.05-0.70). Those aged ≥60 years were significantly more likely to report mobility problems (OR 3.29, 95%CI 1.34-8.08). All the EQ-5D variables correlated with the Karnofsky score, but the correlation was relatively weak for anxiety/depression.

Conclusion: The EQ-5D provides important information on HRQOL in TB patients, particularly in understanding pain/discomfort and anxiety/depression. Poorer TB patients are likely to have other concerns that affect their HRQOL. The EQ-5D can provide clinicians with insights into patients' HRQOL that may be amenable to intervention.

PC-1238-06 Audit and improvement of the clinical pathway for adult pulmonary tuberculosis in Bethesda Hospital, Yogyakarta, Indonesia

T Lestari,¹ A Probandari,^{1,2} H A Sanjoto,¹ H Djasri,¹ Iswanto,³ Y Mahendradhata,¹ A Utarini¹ ¹Center for Health Policy and Management, Yogyakarta, ²Sebelas Maret University, Surakarta, ³Bethesda Hospital, Yogyakarta, Indonesia. Fax: (+62) 27454 9425. e-mail: trisilestari@gmail.com

Background and challenges to implementation: Clinical pathway (CP) is a structured multidisciplinary care plans which detail essential steps in the care of patients with specific clinical problem. Bethesda hospital has been using a CP for adult pulmonary tuberculosis (TB) since 2008 and it has been proven effective to improve compliance of a clinical care team to a standard clinical guideline for TB. However, the CP has not been reviewed since its development.

Intervention or response: This was a one cycle action research to improve the quality of CP for TB in Bethesda hospital as part of a project to develop a sustainable hospital disease management system. In April 2015, a clinical care team audited the CP using the Integrated Clinical Pathway Appraisal Tool (ICPAT) to help the team identified the weakness of the CP and make improvements. There are 6 review dimensions, i.e. the structure, the documentation, the development, the implementation, the maintenance and the role of organisation. Each dimension contains a list of review items to the content and the quality of CP. The CP was revised according to the audit's finding and tested for two months before it is implemented.

Results and lessons learnt: The CP for tuberculosis in Bethesda hospital has fulfilled 42 out of 58 (72%) criterias for good content of CP and 35 out of 49 (71%) criterias for good quality of CP. Appraisal scores for each review dimensions were as followed: 75% in the structure, 56% in the documentation, 73% in the development, 83% in the implementation, 65% in the maintenance, and 100% in the role of organisation. Majority of unmet criterias were related to patient's involvement in the treatment (43%). Other unmet

criteria in the content of CP were the function of CP as a reminder for possible variations in the treatment, structure of the document, legality, and storage of CP. Unmet criteria in the quality of CP were identification of responsible person for each activities, identification of priority activities, schedule for review, and specific code for existing variations. The CP is currently under revision and will be tested in May to June 2015.

Conclusions and key recommendations: The clinical care team has not been considered patient's involvement in making clinical decision in their course of treatment for TB which is important in the era of patient-centeredness. Audit of CP using the ICPAT can improve the quality of care for TB in hospital.

PC-1239-06 Éxito del TAES en personas con TB, afroestizos, mediante la atención centrada por enfermería, en Cuajinicuilapa, Costa Chica, Guerrero, México

R E Huicochea,¹ M Clemente,¹ V Leyva¹ ¹Secretaría de Salud, Chilapancingo, Guerrero, Mexico. Fax: (+52) 55 261 46 438. e-mail: arceliaavena@yahoo.com.mx

Justificación : El municipio de Cuajinicuilapa registra cada año 18 casos nuevos de TB, aportando 8.5% de la morbilidad de la región. El 16.3%, de los enfermos son afroestizos, que de acuerdo a su cosmovisión (creencias de hechicería, brujería), de carácter fuerte, representan un reto para los servicios de salud para llevarlos al éxito del Tratamiento, aunado a factores socioeconómicos, que lo condicionan, lo cual hace necesario brindar la atención centrada en estas personas.

Metodología : Se desarrolló la estrategia "Atención integral", en cinco fases implementadas por la enfermera de Red TAES; la primera empoderamiento al enfermo sobre la TB, haciéndole sentir respeto, confianza y reducción del tiempo en sala de espera, llamándolo por su nombre, monitoreando reacciones adversas; la segunda: visitas domiciliarias mensuales, la tercera: atención psicológica, la cuarta: colectas alimenticias en ferias TB, rifas y boteo económico, quinta: premiación al esfuerzo, otorgando estímulos, resultado de BK de control negativo, ganancia de peso e invitándole un almuerzo; se analizó historial de la TB en este grupo étnico.

Resultados: de 1996 a 2015, se diagnosticaron 59 casos nuevos TBTF, 98.3% TBP y 1.7% miliar, 72.9% fueron detectados en consulta externa, 27.9% en pesquisa casa a casa, 33.9% en contactos. La positividad fue de 28.1% (+), 13.6% (++), 32.2%(+++), 25.4% por Rx; comorbilidades: desnutrición (69.5%), Diabetes Mellitus 23.7% y VIH 5.0%, rango edad 21 a 79 años. 66.1% fueron hombres, 33.6% mujeres, beneficiándose 59 personas afroestizas, dotación alimentaria quincenal, consultas y suplementos alimenticios mensual, pasajes; gestión de actas y constancias de identidad, pólizas de seguro popular, laboratorios, Rx particulares, curó 94.9% y 5.1% continúa en tratamiento.

Conclusiones: La estrategia de atención integral personalizada por enfermería en personas afroestizas afectadas por TB, no modificó la cosmovisión con relación a la

enfermedad, sólo garantizó el éxito del TAES, demostrando la importancia de la detección en los contactos, para incidir en el control de la TB, en el Municipio de Cuajinicuilapa, Guerrero.

PC-1240-06 Patient-centred behaviour change communication materials can help to reduce social stigma and improve treatment adherence

G Mishra,¹ L Lochting,² H Amdal,² B Lamichhane,³ A Thapa³ ¹LHL International Tuberculosis Foundation, Norway, Kathmandu, Nepal; ²LHL International Tuberculosis Foundation, Oslo, Norway; ³National Tuberculosis Centre, Bhaktapur, Nepal. e-mail: gokulmishra@gmail.com

Background and challenges to implementation: There was a serious lack of patient centred behaviour change communication materials in the Nepal National Tuberculosis Programme (NTP). Considering this fact, the LHL International Tuberculosis Foundation, Norway and NTP jointly organised three patient centred needs assessment workshops and two focus group discussions with the health workers and patients together in different parts of Nepal- to assess the real information needs of TB patients on tuberculosis in 2010. This first edition of patient centred TB booklet (first published in 2011) contains a description of how you can use this booklet, basic facts about tuberculosis, facts about DR-TB and HIV/AIDS, how to cope with tuberculosis and the side effects of treatment and keeping body and soul well when you have TB.

Intervention or response: Patient Centred Tuberculosis booklet was developed with patients and health workers together. Health communication trainings were organised for health workers and volunteers and TB booklets were distributed to health workers, volunteers and TB patients at Kathmandu Metropolitan City, Nepal.

Results and lessons learnt: 100% of TB patients shared their knowledge that TB patients should cover their mouth and nose while coughing and sneezing. The majority of the TB patients used a mask for covering their mouth and nose followed by handkerchief (32.8%), blocking with palms (13.8%). 63.9 % TB patients received advice about good nutrition during TB treatment from health workers while 36.1 % of TB patients received the same information from a TB booklet. All respondents reported experiencing less social stigmatism as a result of contracting TB after sharing the TB booklet with their family. Most of the TB patients also reported that the booklet made it easier for them to speak to their family and friends about TB.

Conclusions and key recommendations: The booklet was found to be an effective tool in improving relationships with TB patients, bringing good practices, motivating health workers while dealing with TB patients and reducing discrimination and stigma.

PC-1241-06 Unveiling treatment supporter roles behind completion of treatment by TB patients: implications for a new agenda setting for lung health

R Olukolade,¹ A Hassan,¹ R Kusimo,¹ L Okwuonye,¹ J Okechukwu,² J Osho,¹ S T Abdurrahman,² C Ogbuji¹

¹Association for Reproductive and Family Health, Abuja,

²Federal Capital Territory Tuberculosis and Leprosy Control Programme, Abuja, Nigeria. e-mail: richkolade@gmail.com

Background: Tuberculosis control programme in Nigeria allows for the involvement of Treatment Supporters (TS) basically in monitoring patients' daily drug intake. However, the identification of the support needs of TB patients is more appropriate to inform the engagement and the expected roles of TS. This paper unveils what the roles of TS should be, from the perspectives of TB patients.

Methods: Qualitative data was collected from three categories of participants; TB patients, TS and DOTS Staff, selected from six TB clinics representing each of the six Area Councils of the Federal Capital Territory (FCT) of Abuja, Nigeria. Eleven Focus Group

Discussions; (5 male and 6 female groups) was conducted among TB patients currently on treatment. Fifteen (15) TS identified from the facilities' TB registers were interviewed as key informants. In-depth interview was conducted with one (1) TB clinic staff, in each of the six facilities where the FGDs were conducted. Data generated was content analyzed and interpreted in relation to the objectives of the study and themes in the Discussion Guide.

Results: Majority of TB patients expressed their challenges while on treatment. Four key areas of TB patients support needs were identified; (1) monitoring and supervision of daily drug in-take, (2) motivational support to take the drugs as expected, (3) provision of support in feeding (when there is no food or means of eating), and (4) provision of support in supplying transportation cost to visit TB clinic if there is no means of doing so. Left on their own, TB patients may not be committed to taking their drugs and complete their treatment regimen, if any of these supports is lacking when needed. Patients with TS who offer these supports tend to complete their treatment regimen and not likely to default.

Recommendations: Although TB drugs are free in Nigeria and TS are being engaged to support Treatment, TB patients' support needs should inform the design of Community TB care.

PC-1242-06 A patient-centered TB counseling strategy impacts out-patient follow-up in Yunnan, China

M Li,¹ A Innes,^{2,4} X Zhao,³ I Ling,³ M Ma,¹ M Li,¹ C Du,¹ X Xu³ ¹Kunming No. 3 Hospital, Kunming, Yunnan Province, China; ²FHI 360, Bangkok, Thailand; ³FHI 360 China, Kunming, Yunnan Province, China; ⁴FHI 360 Asia Pacific Regional Office, Bangkok, Thailand. e-mail: ainnes@fhi360.org

Background: Adherence counseling on TB and multi-drug resistant tuberculosis (MDR-TB) using a patient-centered strategy is unique in China, where communication is normally approached from a provider's perspective. The USAID Control and Prevention-Tuberculosis (CAP-TB) China program, managed by FHI 360, partnered with Kunming No.3 Hospital to use a patient-centered counseling strategy that was integrated into daily education. The goal was to prepare inpatients for outpatient treatment and adherence following hospital discharge.

Intervention: A total of 150 newly registered TB inpatients at Kunming No. 3 Hospital participated over four months in 2014. During inpatient hospitalization, nurses or TB peer educators provided each patient with at least three in-depth, one-on-one counseling sessions: upon admission, during inpatient hospitalization, and prior to discharge. On the day of TB treatment initiation and on the day before hospital discharge, patients were tested on their basic TB knowledge and awareness. Pre- and post- counseling TB knowledge was compared using Z-test for proportions.

Results: Among the 150 patients, 133 (89%) were newly diagnosed TB cases, and 17 (11%) were previously treated. Seventy-five of the patients were from outside Kunming City; 58% had lower than secondary education; and 63% self-reported as farmers, migrant or mobile workers, or unemployed. Twenty (13%) reported previous history of TB among family members. TB knowledge increased significantly after inpatient counseling when compared to pre-counseling (all $P < 0.005$). The post-counseling test showed that 98% knew their TB status correctly, compared to 49% on the pre-test. Knowledge of TB transmission increased (from 16.7% to 74%); as well as knowledge on drug-susceptible treatment course (from 50.7% to 92.7%) and MDR-TB treatment course (41% to 85%). Patients also improved their knowledge on timing for follow-up sputum testing (60% increase). After this inpatient counseling strategy was implemented, the number of TB outpatients at Kunming No.3 Hospital nearly doubled and was maintained at increased levels compared to pre-counseling intervention.

Conclusions: Using a patient-centered TB counseling strategy increased inpatient TB knowledge and was associated with improved attendance for outpatient follow-up visits. Longer-term outcomes, such as impact on treatment completion and cure, are still to be determined and will be followed for this cohort.

Table 1: TB knowledge and awareness in pre- and post-counseling tests among TB inpatients at Kunming No. 3 Hospital

TB knowledge and awareness	Pre-counseling		Post-counseling		p-value
	N	%	N	%	
Total number of patients	150	100	150	100	
• Know their TB category (TB,MDR-TB, newly treated or retreatment)	74	49.3	147	98.0	<0.001
• Know TB transmission route	25	16.7	111	74.0	<0.001
• Know TB symptoms	95	63.3	131	87.3	<0.001
• Know TB and MDR-TB are curable	61	40.7	111	74.0	<0.001
• Know treatment course for TB	76	50.7	139	92.7	<0.001
• Know treatment course for MDR-TB	62	41.3	128	85.3	<0.001
• Know TB medication has side effects	113	75.3	132	88.0	<0.005
• Know TB treatment principles	96	64.0	137	91.3	<0.001
• Know when a newly treated patient should return for sputum test	20	13.3	119	79.3	<0.001
• Know when a retreatment patient should return for sputum test	15	10.0	105	70.0	<0.001
• Know what causes MDR-TB	27	18.0	59	40.0	<0.001

PC-1243-06 Barriers and facilitators to treatment adherence among MDR-TB patients in Yunnan, China

X Lin,¹ I Ling,² X Xu,² C Wong,³ Y Guo,¹ A Innes⁴ ¹Yunnan Center for Disease Control and Prevention, Kunming, Yunnan Province, ²FHI 360 China, Kunming, Yunnan Province, China; ³FHI 360, Durham, NC, USA; ⁴FHI 360 Asia Pacific Regional Office, Bangkok, Thailand. e-mail: ainnes@fhi360.org

Background: China is a high-burden TB country with the second highest number of multi-drug resistant (MDR) TB cases worldwide. Although TB prevalence in China declined from 2000-2010, the MDR-TB burden is high, underscoring challenges to treatment adherence. We explored the barriers and facilitators to treatment adherence in order to develop communication and support strategies for MDR-TB patients, with the goal to improve treatment outcomes.

Intervention: Semi-structured interviews were conducted with the first 24 MDR-TB patients enrolled in the China Global Fund TB program in Yunnan, China in 2013. Patients were asked how they were diagnosed with TB or MDR-TB; about the barriers and facilitators for treatment adherence; and the impact of TB and MDR-TB on their lives, with a specific focus on issues impacting treatment adherence. Interviews were transcribed or written up as expanded notes and analyzed using applied thematic analysis.

Results: We identified four overarching barriers to treatment adherence: economic and geographic factors that influence access to care; experience-based knowledge or beliefs about healthcare choices; perceived and actual fears of treatment side effects; and complexity of information on TB treatment. Economic hardship was the most frequently reported barrier, when patients could not pay for drugs, hospitalization, and transportation. Some patients from rural areas discontinued follow-up visits and then bought drugs from private pharmacies when they felt sick, or they took Chinese traditional medicine. Some also stopped treatment when their cough disappeared, thinking that they had fully recovered. Other barriers included self-stigma around TB and the perceived fear of how the side effects would disrupt their lives, as well as the actual side effects experienced, which led to reduction or discontinuation of treatment. In contrast, facilitators of adherence included physician support and encouragement during clinic visits and phone calls. Communication among patients was also important for facilitating adherence, enabling them to learn from their peers about TB and how to overcome challenges.

Conclusions: There are many barriers that impact MDR-TB treatment adherence. To improve treatment outcomes, a patient-centered strategy should be used that addresses stigma, economic, and other barriers; that simplifies TB education to improve comprehension; and that teaches about side effects and their treatment.

PC-1244-06 Patient satisfaction and adherence to medication among adult patients with pulmonary tuberculosis in Uganda

H Babikako,¹ D Neuhauser,² A Katamba,³ E Mupere,³ C C Whalen⁴ ¹Makerere University, College of Health Sciences, School of Medicine, Kampala, ²Case Western Reserve University, Kampala, ³College of Health Sciences, Makerere University, Kampala, Uganda; ⁴College of Public Health, University of Georgia, Athens, GA, USA. Fax: (+256) 414 533 531. e-mail: mupez@yahoo.com

Background: Non-adherence to tuberculosis (TB) treatment arises from the interaction of multiple factors affecting the quality of TB care. Current TB program services and clinical research have focused largely on outcomes of mortality and microbiologic cure, and have not considered patient's preferences; yet patients' beliefs and attitudes may influence how patients take drugs. We therefore established whether patient satisfaction was associated with non-adherence to prescribed TB treatment in urban Uganda.

Methods: In a cross-sectional study of 469 smear positive TB patients attending five program clinics in Kampala city, we measured patient satisfaction with service care (PS) and satisfaction with TB medication information received (SIMS) using a PS 13-item and SIMS 17-item questionnaires, respectively, and non-adherence using Morisky scale among patients completing 2, 5 and 8 months of treatment. We used our previously published subscales for PS 13-item of clinic organization set-up, technical quality, and hospital care; and for SIMS 17-

item of information about action and about effects of medication. Sub-scales were scored as summated scales on a 0 – 100 level where higher scores indicated better satisfaction.

Results: Scores for satisfaction with information about action and about effects of medication were all below 50% at 49.8 ± 14.9 and 28.2 ± 28.2 , respectively. Of the three subscales for PS 13-item tool, clinic organization set-up had the lowest score at 63.3 ± 7.8 . Scores for clinic organization set-up, hospital care and information about effects of the medication were significantly higher in HIV positive compared to negative patients. For example, among 135 HIV positive patients, score for clinic organization set-up was 64.5 ± 6.1 versus 62.6 ± 8.6 in 314 HIV negative patients, respectively ($P = 0.016$). Among 135 non-adherent patients, clinic organization satisfaction score was significantly lower 62.1 ± 8.8 versus 63.8 ± 7.3 in 334 adherent patients, respectively ($P = 0.014$). A unit increase in clinic organization set-up satisfaction score was associated with a 4% less likelihood for adherence (OR = 0.964; (95%CI: 0.933, 0.995)) among HIV negative patients.

Conclusion: We found sub-optimal patient satisfaction with information about action and about effects of medication, and HIV positive status was associated with improved satisfaction. Low satisfaction with clinic organization was associated with non-adherent in HIV negative patients.

PC-1245-06 The effects of peer education on treatment adherence of MDR-TB patients in Kunming, China

G Nie,¹ W Zhang¹ ¹Institute of Tuberculosis Prevention and Control, Yunnan Center for Disease Control and Prevention, Kunming, China. e-mail: tudor@icn.ch

Background: The incidence of MDR-TB in China is 8.3%, and 7.0% in Kunming, Yunnan Province. Primary cause of MDR-TB is irregular treatment of drug-susceptible TB. This study sought to explore the influence of peer education on treatment adherence for patients with multi-drug resistant tuberculosis (MDR-TB).

Design/Methods: 157 patients with MDR-TB were randomly divided into an observation group (77 patients) and control group (80 patients). The patients in the observation group received peer education and routine health education. The patients in the control group received routine health education. We compared patient knowledge about MDR-TB, changes in mood and anxiety and treatment adherence between the two groups after a six-month intervention.

Results: Patients in the peer education group had significantly better knowledge about MDR-TB ($P < 0.01$), reduced anxiety ($P = 0.05$), and improved treatment adherence than the control group ($P = 0.01$).

Conclusion: Peer education can significantly improve patient knowledge about MDR-TB, reduce anxiety and improve treatment adherence in patients with MDR-TB.

PC-1246-06 Where there is hope: a qualitative study examining adherence to MDR-TB treatment in Karakalpakstan, Uzbekistan

S Horter,¹ B Stringer,¹ J Greig,¹ P Du Cros,¹ S Dietrich,² M Tillyashaykhov,³ N N Parpieva,³ Z Tigay⁴ ¹Médecins Sans Frontières (MSF), London, UK; ²MSF, Berlin, Germany; ³Ministry of Health of the Republic of Uzbekistan, Tashkent, ⁴TB II Hospital, Nukus, Uzbekistan. e-mail: shona.horter@london.msf.org

Background: Multi-drug resistant tuberculosis (MDR-TB) treatment is complex and lengthy, with a cocktail of toxic drugs that have limited efficacy. Adherence to treatment is challenging, and non-completion of treatment has significant medical and public health implications. A qualitative study was conducted to understand patients' experiences with adherence to MDR-TB treatment in Karakalpakstan, Uzbekistan, to inform future strategies of adherence support.

Methods: Participants were recruited purposively to ensure a variety of treatment experiences, patient characteristics, and health practitioner perspectives. 52 in-depth interviews were conducted with MDR-TB patients ($n = 35$) and health practitioners ($n = 12$), including 5 follow-up interviews to probe emerging themes. Interview transcripts were analysed thematically using coding. Analysis drew upon principles of grounded theory, with constant comparison of codes and categories within and between cases to actively seek discrepancies and generate concepts from participant accounts.

Results: Several factors affected patients' adherence to MDR-TB treatment. Many patients had limited TB knowledge, influencing their belief in the need for and value of treatment and their hope for cure, and undermining their motivation for treatment. Patients' ability to choose treatment and prioritise it over conflicting demands within their lives relied on their sense of autonomy and control, as well as their ownership and self-responsibility for treatment. Patients' authority over their treatment-taking and their engagement with it was influenced by common beliefs, myths and stigma, as well as by hierarchical practitioner-patient relationships. Women's societal role as daughter-in-law could undermine their authority over treatment. Patients' tolerance of treatment was linked to their views about drug effects, with a positive mindset seen as improving side effects experienced.

Conclusion: This qualitative study reveals three main themes influencing adherence to MDR-TB treatment: disease knowledge and belief, patient autonomy and control, and views on TB drugs. It reinforces the policy for an individualised, holistic and patient-centred approach to treatment support for effective TB control and treatment. Patient knowledge about their disease and treatment, and engagement of patients as active participants in their care was endorsed as a key enabler for adherence, strategies that acknowledge this should be included in programming.

65. Why are you late? Delay in treatment access

PC-1247-06 Delays in TB diagnosis at Parakou, Benin

S Amidou,¹ R Baguidi,² A Wachinou³ ¹RESEARCH, National Programme against HIV, Parakou, ²National Programme against TB, Parakou, ³RESEARCH, National Programme against TB, Parakou, Benin. e-mail: salmaneamidou@gmail.com

Background and challenges to implementation: Delays in Tuberculosis disease (TB) diagnosis may lead to death even with appropriate TB treatment or significant decline in lung function after recovery. The main objective of this study was to determine the factors related to delay before TB care.

Intervention or response: A cross sectional study was conducted among TB patient enrolled in 2011 at the center of detection and treatment of TB at Parakou. Two types of delay were defined. Patient delay was related to the length of time between the onset of the symptoms and the first contact with a health facility and System delay related to the period between the first contact with a health centre and the beginning of the TB treatment. A standardized questionnaire was use to collect data.

Results and lessons learnt: Sixty six patients were interviewed and 72.7% had delayed over 21 days. The burden of delay was due mostly to patient's delay which represented 84.4% of Total delay. The means of Total delay per patient was 90 + 169 days, Patient delay mean was 76 + 157 days and System delay was 14 + 28 days. The 3rd quartiles for System, Patient and Total delays were respectively 12, 67 and 82 days. Access to health centre was good (82.5% lived near a health centre), but TB facilities were not available in the nearest centre from patient's house (90.5%). Most of patient (93.6%) usually go to health centre first when sick, but also use alternative options like self-medication, praise or plants (52.4%). Highest delays were not related to income, knowledge, access to health centre, nor treatment first choice when sick but System's delay above 3rd quartile (12 days) were more observed among patient who firstly sought care in public centre than those who chose private clinic (OR=6.4; C.I.5%:[1.5-27.2]).

Conclusions and key recommendations: The main delay to TB care occurs before contact with the health system. System delay was mainly due to unavailability of TB facilities. To reduce delay, the National TB Programme must improve policies, give more training to health workers, and expand TB care availability. Population's education should continue to improve global use of modern health care facilities as first option.

PC-1248-06 Patient and provider delay in pulmonary tuberculosis patients: a cross-sectional study in Addis Ababa city, Ethiopia

D Assefa Lemma,¹ N Kamp,² E Klinkenberg³ ¹KNCV Tuberculosis Foundation, Addis Ababa, Ethiopia; ²KNCV Tuberculosis Foundation, The Hague, The Hague, Netherlands; ³RESEARCH, KNCV Tuberculosis Foundation, The Hague, Netherlands. e-mail: dawita8246@gmail.com

Background: Ethiopia is one of the high TB burden countries, and is implementing TB control strategies which are fully aligned with the globally recommended 'Stop TB Strategy'. High level of public awareness is believed to influence health seeking behavior positively and this may contribute to early TB case identification and hence limit transmission of the disease in the community. This study aims to assess the extent of pulmonary TB patient delay and associated factors in Addis Ababa.

Design/Methods: Cross sectional survey was employed to interview pulmonary TB patients during their intensive phase of daily supervised treatment. Study conducted in Addis Ababa, in four purposely selected high TB burden sub-cities from Aug 1- Oct 31, 2014.

Results: A total of 535 pulmonary TB patients (59.5% being male) were enrolled. Average household size was 3.8 (SD 1.81) and average rooms per house were 2.12 (SD 1.47). The median patient delay was 30 days (IQR 30 - 60) while provide delay was 5 days (IQR 3 - 15). Only 2 (0.4%) of PTB patients had correct knowledge on the mode of TB transmission that said through breathing when someone cough or sneeze but 109 (20.5%) PTB patients said by sharing household utensils and 422 (79.2%) eating together from the same plate. When asked about the practice at the start of TB related symptoms, 82 (15.5%) reported they tried home remedies, 49 (9.2%) reported to have visited a pharmacy while 18 (3.4%) sought care from traditional healer. When PTB patients requested what made them to seek health care at health facility, 435 (81.6%) reported self and advise from family members while only 17 (3%) said the community Health Extension Workers (HEW).

Conclusion: Patient delay is a problem for TB control and majority of PTB patients sought health care by themselves or family advice. PTB patients' knowledge on the mode of TB transmission in an urban setting like Addis Ababa was found to be very limited. Community TB care implementation through HEWs in order to improve public awareness and health seeking behavior need to be strengthened.

Table 1: Who informed PTB patients to seek care at health facility

Who made you seek care?	Number / percentage
Myself and family member	435 (81.6%)
Community HEWs advice / refer	17 (3.2%)
Civil society organization members	4 (0.8%)
Other, e.g. someone I know, etc	77 (14.5%)
Total	533 (100%)

PC-1249-06 TB treatment delays in Odisha, India: is it expected even after so many years of RNTCP implementation?

K Ilangoan,¹ S Burugina Nagaraja,² R Ananthakrishnan,³ A Jacob,⁴ J Tripathy,⁵ D Tamang⁴

¹Health Systems Research India Initiative, Thiruvananthapuram, ²ESIC Medical College and PGIMSR, Bengaluru, ³Resource Group for Education and Advocacy for Community Health, Chennai, ⁴International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ⁵School of Public Health, PGIMER, Chandigarh, India. Fax: (+914) 428 173 947. e-mail: kumaravelilangoan@gmail.com

Background: In India, the Revised National TB Control Programme (RNTCP) envisages initiation of TB treatment within seven days of diagnosis among smear positive patients. After nearly two decades of RNTCP implementation treatment delays are usually not expected. We conducted this study to determine the proportion of sputum smear positive TB patients who were initiated on treatment after seven days and their associated risk factors.

Methods: The study was conducted in Cuttack and Rayagada districts of Odisha. It was a retrospective cohort study that involves reviews of TB treatment registers and laboratory registers for 2013.

Results: Among 1800 pulmonary TB (PTB) patients, 1074 (60%) had been initiated on treatment within seven days of diagnosis, 721 (40%) initiated on treatment more than seven days and 354 (20%) had delays of more than 15 days. The mean duration between diagnosis and treatment initiation was 21 days with range of 8-207 days (Median = 14days). Odds of treatment delay of more than seven days were 4.9 times (95% confidence interval [CI] 3.3-6.6) among those who had been previously treated, 6.2 times (95%CI 1.3-29.7) among those infected with HIV and 1.8 times (95%CI 1.1-2.9) among those diagnosed outside district designated microscopy centre (DMC).

Conclusion: Delay in initiation of TB treatment occurred in majority of the smear positive patients. The RNTCP should focus on the core areas of providing quality TB services with time tested strategies. To have real time monitoring mechanism for diagnosed smear positive TB patients is expected to be the way forward.

PC-1250-06 Health-seeking behaviour and delay in diagnosis of tuberculosis in India

S Nayak,¹ P Sharma¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. Fax: (+91) 4605 4429. e-mail: SNayak.HR@theunion.org

Background and challenges to implementation: The health seeking behaviour of those with TB determines different degrees of engagement with the public health system due to many reasons. Thus utilization of health services can be influenced by availability, distance factor, economic loss, perceived monetary value of the public health system's quality services. There is limited infor-

mation in India about the TB patients' perspective in explaining health-seeking behaviour to address the issue of delay / discontinuity in managing people with TB. To identify and measure the health seeking behaviour, challenges faced by presumptive TB patients in accessing public health facilities and delay in diagnosis of TB by using data from Project Axshya's intervention in 30 districts of India from November 2012 and April 2013.

Intervention or response: A cross sectional community-based survey in 30 districts of India conducted by the trained field investigators appointed by The Union. The respondents (4804) including general population, TB patients (496), health service providers, opinion leaders, representatives of NGOs identified and interviewed through a door-to-door survey by using semi-structured questionnaire.

Results and lessons learnt: Onset of symptoms 27% preferred qualified private doctor/clinic their first point of contact. While 73% with symptoms actively sought health care between 1 week to 1 month after diagnosis. (71%) aware of diagnosis / symptoms, consider TB a serious disease, heard of free diagnosis, (83%) as curable. (21%) had cough for < 3 weeks and 9% by 2 weeks. The current strategy of identifying TB suspect, delays the diagnosis of TB cases (21-9) by 15%. Hospital/ doctors/TV are major source of information related to TB and treatment is free of cost under DOTS known by 59%. 76% take treatment regularly and 55% about correct duration of treatment (6-8 months). 81% respondents visited 2 or more providers prior diagnosis. 39% sought health care from private health care sector due to a perception that government centres are distantly located and long waiting hours. The results show that not only in terms of delays in diagnosis (and finally the treatment) is attributable to the long distance of government facility, socioeconomic condition of TB patient, which force them to continue for daily wage for family sustenance instead to hospitals.

Conclusions and key recommendations: Increased access to health care by increasing the frequency of mobile clinic services and strengthening the community health worker strategy are possible options.

PC-1251-06 Clinical characteristics and diagnostic delay in spinal tuberculosis patients in the Netherlands

D Ijdema,¹ C Magis-Escurra,¹ P Horsting,² C Erkens,³ R Aarnoutse,¹ M Boeree¹ ¹Radboud University Medical Centre, Nijmegen, ²Maartenskliniek, Nijmegen, ³KNCV, The Hague, Netherlands. e-mail: cecile.magis-escurra@radboudumc.nl

Background: With declining TB incidences diagnostic delays, especially in extra-pulmonary TB, may increase. We describe the patient and clinical characteristics of patients with spinal TB and assessed the course of diagnostic delays of spinal TB from 2000-2011 in The Netherlands.

Table Determinants of delay

Determinant	value	Patients' delay Median in months (min-max)		Doctors' delay Median in months (min-max)		Diagnostic delay Median in months (min-max)	
Sex*	M	0.75 (0-37.5)	P= 0.139	2.25 (0-24)	P= 0.052	4.5 (0.25-38.5)	P= 0.004
	F	1.00 (0-72)		4.00 (0-52)		5.5 (0-76)	
Age [#]	0-34 ys	0.75 (0-9)	P= 0.235	2.00 (0-52)	P= 0.022	4.5 (0.25-52)	P= 0.006
	35-64 ys	1.00 (0-72)		4.00 (0.25-27)		5.75 (0.75-76)	
	> 65 ys	1.50 (0-18)		3.25 (0-24)		5.00 (0-25)	
Origin*	NL	1.5 (0-12)	P= 0.883	2.5 (0-24)	P= 0.370	5.0 (0-30)	P= 0.665
	Fb [‡]	1.0 (0-72)		3.0 (0-52)		5.0 (0.25-76)	
Risk factors*	Yes	1.0 (0-72)	P= 0.967	3.0 (0-12.5)	P= 0.581	5.0 (0.75-46)	P= 0.889
	No	1.0 (0-37.5)		3.0 (0-52)		5.25 (0-52)	
Trias of symp-toms*	Yes	0.5 (0-35)	P= 0.483	4.0 (0-27)	P= 0.050	5.50 (0.5-46)	P= 0.582
	No	1.0 (0-72)		2.0 (0-24)		5.0 (0-76)	
Neurol sympt*	Yes	0.88 (0-18)	P= 0.049	3.75 (0.25-24)	P= 0.403	4.25 (0.25-24)	P= 0.070
	No	1.0 (0-72)		2.25 (0-13)		5.5 (0-76)	

*Mann-Whitney test, [#]Kruskal Wallis test, [‡]Fb = foreign born, Trias of symptoms = night sweats, weight loss and back pain, Neurol sympt = neurological symptoms at presentation.

Design/Methods: Data from the Netherlands Tuberculosis Registry were studied, completed with basic demographic data and data considering patients-, doctors- and total diagnostic delay retrieved from the patient records at the public municipal health services.

Results: A total of 274 cases were studied. Median diagnostic delay was five months and stable during this period. Sex and age groups were associated with significant differences in diagnostic delay (male 4.5 vs. female 5.5 months), and 4.5-5 months in the youngest age group and persons >65 years but 5.75 months in patients aged 35-64 years. No difference was observed between origin of patients, patients presenting with TB risk factors or with neurological symptoms. Typical TB symptoms at presentation lead, surprisingly, to significantly increased doctors' delay (typical symptoms 4.0 vs. no typical symptoms 2.0 months, $P = 0.05$).

Conclusion: Considering spinal TB diagnosis and act expeditious is necessary to limit the time to diagnosis in spinal TB. Refresher courses should be offered both to family physicians and clinical specialists in The Netherlands.

PC-1252-06 Barriers to accessing rapid second-line treatment initiation for drug-resistant TB in South Africa

L Dickson-Hall,¹ C Tomlinson,¹ H Cox,¹ J Furin,² A Van't Hoog,³ A Grant,⁴ C Oosthuizen,¹ M Nicol^{1,5}

¹University of Cape Town, Cape Town, South Africa; ²Harvard Medical School, Boston, MA, USA; ³University of Amsterdam, Amsterdam, Netherlands; ⁴London School of Hygiene & Tropical Medicine, London, UK; ⁵National Health Laboratory Services, Cape Town, South Africa. e-mail: lindydickson4@gmail.com

Background: Following the roll-out of the Xpert MTB/RIF rapid test in South Africa, early reports suggested that the number of patients subsequently initiating treatment and the time taken for this to be achieved fell short of what was expected. We aimed to assess health system and patient level barriers that may impact on treatment access and time to RR-TB treatment initiation.

Methods: A mixed methods approach was used to identify factors associated with time to RR-TB treatment initiation in South Africa. 40 successive cases with RR TB were identified within National Health Laboratory records in early 2013 from selected urban and rural areas in each of 3 provinces. Cases were classified into those that initiated treatment rapidly (within 0-30 days), delayed treatment (31-180 days) and did not initiate treatment (>180 days, if at all). Semi-structured interviews were recorded and transcribed from patients, family members or friends and health care workers, who were presumed to have insight into the patient's care initiation. The data was manually analysed for themes denoting barriers, enablers and missed opportunities for care linkage and more rapid treatment initiation.

Results: Among the 91 patients included, 78 cases initiated treatment at a median of 29.5 days after the diagnostic specimen was taken; 24 patients initiated treatment within 10 days, 45 between 11-60 days, 9 between 2-6 months. 13 patients had not initiated treatment by 6 months. Factors most commonly mentioned as barriers to care from a health care perspective included: Difficulties in accessing and actioning laboratory results, challenges tracing patients for result provision due to administrative deficiencies, complexities in referring patients to centralised facilities and patient socio-economic situations. Factors most mentioned as barriers to care from a patient perspective included: Low levels of family or staff support, socio-economic challenges, and having to leave the household or work place to initiate treatment in a hospital or at a distant site. Enablers and missed opportunities most mentioned related to communication between different health care providers and efforts made advising and encouraging patients.

Conclusions: A laboratory record showing RR-TB does not guarantee access to treatment. Exploring barriers to care, enablers and missed opportunities yields important insights which can be used to direct improvement initiatives involving treatment access and time to treatment.

PC-1253-06 Why they said they got tested for TB

D Skinner,¹ M Claassens² ¹Research on Health and Society, Cape Town, ²Desmond Tutu TB Treatment Centre, Cape Town, South Africa. e-mail: dskinner@sun.ac.za

Background: Patients may be infectious with TB for an extended period for they begin treatment. Early testing for TB is crucial for controlling the epidemic, especially in communities where there are high existing levels of disease such as in South Africa, which has one of the highest rates of TB internationally. It is particularly important now with the overlapping HIV epidemic and the increasing prevalence of drug resistant TB. The objective of the study was to understand why people who had presented to be tested for TB initially opted to do this at the time that they were tested and the context in which this occurred.

Design/Methods: This study was nested in a larger study looking at patients who do not present for treatment. Depth interviews were done with 41 patients across five provinces in South Africa. Generally only one patient was interviewed from a clinic and the sample covered patients who had taken their treatment regularly and others who did not. All interviews were recorded and then transcribed and translated into English. A contextualised interpretative content analysis method was used.

Results: The reason why people present themselves for testing included an awareness of having symptoms of TB and wanting to protect family. Knowledge of TB was high in the community. Unfortunately many wait until severe symptoms start and thus remain infectious for longer. There were concerns about stigma and the problems of being on treatment especially having to visit the clinic daily for DOTS. Many are tested as part of screening programmes run in the community or when they come to the clinic for a different purpose. While this is an important intervention in the epidemic, some respondents reported being unclear of the nature of the tests being done and the implications of the test. A number claimed that they were not told what the tests were for or felt forced into being tested. Some expressed shock when they were given the results of the test.

Conclusion: Patients do present for testing, but despite high levels of knowledge of the symptoms, do not take fully into account that they may be infectious in the early part of their illness. The screening was accepted as an important intervention, but a number did feel that they were not respected in the process. More education is needed on the need for testing and to encourage testing before severe symptoms develop.

PC-1254-06 Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania

K Ibrahim,^{1,2,3} J Hella,^{1,2,3} F Mhimbira,^{1,2,3} L Fenner,^{1,2} T Maroa,³ M Chiryamkubi,⁴ T Maroa³ ¹Swiss Tropical and Public Health Institute, Basel, ²University of Basel, Basel, Switzerland; ³Ifakara Health Institute, Dar Es Salaam, ⁴National TB and Leprosy Control Programme, Dar Es Salaam, Tanzania. e-mail: ksaid@ihi.or.tz

Background: Tuberculosis (TB) has a long infectious period, and therefore early diagnosis and reduction of undiagnosed TB is crucial to minimize the spread of disease in the community. We aimed to assess the diagnostic delay of infectious TB and to identify associated risk factors.

Methods: We analysed new adult smear-positive TB patients enrolled in an on-going TB Cohort Study in Dar es Salaam, Tanzania between 2013 and 2015. TB patients were interviewed to collect information on their health seeking behaviours. Diagnostic delay was defined as the interval from onset of TB symptoms until the time of TB diagnosis (≤ 3 or > 3 weeks). All patients were put on treatment within the first two days of TB diagnosis. We used logistic regression models to identify risk factors for diagnostic delay.

Results: We included data from 452 new adult TB patients. The median age was 34 years (interquartile range [IQR] 28-42), 310 (69%) were males, and 148 (33%) were HIV-positive, 64/148 (43%) on ART. More than half of the patients (251, 56%) lived in rented houses, median household size was 3 persons (IQR 2-4), and 354 (78%) of the patients earned <200 USD per month. Almost all patients (449/452) reported coughing at time of diagnosis. Median delay time was 3 weeks (IQR 3.0-3.0), 24 (5%) had a delay of more than four weeks. Majority of patients reported taking self-treatment prior to TB diagnosis (403, 89%), amoxicillin was the first drug of choice (377, 93%) and ampicillin was taken by 12 (3%). Prior to TB diagnosis, 389 (86%) reported seeking care from formal health providers, of those, 207 (53%) sought care 3 times or more. Only 5 (1%) visited traditional healers. In univariate analysis, diagnostic delay was significantly associated with higher income level, smaller household size, no previous visit to a health facility, non-use of self-treatment and chest pain (Table). Age, sex, education level and HIV status did not show significant association. In multivariate analysis, higher income level, smaller household size, and no previous visit to a health facility were predictors of treatment delay of more than 3 weeks.

Conclusion: In urban Tanzania, diagnostic delay of TB was more common among patients with higher income and smaller household size, but less likely in patients seeking health care multiple times. Consequent systematic screening for TB at facilities and community-level could further reduce the delay to interrupt transmission and control of TB in the communities.

Table. Association of socio-demographic and health related factors with patient delay (defined as three or more weeks) among 452 pulmonary tuberculosis patients in Dar es Salaam, Tanzania.

Characteristic	Cases n (%)	OR (95% CI)	p value	aOR (95% CI)	p value
Age			0.4		0.7
18-24	57 (13)	1		1	
25-44	302 (67)	0.42 (0.14-1.21)		0.65 (0.29-1.43)	
>44	93 (93)	0.5 (0.15-1.64)		0.99 (0.39-2.50)	
Sex			0.9		0.5
Female	142 (31)	1		1	
Male	310 (69)	0.97 (0.60-1.58)		0.81 (0.46-1.44)	
HIV status			0.66		0.8
Positive	148 (33)	1		1	
Negative	304 (67)	1.11 (0.69-1.81)		1.02 (0.58-1.78)	
Occupation			0.2		0.5
Unemployed	89 (20)	1		1	
Unskilled labour	60 (13)	1.79 (0.79-4.04)		1.17 (0.45-3.05)	
Semiskilled labour	303 (67)	1.55 (0.83-2.93)		0.86 (0.39-1.89)	
Income class			<0.001		0.001
Earns less than \$120	177 (39)	1		1	
Earns \$120 or more	275 (61)	3.31 (1.92-5.70)		3.00 (1.59-5.66)	
Household size			<0.001		<0.001
1 in the household	41 (9)	1		1	
2-3 in the household	292 (65)	0.45 (0.23-0.88)		0.37 (0.18-0.78)	
≥4 in the household	119 (26)	0.13 (0.05-0.32)		0.14 (0.05-0.36)	
Visiting health facility			<0.001		0.003
No visit	58 (13)	1		1	
1-2 visits	182 (40)	0.66 (0.35-1.23)		0.95 (0.31-2.94)	
3 or more visit	207 (47)	0.20 (0.10-0.39)		0.35 (0.08-1.19)	
Self-treatment			0.002		0.6
No	49 (11)	1		1	
Yes	403 (89)	0.38 (0.02-0.71)		0.77 (0.25-2.40)	
Chest pain			0.002		0.4
No chest pain	102 (23)	1		1	
Chest pain	350 (77)	0.46 (0.28-0.75)		1.39 (0.70-2.74)	

OR, Odds Ratio; aOR adjusted Odds Ratio; 95% CI, 95% Confidence Interval.

All variables in the table were included in the multivariate model.

PC-1255-06 Patients suspecting TB are diagnosed earlier

S Mutembo,^{1,2} J M Mutanga,^{1,2} J Sekandi Nabbuye,^{1,3}

B Mwangelwa,² C Kanene,⁴ K Musokotwane,²

J Chinyonga,² C C Whalen¹ ¹University of Georgia, Athens,

GA, USA; ²Ministry of Health, Zambia, Choma, Zambia;

³University of Makerere, Kampala, Uganda; ⁴Center for

Disease Control and Prevention Zambia Country Office,

Choma, Zambia. Fax: (+26) 213 221 446. e-mail:

simon.mutembo@gmail.com

Background: Early diagnosis of Tuberculosis (TB) and treatment are essential for an effective TB control program. Delay in diagnosis affects both disease prognosis at the individual level and transmission within the community. This study aims to determine the magnitude of delay to diagnosis and the associated risk factors in a rural setting where HIV prevalence is high.

Methods: We conducted a retrospective cohort study of patients aged ≥16 years who were treated for TB at Mazabuka District Hospital in Zambia between March and July 2014. We administered a questionnaire to TB patients who were on treatment for less than 6 months. Descriptive analysis was performed followed by survival analysis to estimate the time to final diagnosis from onset of symptoms. We performed a cox proportion hazard analysis to evaluate patient and health provider factors associated with time to final diagnosis.

Results: We enrolled 171 participants with a median age of 34 years (IQR 27, 42), of whom 63% were male. One hundred and twenty patients (71%) were HIV positive and 94% of these were on combination antiretroviral treatment. The overall median time from the onset of symptoms to diagnosis was 101 days (IQR; 68, 152). The median time from first contact with health care provider to diagnosis was 28 days (IQR 14, 56). All patients received TB drugs the day that the diagnosis of TB was made. The first point of contact for 84% of the patients was a family member and 26% first visited either a drug store or a traditional healer. None of the participants consulted a health care provider in the initial step. Patients who suspected that they had TB were 61% more likely to achieve an earlier diagnosis (HR = 1.6; 95%CI: 1.1, 2.3). Time to diagnosis was similar between HIV negative and positive patients.

Conclusion: The largest delay in diagnosis occurred before patients reached the health care system but in patients who suspected that they had TB, the diagnosis was often made earlier. We recommend community programs to raise awareness on TB and influence change of health seeking behavior.

PC-1256-06 Specimen transportation system in Zimbabwe: an innovative way to overcome barriers to accessing early TB diagnosis in a resource limited settings

C Zishiri,¹ R Ncube,¹ M Nqobile,¹ K Charambira,¹ C Sandy,² A Kanjanga,³ M Jonasi,¹ P Shiri² ¹International Union Against Tuberculosis and Lung Disease, Harare, ²Ministry of Health and Child Care, Harare, ³Riders for Health, Harare, Zimbabwe. e-mail: czishiri@theunion.org

Background and challenges to implementation: Tuberculosis (TB) case detection rate in Zimbabwe has fallen from 56% in 2000 to 42% in 2013 according to the WHO 2014 Global TB report. This decline calls for a real need to strengthen efforts for TB case finding at all levels. The country is one of the top 22 high burdened countries which account for more than 80% of the TB cases globally. Sputum smear microscopy remains the first line laboratory diagnostic technique for pulmonary tuberculosis (TB) in Zimbabwe. Despite significant investment in the infrastructure of TB laboratories in recent years, most rural communities remain with sputum smear microscopy access challenges.

Intervention or response: To overcome barriers to accessing sputum smear microscopy, TB CARE I in partnership with Riders for Health launched a specimen transport (ST) system in June 2010. The system transports sputum and other samples using motorcycles to bring specimens to the nearest diagnostic centre. This is currently a daily routine and where large distances are covered this becomes a weekly routine.

Results and lessons learnt: The system now covers up to 24 districts with 42 motorcycles which serve 649 health facilities (40%) of all health facilities in Zimbabwe. There was a fourfold increase in specimens transported from 38,663 in 2010 to 182,265 in 2014. The proportion of other non sputum specimens increased from 56% in 2010 to 70% in 2014. This increase represents a notable overall strengthening of the health systems. The turnaround time for sputum specimen results decreased from a range of two to three weeks (pre ST period) to a range of one to seven days with ST. The percentage of TB patients with sputum not done plummeted from 19% in 2010 to 7% in 2014 and through improved access to follow up specimens, the cure rate increased from 71% in 2010 to 75% in 2013.

Conclusions and key recommendations: The ST system is a reliable and efficient system that minimises barriers to accessing TB diagnostic services, delays in diagnosis and barriers to follow up sputum specimens for monitoring treatment response.

66. Gender issues in TB and tobacco

PC-1257-06 Involvement of female community health workers in BRAC-supported areas for TB control

S Alam,¹ S Reza,¹ M Basher,¹ M Rana,¹ M Akramul Islam,¹ M Chowdhury,¹ M Haque² ¹BRAC, Dhaka, ²NTP, Dhaka, Bangladesh. Fax: (+88) 2988 8026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: Community based tuberculosis control program in Bangladesh has been implementing by BRAC since 1994 under the stewardship of National TB Control Program (NTP). Recently BRAC is working following this model in two-thirds of the country covering approximately 93 million population in both rural and urban areas. Female community health workers (Shasthya Shebikas) are the nucleus in TB control activities at community level. Increase accessibility of TB services and ensuring daily intake of drugs (DOT) are disputes for TB control.

Intervention or response: Shasthya Shebikas are usually being selected from BRAC's village microcredit organizations. Each Shebika provides essential health care services to about 250 households. They receive basic training before starting work and a one-day refresher training in every month. During the routine household visits, they disseminate TB information, identify TB presumptive and refer them for sputum test, provide home-based DOT and refer TB patients for any side-effects. Patients are encouraged to deposit taka 200 (US\$2.5) as bond money for treatment completions which is totally refundable. Respective Shebikas receive taka 500 (US\$6) for successful DOT treatment completion of each patient from program as an incentive.

Results and lessons learnt: Currently about 63 810 Shasthya Shebikas are actively involved in TB control activities in BRAC supported areas and more than 80% DOT is ensured by these Shasthya Shebikas. In 2014, a total of 124 286 patients diagnosed in BRAC supported areas. Of them, 72,231 were new smear positive and case notification rate was 78 and 134 per 100 000 population for new smear positive and all cases respectively. Treatment success rate in 2013 was 95% among new smear positive patients.

Conclusions and key recommendations: As Shasthya Shebikas are the residences of community, they can enhance early detection of TB cases and better treatment compliance. To sustain a favorable treatment outcome more than 90% is also possible through implementation of daily DOT by them.

PC-1258-06 Smoking-attributed mortality in women in Tianjin, China: case-control study of all adult deaths from 2010 to 2013

W Li,¹ G H Jiang,^{1,2} Z L Xu,¹ D Z Wang,¹ W Zheng¹ ¹Tianjin Centers for Disease Control and Prevention, Tianjin, ²Tianjin Medical University, Tianjin, China. e-mail: liweicdc@126.com

Objectives: In 2009, Tianjin became the first city which added questions on smoking of the deceased in the death certificate in China and Asia. We used the information from the death certificate to analyze all cause of deaths attributable to smoking in women age 35-79 years in Tianjin. To assess smoking induced mortality in women in Tianjin.

Methods: Death data were recorded from death certificates collected through the Cause of Death Registration System (CDRS) maintained by the Tianjin Centers for Disease Control and Prevention (TJCDC), which monitors the entire household population in Tianjin. The information about smoking was obtained by doctors through inquiring the relative living together with the deceased. From 2010 to 2013, 50 412 (current smokers & never smokers) were included in this analysis (44 145 cases & 98 67 controls). Unmatched multiple logistic regression was used to calculate odds ratios (OR) of mortality for current smokers vs. never smokers adjusted by five year age group, education, year of death and marital status.

Results: 6.72% of the women death cases were caused by smoking in Tianjin and smokers lost 5 years of life due to the habit of smoking. Compared to the non-smokers, the most extreme OR was in lung cancer group, and it was highest in 65-79 years group, the OR was 5.22 (4.73-5.76). The ORs were 3.27 (2.70, 3.96) and 2.13 (1.20-3.78) in 50-64 and 35-49 years group respectively. Factors as longer smoking years and plenty daily cigarette consumption were both associated with risk of high mortality. The all-cause OR was highest in smokers aged 50-64 years who consumed ≥ 15 cigarettes per day (2.11, 1.69-2.63) when compared with never smokers, than those who consumed 1-14 cigarettes (1.40, 1.13-1.73). Smokers who smoking more than 15 years showed a greater OR than those who smoking less or on 15 years (OR: 1.63 vs. 1.28).

Conclusions: Results from our study addressed the problem that smoking had been a major risk factor for mortality and productivity loss in female adults in Tianjin and also highlight the early effect the tobacco control work in Tianjin and the continued need to take urgent programs to reduce the tobacco use in Tianjin, and even China, because comprehensive tobacco control programs and policies have been proven effective for controlling tobacco use.

PC-1259-06 Gender differences in the presentation of tuberculosis, Medellin, Colombia, 2010

L Villa,¹ M P Arbeláez¹ ¹Universidad de Antioquia, Medellin, Colombia. e-mail: lvillavelez@gmail.com

Background: In Colombia, Tuberculosis (TB) is still a public health problem. TB is a relevant cause of mortality in low-income populations and women (most during reproductive ages), which generates a bigger social problem given that many of them are head of household mothers. The objective of this study is to determine gender differences in the presentation of tuberculosis (TB) in a group of patients from Colombia

Design/Methods: The target population was identified from the databases of a cohort study of cohabitants conducted in the cities of Medellin, Popayan and Cali (Colombia) as part of the activities of the Colombian TB Research Center (CCITB) between 2005 and 2008. The sample included 492 pulmonary TB index cases and 2816 household contacts

Results: 55.3% of the index cases were men who correspond to a male/female ratio of 1.2. Most cases of TB occurred in men over 50 years old and women at younger ages (15-49 year old). More cases of coinfection with HIV were found in men 13 (4.9%) compared to women 5 (2.3%). At follow-up 36 incident cases were found, of which 22 (61.1%) corresponded to women, with a slightly increased risk among those between 15-24 years of age and a higher incidence of disease (RR 1.55 95%CI 0.5-5.1). Women showed less evidence of BCG vaccination; and higher incidence of TB compared to men when they were malnourished, living in overcrowded conditions, had fewer open areas in the household or perceived to have poor ventilation in it. There was delay in the diagnosis (56 days) and treatment (12 days) in men, while for women was 38 and 2 days respectively. Symptoms like cough and expectoration were found to be more common among women. More cases of mixed TB in men and extra-pulmonary TB were found in women; additionally, women possessed higher bacterial load and higher co-morbidity with diabetes mellitus.

Conclusion: This study is relevant for TB control programs in order seek, treat and follow the cases from a patient-centered care perspective, because it is focused on vulnerable and special populations. In the local context must be considered the fact that TB incidence is higher in younger women and older men, and the risk is associated with gender and age. Additionally, in Colombia the burden of TB significantly affects women in their reproductive age. Moreover comorbidity of diabetes must be addressed because their risk of developing TB becomes higher and requires active search strategies especially in their family environment.

PC-1260-06 TB control amongst brothel- and street-based female sex workers: findings from the Western sex corridor, Maharashtra

O Bera,¹ M Chandge,² S Kamble,³ S Nayak,¹ S Mohanty,¹ R Deshmukh,⁴ S Chadha,¹ P Banuru Muralidhara¹

¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ²District TB Office, Mumbai, ³State TB Office, Pune, ⁴World Health Organization South East Asia Office, New Delhi, India. e-mail: oprakash@theunion.org

Background: Female sex workers (FSW) are usually transient, hard to reach group, often new migrants living in crowded conditions coming in contact with number of clients and associated TB-HIV co-infection amplifies the risk of spread of tuberculosis (TB). FSWs risk of acquiring HIV is reduced in recent years; however, the risk of getting TB infection has remained the same. The intervention study was designed with the objective of assessing awareness level of tuberculosis and impact of communication intervention among brothel based and street based female sex workers of Pune and Sangli, Maharashtra.

Intervention: At the onset, brothel based and street based FSWs were mapped and baseline knowledge, attitude and practice (KAP) survey was done using questionnaire prepared in local language among randomly selected 200 brothel based and 200 street based FSW in Jan 2014. It was followed by interventions which included intensive three months door to door brothel campaign and personal sensitization of street based FSW by trained NGO health staff using pictorial tool kits developed by project Axshya (Global fund round 9 Project) imparting knowledge on TB disease, diagnosis, treatment to 3000 FSW in Pune and 2000 FSW in Sangli and was overall monitored and supervised by corporation health officials. An observatory period of nine months was maintained before the end line knowledge and practice assessment of new batch of randomly selected 200 brothel based and 200 street sex workers was conducted in Dec 2014.

Results and lessons learnt: Amongst brothel based FSWs of the 200 interviews in base line survey only 105 (52.5%) heard of TB as compared to 146 (73%) in end line survey. Significant ($P < 0.05$) increase of knowledge was observed in end line as compared to base line in variables such as cough of two week as major symptom (71%), sputum testing as method of diagnosis (78.7%), high chance of acquiring TB in HIV patients (72%), free treatment at all government health facilities (47.3%). Significant positive change of attitude regarding decreased stigma associated with TB (12.3%), increased sharing of TB Status (46%) and increased acceptance of TB treatment at Government and NGO health facility (57.5%). Practice of covering face while coughing or sneezing (21.2%) and HIV infected FSW to visit health facility even if cough of one day (48.6%) was significantly higher as compared to baseline study. Street based FSW were not having any knowledge of cough of two weeks as main symptom of TB, contact examination, DOT as treatment of TB during baseline study. After the

intervention, there was significant change in knowledge of cough of two week as major symptom, sputum testing, increased chances of having TB in HIV infected, DOTS as preferred treatment and treatment is free in government health facilities. It was disappointing that the attitude of status sharing and stigma attached didn't change much.

Table: Comparative analysis of baseline and end line KAP survey among Female Sex Workers (Brothel based and Street Based)

Variables	Brothel Based FSW		Street based FSW	
	Baseline KAP Study (Total=200) N (%)	End line KAP Study (Total=200) N (%)	Baseline KAP Study (Total=200) N (%)	End line KAP Study (Total=200) N (%)
Knowledge				
Heard of TB	105(52.5)	146(73)	76(38)	102(51)
**Cough of two weeks as symptom of TB	38(36.2)	104(71.2)	12(15.7)	48(47.1)
**TB spreads when a person having TB cough or sneezes	25(23.8)	111(76)	10(13.2)	52(51)
**Sputum testing as method of diagnosis	32(30.4)	115(78.7)	16(21)	47(46.1)
**HIV increases the chances of having TB	18(17)	105(72)	2(2.6)	27(26.4)
** Knowledge of TB Contact examination	26(24.7)	90(61.6)	0	21(20.5)
**DOTS as TB treatment	11(10.4)	76(52.1)	0	34(33.3)
**TB treatment better in private health facility	78(74.2)	75(51.2)	52(68.4)	54(53)
**TB Treatment free in nearest government health facility.	32(30.4)	69(47.3)	23(30.2)	85(83.3)
** TB is curable	45(43)	108(74)	43(56.5)	88(86.3)
Attitude				
**TB creates stigma	42(40)	18(12.3)	65(85.5)	83(81.3)
**TB Status sharing	11(10.5)	68(46.6)	0	18(17.6)
**TB treatment in Govt./ NGO Health facility	30(28.5)	84(57.5)	57(75)	82(80.4)
Practice				
**Cover your face with cloth while coughing	12(11.4)	31(21.2)	5(7)	43(42)
**Cough of 2 weeks is a must to attend health clinics	22(21)	120(82.2)	0	37(36.3)
**HIV patient to attend health facility even if cough of one or more day.	13(12.4)	71(48.6)	0	27(26.5)

** This questions are only for those "who have heard of TB"

Conclusions and key recommendations: This study is the first of its kind in bringing the impact of health

communication intervention amongst brothel based and street based FSWs. The above study demonstrates the importance of customized active awareness campaign for high risk populations. Even though there is low awareness and least health seeking behaviour amongst FSWs, there is no established health promotion strategy for this marginalised and vulnerable community. FSWs have the potential to be moving time bombs of TB-HIV co-infection and coupled with low socio-economic conditions and the huge clientele they serve, it is the right time to create high impact large scale awareness campaigns coupled with active screening in high risk populations.

PC-1261-06 TB screening and testing at antenatal care clinics in Burkina Faso

A Roggi,¹ Y Moyenga,² G Sulis,¹ S Gnanou,² I Zombra,² S Diandé,² F Castelli,¹ A Matteelli¹ ¹Clinic of Infectious and Tropical Diseases, University of Brescia (UNIBS), WHO Collaborating Centre for TB-HIV and TB Elimination, Brescia, Italy, ²National Tuberculosis Programme (NTP), Ministry of Health, Ouagadougou, Burkina Faso, e-mail: al.roggi@gmail.com

Background and challenges to implementation: In Burkina Faso 5520 case of tuberculosis (TB) all forms were reported in 2013, including 3616 case of smear positive pulmonary TB (941 women and 2676 men). Figures on notification rates among pregnant women are not routinely available in the country. In 2014 the NTP initiated a project to introduce TB screening and testing among pregnant women attending antenatal care clinics (ANC) in the Central region of Burkina Faso. Technical assistance was provided by the University of Brescia and financial support by WHO.

Intervention or response: Women attending 55 ANC in 4 Districts were screened for signs or symptoms of active TB, using a standardized WHO questionnaire. Women with presumptive TB were expected to give sputum samples to be analyzed at the National Reference Laboratory (NRL). At NRL samples were tested for TB and rifampicin resistance using the Xpert MTB/RIF platform. A two-day training course for health workers was performed in all selected ANC prior to the intervention. Data were recorded on ANC registers and collected during supervisory visits by NTP staff.

Results and lessons learnt: Between August 2014 and March 2015, 73 289 pregnant women were seen at intervention sites and 2035 (2.8%) reported TB signs or symptoms. However, only 31 samples were collected and referred for Xpert MTB/RIF analysis. All tests were negatives for *M. tuberculosis*. The average time between sputum collection and analysis was 3.3 days. During the same period of time no case of TB was notified among pregnant women in the intervention area, though 33 had been estimated to occur.

Conclusions and key recommendations: TB is likely severely underdiagnosed among ANC clinic attendants in Burkina Faso. Questionnaire screening was feasible and identified a significant number of women with presumptive TB, however, only a small fraction of

women with presumptive TB were tested for TB. To promote appropriate diagnostic procedures in these cases, additional targeted interventions are warranted including training, supervision, and staff retention measures. Regional Health Offices, rather than PNT should take primary responsibility to integrate TB into the ANC prevention and care package.

PC-1262-06 Frequency and predictors of oral lesions in women with smokeless tobacco use: a cross-sectional study in squatter settlements of Karachi, Pakistan

M Irfan,¹ F Idrees,¹ J Khan¹ ¹Aga Khan University, Karachi, Pakistan. Fax: (+92) 213 493 4294. e-mail: muhammad.irfan@aku.edu

Background: Incidence of oral cancers is rising in Pakistan, particularly in women who use smokeless tobacco (SLT). Oral malignancy is usually preceded by a pre-malignant lesion such as leukoplakia, erythroplakia etc. Increased incidence of such lesion in women would indicate a further rise in oral malignancy in future. Objective: To determine the frequency and predictors of oral lesions in women with habitual use of SLT.

Methods: A cross-sectional survey was done in January 2015, in two squatter settlements of Karachi on women aged 15-75 years. A questionnaire was filled after consent, including details of SLT use. The oral cavity of each subject was examined after rinsing the mouth with water and pre-malignant lesions, if any, were noted.

Results: Of the 385 women, 277 (72%) were using SLT, however only 102 consented to take part in the study. The mean age was 36.6 ± 12.4 years. 20 (19.6 %) were working as housemaids. The starting age was 20.5 ± 10.9 years. About 48 (47%) were found to have oral lesions, 8 had 3, 22 had 2 and 48 had at least 1 lesions. The most common lesions were oral ulcers 42 (41%), leukoplakia 22 (21%), melanotic macules 19 (18%), submucous fibrosis 5 (4%) and erythroplakia 3(2%). Two patients were found to have large irregular oral lesions suspicious of malignancy. 42% ($n = 43$) women had gingivitis and loosening of teeth. The highest frequency of oral lesions were found in ghutka users 57.4% ($n = 27/47$), followed by Naswaar 53.3% ($n = 8/15$), Paan 25.9% (7/27) and Mawa 25%(3/12) . 98 (97%) reported at least one of the family members using some forms of tobacco. 43 women reported at least 1 child below 10 using SLT. The frequency of use greater than 3 times /day (OR 2.62, 95%CI (1.17-5.86), the age of initiation below 20(OR 4.173, 95%CI (1.74-10.01) and duration of use greater than 10 years (OR 4.917, 95%CI (2.07-11.67) were independent predictors associated with increased incidence of oral lesions.

Conclusion: A high incidence of oral lesions including the pre-malignant ones among women with habitual use of smokeless tobacco is a cause of concern as it is an indicator of increased morbidity and mortality in Pakistan in the future due to oral cancer. Appropriate measures are required to address this issue.

PC-1263-06 Gender profile of TB screening and diagnosis in Ugu District, South Africa

L Oldja,¹ R Forse,¹ A Mohiuddin,¹ S Khowaja,² A Khan,¹ L Page-Shipp³ ¹IRD SA, Johannesburg, South Africa; ²IRD, Karachi, Pakistan; ³The Aurum Institute, Johannesburg, South Africa. e-mail: loldja@gmail.com

Background: The primary driver of the TB epidemic in South Africa is HIV/AIDS, with over 60% of TB patients being co-infected. In this setting, young women face the highest risk of HIV, which consequently feminizes the TB epidemic compared to other settings. The female-to-male TB incidence ratio in South Africa (0.83) is among the highest in the world, yet males still bear the majority of the disease burden.

Design/Methods: Between February and mid-April 2015, systematic TB symptom screening was implemented at 14 high-volume Department of Health facilities in Ugu District, KwaZulu-Natal, South Africa. Screeners used a 4-symptom verbal questionnaire to identify people to send for testing among patients and attendants over 5 years of age. All samples were transported to the National Health Laboratory Service (NHLS) for testing with the Xpert MTB/RIF assay. Each step of the TB care pathway was analysed, disaggregated by age and gender. **Results:** Twice as many females (6335) as males (3108) were screened, yet males were more likely to be symptomatic (41% of males vs. 32% of females, $P < 0.0001$). Adolescent (5-15 years) females were the only age group in which more females among those screened reported symptoms than males (60% of females vs. 48% of males, $P = 0.0343$). There were no significant differences in sputum submission rates, transport to NHLS or lab-reported errors (e.g. not leaked, insufficient, etc) between genders. Among valid, returned test results, MTB-positivity in males was two-times higher than that of females (14% vs. 7%, $P < 0.0001$). Even though twice as many females were screened, 48% more bacteriologically confirmed pulmonary TB patients were detected among males. Of these, 17% of male cases and 9% of female cases were MTB/Rif+, although these findings do not show a significant difference between the groups. Among patients without prior self-reported history of TB diagnosis and treatment, 60 males (14.6% of Xpert MTB+/- results returned) and 44 females (6.9% of Xpert MTB+/- results returned, $P < 0.0001$) were found to be positive for TB. Male Female Indicator N (%) N (%) P Number Screened 3108 (33%) 6335 (67%) Number Presumptive TB 1267 (40.8%) 2038 (32.2%) <0.0001 Number able to produce sputum for Xpert testing 847 (66.9%) 1261 (61.9%) 0.0041 Number of samples collected & sent for testing on Xpert 842 (99.4%) 1254 (99.4%) 0.9999 Number of Xpert results obtained (any) 611 (72.6%) 877 (69.9%) 0.2020 Number of Xpert results (MTB +/-) 501 (82.0%) 714 (81.4%) 0.7858 Number of cases detected with TB SS+/B 70 (14.0%) 47 (6.6%) <0.0001 Number of Rif+ TB SS+/B cases detected 12 (17.1%) 4 (8.5%) 0.2728.

Conclusion: Early and frequent engagement with the health system is critical to combat TB-HIV. The higher numbers of women screened indicates gender-based

differences in accessing care, due in part to utilizing maternal and child health services and experiencing less stigma when accessing care. Despite higher rates of HIV in young women, men continue to present higher TB positivity rates, which may reflect delays in patient care-seeking. This pattern can be generalized across both new and retreatment cases. The gendered barriers to care in South Africa need further exploration to improve early TB case detection.

PC-1264-06 Gender differences in treatment completion of tuberculosis patients in Kampala City, Uganda

A Etwom,¹ D Mumpe Mwanja,² M Kenneth,¹ D Sama,¹ D Lukoye,¹ D Kimuli,¹ W Amutuhaire,³ M Ruhweza,¹ P G Suarez¹ ¹Management Sciences for Health, Kampala, ²Ministry of Health, Kampala, ³Kampala Capital City Authorities, Kampala, Uganda. e-mail: etwoma@yahoo.com

Background and challenges to implementation: Gender disparities in tuberculosis (TB) treatment outcomes have been reported worldwide. Though socio-cultural factors have been implicated elsewhere, the disparities in treatment outcomes by gender for patients in Kampala had not been documented before. An analysis of TB treatment outcomes was conducted to compare treatment completion by gender among patients treated for tuberculosis in Kampala.

Intervention or response: KCCA health team with support from the USAID funded TRACK TB Project conducted a retrospective study to determine gender associated factors influencing treatment outcomes of newly diagnosed TB patients. Records of patients started on anti TB treatment from July to December 2012 in 15 public (PHF) and 35 private (PPF) TB Diagnostic and Treatment Units (DTUs) in Kampala were extracted from the DTU databases. Gender based comparative bivariate and multivariate logistic regression analysis by Age, HIV Status, Ownership of treating facility and DOT status was done.

Results and lessons learnt: A total of 4142 records were extracted, of which 1609 (38.8%) belonged to female patients. Overall treatment completion for the cohort was 75% and the variation by gender and other parameters is illustrated in Figure 1. A comparison of treatment completion by gender showed that females from PPF had better odds ratios (OR) of successfully completing treatment compared to females in the PHF (OR 1.43, $P < 0.001$). Also males from PPF were more likely to successfully complete treatment compared to males in the PHF (OR 1.39, $P = 0.019$). Pulmonary Bacteriologically Confirmed (PBC) females and males had better chances of successfully completing treatment compared to those in other diagnostic categories. Females on DOT had better treatment completion (OR 1.82, $P < 0.001$) compared to males (OR 1.60, $P < 0.001$) under same conditions. Furthermore, HIV negative females had better odds (OR 1.63, $P < 0.001$, OR 1.57, $P < 0.001$) of completing treatment compared to HIV negative males.

Conclusion: Females diagnosed with TB have better odds of completing treatment compared to their male counterparts despite case notification being higher among males. TB patients accessing treatment from PFPs are more likely to complete treatment compared to those receiving care from PFPs. We recommend further qualitative research to establish the determinants of these outcomes and to inform interventions to improve treatment completion among males and patients attending PFPs in urban settings.

PC-1265-06 Capacity building among women in tobacco control

B I Chitindi,¹ B Chipopo² ¹Advocacy, Tobacco Free Association of Zambia, Lusaka, ²Advocacy, Zambia Heart and Stroke Foundation, Lusaka, Zambia. e-mail: bichitindi@yahoo.com

Background and challenges to implementation: Due to lack of policy and inadequate enforcing mechanism for existing laws, control of tobacco use is nonexistence in Zambia. Zambian population can substantively reduce and not initiate tobacco use with a comprehensive community prevention programs. Communities influence social norms and reach people where they live, work, and play, learn, associate and worship. In line with Zambia's traditional values, women in the community face higher health risk factors and costs than men, due to their greater use of health care, yet they are more likely than their male counterparts to be poor and unemployed. Women are major contributors to health systems through their roles as primary care givers in the family and are a backbone and are exposed to greater occupational health risks in their roles as informal health care providers in the communities. They are unremunerated in their voluntary work, but have a voice that can make change.

Interventions or response: Women health and the participation of women in health systems has been a concern for World Health Organization. The life-course approach reveals the importance of women's multiple contributions to society, in both their productive and reproductive roles. In 2012 women in four communities, three in urban and one in rural areas of Zambia, a total number 320 women were mobilized, trained and empowered with the knowledge in tobacco control to be peer educators in communities. Women were eager to take responsibilities to form support groups to advance tobacco control in the nation of Zambia.

Results and lessons learnt: After acquiring knowledge, women formed support groups voluntary, created tobacco control corners in health centers. Sensitized on the harmful use of tobacco. The program has voluntarily spread to other parts of the country. The International Tobacco Control (ITC) Zambia Wave 1 Survey report indicates that 82% of tobacco users in Zambia are supportive to stronger tobacco control policies and they are ready to support the policies if implemented.

Conclusion and key recommendations: From both women training and ITC Zambia Wave 1 Survey report, the Zambian population are aware of the harms of

tobacco use and that government should play a stronger role in tobacco control. Policy makers should create a stronger and more comprehensive tobacco control programs and ensure that they are supported, implemented and enforced.

67. The spectrum of life: miners, drug users, the elderly

PC-1266-06 Active case finding for tuberculosis among elderly individuals (55 years and older) in Tboung Khmum Operational District, Cambodia

S Scholtissen,¹ O Camelique,¹ M Bonnet,² M Bastard,² C Hewison,¹ A Palomares,¹ D Dowdy,³ I Chikwanha¹ ¹Médecins Sans Frontières France, Paris, ²Epicentre, Paris, France; ³Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. e-mail: sofschol@yahoo.com

Background: If declines in tuberculosis (TB) prevalence in Cambodia are to be accelerated, novel approaches are required to identify populations with high prevalence of undiagnosed TB, such as the growing number of elderly. As shown in the national TB prevalence survey, older patients are also under-diagnosed as they do not present themselves to health facilities. We therefore sought to screen a population of age 55 years or more using chest X-ray (CXR) and TB symptoms, with an ultimate goal to develop an appropriate Active Case Finding model for this population.

Methods: We targeted a total of 17 health centers (HC) in two phases. The first phase screened the elderly population of 6 HCs at a single site, whereas the second phase used decentralized screening (8 sites for 11 HCs). Participants meeting any of the following definitions had a sputum specimen collected for GeneXpert MTB/RIF (Xpert) and/or culture testing: (a) cough $\geq$ 2 weeks; (b) cough < 2 weeks with any TB symptoms (sputum/hemoptysis, fever, weight or appetite loss, night sweats, lymph nodes); (c) CXR abnormal possibly or likely active TB (grade 2 or 3); or (d) for phase 2 only, sputum production/hemoptysis with no cough. All TB cases were referred for treatment.

Results: In the first phase (centralized), we screened 4098 individuals from a target population of 9517 (43% participation). Among them, 1352 (33%) had a positive screening, of whom 831 (62%) received Xpert testing. A total of 125 TB cases were identified, which is 3.1% of the screened population: 52 bacteriologically confirmed (1.3%, 47 by Xpert, 5 by culture), 68 bacteriologically negative, and 5 Extra-pulmonary TB (EPTB). In the second phase (decentralized), 8237 participants were screened from a target population of 13 994 (59% participation). Among them, 3091 (37.5%) had a positive screening, of whom 3048 (99%) were sent for testing. So far, 158 TB cases were identified, which is 1.9% of the screened population: 92 bacteriologically confirmed (1.1%, 79 by Xpert, 13 by culture), 65

bacteriologically negative (6 Xpert negative with cultures ongoing), and 1 EPTB.

Conclusions: Active Case Finding among elderly in Cambodia identified a large proportion of individuals with active TB, who may be sources of ongoing transmission in the community. A decentralized approach improved participation. The large-scale feasibility and cost-effectiveness of screening older population in Southeast Asian settings merit further investigation.

Table 1 - Proportion of Pulmonary TB cases bacteriologically confirmed among those tested by GeneXpert and distribution of screening criteria. ACF phase 1 & 2.

	X-RAY SCREENING*			
SYMPTOMS SCREENING	Abnormal unlikely active TB (Grade 1)	Abnormal possibly active TB (Grade 2)	Abnormal likely active TB (Grade 3)	Total
PHASE 1 (n=47)				
Cough ≥ 2 weeks	2/157 (1.3%)	5/109 (4.6%)	13/36 (36.1%)	20/302 (6.6%)
Cough < 2 weeks + Any TB symptoms**	1/120 (0.8%)	1/69 (1.4%)	3/11 (27.3%)	5/200 (2.5%)
No cough + Sputum/ hemoptysis Negative	1/84 (1.2%)	2/43 (4.7%)	4/12 (33.3%)	7/139 (5.0%)
	0/50	4/150 (2.7%)	11/35 (31.4%)	15/235 (6.4%)
Total	4/411 (1.0%)	12/371 (3.2%)	31/94 (33.0%)	47/876 (5.4%)
PHASE 2 (n=79)				
Cough ≥ 2 weeks	2/258 (0.8%)	7/218 (3.2%)	18/42 (42.9%)	27/518 (5.2%)
Cough < 2 weeks + Any TB symptoms**	2/353 (0.6%)	5/198 (2.5%)	15/38 (39.5%)	22/589 (3.7%)
No cough + Sputum/ hemoptysis Negative	0/78	3/33 (9.1%)	2/5 (40.0%)	5/116 (4.3%)
	0/7	16/688 (2.3%)	9/75 (12.0%)	25/770 (3.3%)
Total	4/696 (0.6%)	31/1137 (2.7%)	44/160 (27.5%)	79/1993 (4.0%)

* Normal X-rays were not integrated in this table as no TB case was found in this group of participants.

** Sputum/hemoptysis, fever, weight loss, loss of appetite, night sweats, lymph nodes.

PC-1267-06 Identification of rifampicin resistance among injecting drug users at entry screening in Cipinang DC: where will it lead?

Y N Sumarli,¹ E Nurhidayat,¹ Y I Hiola,² U Salamah,³ N Tandirerung,⁴ M Samsuri,⁵ M R Christian⁶ ¹Cipinang Detention Center, Jakarta, ²Provincial Office of Law and Human Right, Jakarta, ³Ministry of Law and Human Rights, Jakarta, ⁴Ministry of Health, Jakarta, ⁵Family Health International 360, Jakarta, ⁶World Health Organization, Jakarta, Indonesia. Fax: (+62) 218 591 1415. e-mail: dr.yulius.st@gmail.com

Background and challenges to implementation: A study in Indonesia in 2011 has found that people with HIV who injected drugs were 85% more likely to have HIV-associated tuberculosis than those who were not injecting drug users. Drug use has been associated with higher prevalence of latent TB infection (LTBI) and incidence of

TB disease. Over capacity is also a risk to accelerate TB transmission. Cipinang detention center has capacity of 1136 inmates but was occupied by 3487 inmates. In 2014 there were 27 TB Patients and 117 HIV patients. The high turnover of the prison population, between prisons and to the wider community, is a major challenge. This facilitates transmission and consequently the spread of both drug-sensitive and drug-resistant forms of TB.

Intervention or response: To have an overview of injecting drug users burden among new inmates and enhance the process of early detection of drug resistant TB, a structured questionnaire of Injecting drug profile was integrated in the entry screening form. All new inmates will be screened upon entry for TB and HIV using this questionnaire. Inmates with smear negative and HIV positive will be further screened by geneXpert.

Results and lessons learnt: In 2014, from 4432 new inmates, we identified 106 PWID, of whom all were tested for HIV, and 80 (75.6%) were HIV positive and 26 (24.4%) were HIV negative. We performed sputum examination to those with HIV positive, and we found 6 were positive for TB. From those with negative result, we performed 28 GeneXpert testing and found out that 24 were negative for MTB, and 2 were MTB Positive Rifampicin susceptible and 2 were MTB Positive Rifampicin Resistant. In total, out of 106 PWID there were 8 (7.5%) TB cases and 2 (1.9%) were RR TB patients.

Conclusions and key recommendations: Through a comprehensive entry screening, Cipinang DC managed to identify PWID with Rifampicin resistant early. The barriers to access a comprehensive care for Rifampicin resistant Tuberculosis may lead to the high prevalence of MDR-TB among drug users in Cipinang DC as well as the physiological effects of drug use, along with the environment and risk behaviors of drug users. Therefore a specific intervention and in Cipinang Detention should be addressed.

PC-1268-06 Characteristics of tuberculosis among elderly TB patients in Kenya

R Muthee,¹ D Nyangahu,¹ B Langat,² R Kiplimo,¹ M Githiomi¹ ¹National Tuberculosis, Leprosy and Lung Disease Program, Nairobi, ²National Treasury, Nairobi, Kenya. e-mail: mutheewanjiru@gmail.com

Background: Aging is an emerging risk factor for Tuberculosis (TB) disease. The great longevity of tubercle bacilli permits them to remain viable within a healthy host for many years. Majority of TB in the elderly is secondary to reactivation of latent TB infection to active TB. Factors contributing to this include age-associated diseases and poor nutrition. The elderly account for a large proportion of TB cases discovered at autopsy illustrating the difficulty of clinical diagnosis in this age group. This paper identified the characteristics of elderly TB patients (55 years and over) notified to the TB program and compared their treatment outcomes to

assess whether there are any peculiar factors fueling the TB burden in this cohort.

Design/Methods: A retrospective study based on the Kenya National TB Surveillance data for 2013 and 2014 (Q1-Q3). The study population was all elderly TB patients registered during the period. Descriptive statistics were generated and χ^2 tests were applied to establish if there was any association among the paired variables using SPSS.

Results: In 2013, 11.2% of all TB cases were the elderly while in 2014, this increased to 14%. Male preponderance was noted which accounted for 63.5 % of all cases. 81 % of the cases notified from the whole country had pulmonary TB. In 2013, Uasin Gishu County recorded the highest (38%) number of Extra Pulmonary TB cases while in 2014 Nairobi County recorded the highest (37%). Overall, 21% of all the elderly cases received food support. This was more than half of the moderately and severely malnourished. 19.5% of all the elderly cases were HIV positive with Homabay and Kisumu Counties displaying the greatest burden in both years. 30% of all the elderly TB cases were smear positive. 19.5% of the cases were from the private sector and faith-based organizations with 1% from the prisons. Further analysis on revealed that there was no statistical significance between treatment outcomes and HIV status ($P = 0.18$). Also, there was a positive correlation in the treatment outcome between the elderly and the young.

Conclusion: There was an uneven distribution of elderly in different counties which elicits the need for targeted county-specific fact-finding missions to elucidate these reasons and enact plausible interventions. In addition, an interplay of factors such as quality of care, health-seeking patterns, nutritional support and treatment adherence behavior among the elderly should be explored.

PC-1269-06 Situational assessment of tuberculosis in mines in Myanmar

S T Aung,¹ O Myint,² T Kyaw,³ E Cooreman³ ¹National TB Programme, Nay Pyi Taw, ²Ayeyarwaddy Regional TB Center, National TB Programme, Patheingyi, ³TB Unit, Yangon, Myanmar. Fax: (+95) 6742 1201. e-mail: dr.sta.ntp@gmail.com

Background and challenges to implementation: Tuberculosis is one of the major public health problems in Myanmar. Estimated TB prevalence and incidence is 473 and 373 per 100 000 population, respectively. Country-wide case notification rate (all forms) was 297/100 000 in 2013. One of the case finding strategies is screening among high risk groups. Miners were assumed to have higher TB incidence rates. Mobile teams actively screen for TB among the mining population. Though this strategy is not really new to Myanmar, knowledge on TB prevalence in miners was very limited. The situational assessment was conducted for successful implementation and scaling up of the activity. The objectives of the assessment are; to review the geographic, demographic and available health services in mining areas, and to assess TB prevalence in miners, their families and communities.

Intervention or response: Assessment teams used a checklist. The teams visited mines in Shan State and Tanintharyi Region between 2014 and early 2015. Symptoms screening was done with proforma. People with broad symptoms compatible with TB were subjected to digital chest X-ray. Sputum was also checked for those with X-ray compatible with TB.

Results and lessons learnt: Mining areas were hard to reach and accessibility to quality health services was challenging. Total attendees to mobile clinics were 2742 including 779 miners. Nearly 90% of miners did not know their HIV status. Thirty seven miners (4.7%) had history of TB treatment. Cough was the most common (though not universal) symptom among symptomatic people (41.8%). X-ray was taken from 2355 individuals (including 760 miners). Of them, 1900 (81%) were considered as normal, 52 (2.2%) active TB, 91 (3.9%) healed lesions, 127 (5.4%) presumed TB and 185 (7.9%) other pulmonary disease. Sputum was examined from active and presumed TB (179 persons). Sputum was positive in 24 cases (13.4%). In total, 73 people (including 13 miners) were diagnosed with TB. This means an overall prevalence of 2.7% and a prevalence of 1.7% among miners.

Conclusions and key recommendations: Multi-sectorial coordination and collaboration was very important for undertaking this assessment. TB prevalence in mine communities was significantly higher than that of the country. Moreover, mobile team could identify the hidden TB cases in this risk group residing in hard-to-reach areas. Thus, TB screening in mining areas should target the entire mining population and not merely miners.

PC-1270-06 TB case finding among the elderly in a congregate setting

R Fabella,¹ C Malibiran,² R Bunao² ¹Impact Project, Philippine Tuberculosis Society, Inc., Quezon City²Department of Social Welfare and Development, Muntinlupa City, Philippines. e-mail: allanfabella@yahoo.com

Background and challenges to implementation: The elderly, especially those in congregate settings, are vulnerable to tuberculosis. The Philippines has scant TB data and no institutional policy on TB control for this population. The setting of this project is a government facility that provides residential care to abandoned seniors 60 years old and above. From October 1, 2013 to December 5, 2014, the facility conducted TB case finding among its 251 residents using developed protocols.

Interventions or response: Supported by USADI/Philippines, protocols were developed to evaluate clients with TB symptoms and for routine chest X-ray screening. Two rounds of mass screening, using symptomatology with DSSM and chest Xray, respectively, were conducted 9 months apart.

Results and lessons learnt: In the initial screening, a total of 247 residents were screened for TB symptoms, of whom 12 (5%) had cough of more than two weeks. The

number doubles if cough of any duration was used. From the same group 136 clients underwent direct sputum smear microscopy (DSSM); of these, five patients had positive DSSM and were subsequently enrolled for treatment. In the second screening, 193 patients underwent chest X-ray and 41 had positive TB findings. Thirty-five underwent DSSM and one had a positive result. A physician diagnosed TB in all 41 patients, and 31 cases were registered for treatment. The rest were not treated because of non-cooperation of psychiatric patients (8), and no consent for treatment (2). An additional nine patients were subsequently detected and treated after referral for symptoms or on routine chest X-ray upon entry. With a total of 53 new TB patients diagnosed out of 251 clients, computed incidence rate is 20 000 per 100 000 which is 65 times more than community rates. Rate of bacteriologically confirmed TB was 4% (5/136) while rate of clinically diagnosed TB through chest X-ray was 25% (50/205). Even among those with no cough, rate of TB diagnosis was 15% (33/219).

Conclusion: A mix of approaches to TB case finding in congregate settings (e.g., use of chest X-ray as a more sensitive screening tool and lowering symptom threshold from cough of two weeks to cough of any duration) could result in more TB cases detected and treated compared with traditional approaches. This experience provides evidence for the development of national policies and guidelines for TB control among the elderly in congregate setting.

PC-1271-06 Psychological distress and its relationship with non-adherence to TB treatment: findings from a multicentre clinical trial

G Theron,¹ J Peter,¹ L Zijenah,² D M Chanda,³ C Mangu,⁴ P Clowes,⁴ D Stein,¹ K Dheda¹ ¹University of Cape Town, Cape Town, South Africa; ²University of Zimbabwe, Harare, Zimbabwe; ³University Teaching Hospital, Lusaka, Zambia; ⁴Mbeya Medical Research Centre, Mbeya, Tanzania. e-mail: grant.theron@gmail.com

Background: The successful cure of tuberculosis (TB) is dependent on adherence to treatment. Various factors influence adherence, however, few are easily modifiable. There are limited data regarding correlates of psychological distress and their association with treatment adherence.

Design/Methods: In a trial of a new TB test, we measured psychological distress (K-10 score), TB-related health literacy, and morbidity (TBscore) prior to diagnosis in 1502 patients with symptoms of pulmonary TB recruited from clinics in Cape Town ($n = 419$), Harare ($n = 400$), Lusaka ($n = 400$), Durban ($n = 200$), and Mbeya ($n = 83$). Socioeconomic, demographic, and alcohol usage-related data were captured. Patients initiated on treatment had their DOTS cards reviewed at two- and six-months.

Results: 22% (95%CI: 20%, 25%) of patients had severe psychological distress (K-10 ≥ 30). In a multivariable linear regression model, increased K-10 was independently associated with previous TB [estimate (95%CI) $-0.98(0.09-1.87)$; $P = 0.0304$], increased TB score

[1(0.80, 1.20); $P < 0.0001$], and heavy alcohol use [3.08(1.26, 4.91); $P = 0.0010$], whereas male gender was protective [1.47(-2.28, -0.62); $P = 0.0007$]. 26% (95%CI: 21%, 32%) of 261 patients with culture-confirmed TB were non-adherent. In a multivariable logistic regression model, reduced TB score [OR (95%CI) 0.639(0.497, 0.797); $P = 0.0001$], health literacy score [0.798(0.696, 0.906); $P = 0.0008$], and increased K-10 [1.082(1.033, 1.137); $P = 0.0012$], and heavy alcohol usage [14.83(2.083, 122.9); $P = 0.0002$], were independently associated with non-adherence. Culture-positive patients with K-10 ≥ 30 were more-likely to be non-adherent (OR=2.290(1.033-5.126); $P = 0.0416$).

Conclusion: Severe psychological distress is frequent amongst TB patients in Southern Africa. Targeted interventions to alleviate psychological distress, alcohol use, and improve health literacy in newly-diagnosed TB patients could reduce treatment non-adherence.

PC-1272-06 Implementing a high volume TB screening programme in peri-mining communities in South Africa

F Popane,¹ M Radile,¹ C Rithuri,¹ D Ratema,¹ M Dube,¹ L Page-Shipp¹ ¹The Aurum Institute, Johannesburg, South Africa. e-mail: fpopane@auruminstitute.org

Background and challenges to implementation: In collaboration with the National, Provincial and District Departments of Health, we are implementing a high volume TB screening programme between April 2014 and March 2016 in peri-mining communities in 6 districts in South Africa; West Rand, Lejweleputswa, Dr Kenneth Kaunda, Bojanala, Waterberg and Sekhukhune. Peri-mining communities are considered to be vulnerable to TB. Community members are reached in their homes, workplaces, at public events, public places and schools.

Intervention or response: Mobile teams perform a TB symptom screen using the National TB screening tool (cough, weight loss, night sweats and fever >24 hours). Spot specimens are collected where possible or clients are referred to clinics for sputum collection. Xpert MTB/RIF testing is done through the NHLS. Screening includes an HCT offer. Where logistically possible, HCT testing is done in the field; otherwise clients are referred to clinics or other partners. Those diagnosed with TB and those who are HIV positive are referred to clinics for care.

Results and lessons learnt: To date, 253 241 people have been screened for TB: 17 856 (7.1%) were TB symptomatic, of which 10 163 (57%) were able to produce spot sputum, results were received for 9249 (91%); 122 (1.3%) were positive. HCT was offered to 222 113 (88%), 11 296 (5.1%) were performed in the field; others were referred to the nearest facility. Of HCT performed in the field; 785 (7%) tested positive. Strengthening of public-private mix, community engagement and the use of flexible, skilled teams; are critical programme components.

Conclusions and key recommendations: Community screening was widely accepted. Challenges include difficulty collecting quality spot sputum specimens in the field and operational challenges with in-field HIV testing. Investigation is required to further understand the epidemiology of TB in peri-mining communities.

PC-1273-06 Using TB refill sites to determine the burden of TB amongst ex-miners in Swaziland to improve community contact tracin

V Masuku,¹ G Mchunu² ¹University Research South Africa, Mbabane, ²National TB Control Program, Manzini, Swaziland. Fax: (+268) 2505 3248. e-mail: victoriam@urc-sa.com

Background and challenges to implementation: Swaziland has highest TB burden, incidence 1349/100 000 (National Tuberculosis Strategic Plan 2015-2019). Current TB strategy prioritizes mining populations' high risk however, of the over 22 000 Swaziland ex miners, the number with TB is unknown. Routine TB data collection tools have not, tracked TB patients by occupational exposure. There is therefore limited data on the burden of TB amongst ex miners making it difficult to design targeted interventions for this population group. Furthermore, contact tracing strategies are not systematic increasing the risk of TB transmission at household level. **Intervention or response:** In March 2015, University Research South Africa (URSA) worked with the national TB program (NTCP) to profile TB patients' exposure to mining. A total of 8 high volume TB facilities were identified and an interview guide was developed. All TB patients coming to refill medicines over 4 weeks were interviewed. Data was collected using face to face interviews during treatment refill to determine number of TB patients who are miners, ex miners or relatives of ex miners.

Results and lessons learnt: from March to April 2015, of 1218 TB patients who came for treatment refills, 81 (7%) were ex miners, 8 (1%) current miners and 178 (15%) were relatives of ex miners. TB contacts were mapped to guide follow up contact tracing at household level. On the relatives of ex miners with TB, a process is ongoing to confirm ex miner relative having confirmed TB or undergone TB treatment. The NTCP has since revised the TB data collection tools to include occupation.

Conclusions and key recommendations: The NTCP wishes to continue tracing ex miners with TB and linking them with community treatment adherence officers to intensify active case finding amongst high risk populations. With the revision of TB data collection tools in Swaziland, it will now be possible to track and attain routine TB data to facilitate this.

PC-1274-06 Addressing TB among people who inject drugs through the community initiated treatment intervention in Ukraine

O Denisiuk,¹ A Tyshkevych,¹ P Smyrnov¹ ¹ICF International HIV/AIDS Alliance in Ukraine, Kyiv, Ukraine. Fax: (+380) 444 905 489. e-mail: o.denisiuk@gmail.com

Background and challenges to implementation: Access to HIV and TB care for People Who Inject Drugs (PWID) in Ukraine is limited due to stigma and low awareness. Data from Ukrainian National AIDS Center suggest that PWID register for medical care on average 2 years after positive HIV test. Delay in HIV treatment initiation leads to immunosuppression and increase of opportunistic infections such as tuberculosis (TB). In April 2013, the International HIV/AIDS Alliance in Ukraine (Alliance Ukraine) started the Community Initiated Treatment Intervention (CITI) to improve linkage to HIV care and treatment for PWID through peer case-management approach. CITI provides 6 months support to start PWID on ART. During this time PWID are also provided with support in regards of TB diagnostics and treatment. **Intervention or response:** CITI combines peer-navigation, outreach case-management and community support to achieve better treatment uptake and outcomes for HIV-positive PWID. The approach delivers individual care to a client for the purpose of registering at the regional AIDS Centre and getting ART prescribed as well as a comprehensive set of related medical services such as TB diagnosis and treatment. CITI clients are recently tested positive or might know their status for a long time but are not accessing medical services. Most case managers are former outreach workers from harm reduction projects.

Results and lessons learnt: 26 NGOs started CITI in March, 2013 across 11 regions of Ukraine. Since 2013 - 3073 PWID were registered in AIDS clinics, 2778 clients started ART with the support of 60 case-managers. The average time to link PWID to HIV care and treatment is 22 days. Individual data from 3754 clients who finished CITI support program during 2013-2014s shows next results: 503 clients have been diagnosed with TB and started TB treatment, among them -283 started ARV treatment. 485 clients were provided with TB prophylactics after registration in AIDS clinic.

Conclusions and key recommendations: PWID are at increased risk of HIV-TB co-infection and are hard to reach population with medical services. The case-management approach, which is the core component of the CITI, along with HIV services improves PWID engagement in TB care. Peer-navigation, outreach case-management and community support are crucially important interventions to provide timely TB diagnostics and linkage to care for HIV positive PWID.

68. Paediatric TB: IPT, contact tracing and child perspectives

PC-1275-06 Contact screening and expanding childhood TB diagnosis and treatment of TB in Bangladesh

S Islam,¹ S Reza,¹ M Akramul Islam,¹ V Begum,² K Khatun,¹ M Haque³ ¹BRAC, Dhaka, ²World Health Organization, Dhaka, ³NTP, Dhaka, Bangladesh. Fax: (+88) 2988 8026. e-mail: shayla.dhaka@gmail.com

Background and challenges to implementation: Bangladesh is one of the high TB burden countries in the world. BRAC, a non government organization is jointly working with national TB control programme to combat against tuberculosis since 1994. Due to unavailability of diagnostic facilities and scarcity of pediatricians, diagnosis and management of child tuberculosis is still a major challenge for the country especially in rural setting. It is necessary to raise awareness in the community and increase screening through contact tracing of household cases within the existing programme for identifying more child TB cases.

Intervention or response: Considering the different challenges, BRAC started conducting orientation to pediatrician at tertiary hospitals and district levels. A basic training is given to health care providers on sign symptoms of child TB to increase awareness in the community during mobilization. A contact tracing register was introduced in the existing programme of BRAC in late 2013 and contact tracing initiated among the family members who are in close contact with pulmonary TB cases and were sent for screening. During their households visit, BRAC's frontline health workers disseminate basic messages, identify presumptive cases and refer them to the specific centres. Poor child TB symptomatic gets financial support from BRAC for investigation and transportation purpose.

Results and lessons learnt: In 2014, a total of 929 pediatricians were reached through 64 networking meetings on child TB diagnosis and management at tertiary and district level hospitals. In addition, 1029 health care providers were trained on child tuberculosis including basic messages, identification and referral. There was an increase in child case identification from 2865 in 2013 to 3554 in 2014. In 2014, 9.7% of the total child TB cases were identified through contact tracing.

Conclusions and key recommendations: Evaluation of symptomatic contacts may increase identification of child cases. An orientation session could be planned for health care providers to improve the contact tracing skills. The children who are in close contact of pulmonary tuberculosis patient if even asymptomatic should be referred for screening and should do follow-up.

PC-1276-06 INH preventive therapy for under-five children in two regions of Ethiopia

Y Tadesse,¹ M Nigussie,² I Jemal Abdulahi,³ D Habte,¹ S Negash,¹ D J Dare,¹ J Degu,¹ Y Haile,⁴ M Aseresa Melese,¹ P G Suarez⁵ ¹Management Sciences for Health, Addis Ababa, ²Amhara Regional Health Bureau, Bahir Dar, ³Oromia Regional Health Bureau, Addis Ababa, ⁴United States Agency for International Development (USAID), Addis Ababa, Ethiopia; ⁵Management Sciences for Health, Arlington, Virginia, USA. e-mail: ytadesse@msh.org

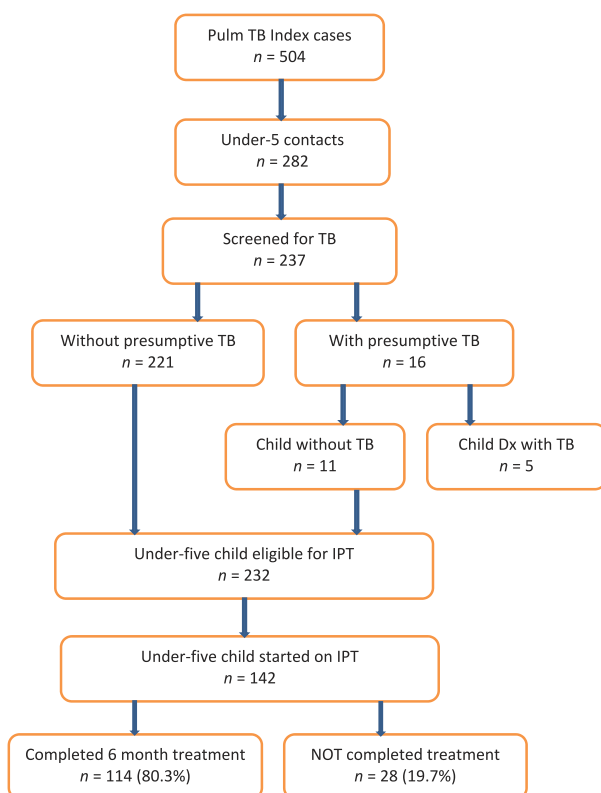
Background and challenges to implementation: A six-month course of Isoniazid preventive therapy (IPT) is among the recommended strategies for prevention of tuberculosis (TB) in under-five (U5) children who are in close contact with active pulmonary TB cases. There is limited experience with implementation of this strategy in high TB burden settings. The objective of this analysis was to share the experience of routine implementation of IPT for U5-children under routine program condition in two regions of Ethiopia.

Intervention or response: The USAID funded HEAL TB project in collaboration with the Amhara and Oromia RHBs introduced contact screening of smear positive pulmonary TB index cases. Using contact screening as entry point, we identified and enrolled eligible U5 contacts to IPT. We oriented the health workers on the importance of IPT, provided job aids, and supplied recording and reporting formats for routine use. We also provided direct site level support through regular mentoring visits and continuing medical education specifically designed for mid-and low-level health workers. In this analysis we included all children who initiated IPT during October 2013– June 2014 in 28 health facilities (7 hospitals and 21 health centers).

Results and lessons learnt: A total of 504 index smear positive pulmonary TB cases were reported during the implementation period. There were 282 U5- children registered as household contacts of the smear positive pulmonary TB index cases accounting for 17.9% of all household contacts. Of these, 237 (84%) were evaluated for active TB and presumptive TB was identified in 16 (6.8%) children. TB diagnosis was confirmed in five children making the overall yield 1.77% (95% Confidence interval, 0.76-4.08%). Of 232 children, 142 (61.2%) received IPT. The proportion who completed the 6 months INH preventive therapy was 114 (80.3%) while 28 (19.7%) interrupted treatment, and no child developed active TB disease while on IPT. The major factors for interruption of IPT were care taker refusal ($n=12$), INH drug stock out ($n=9$) and being lost to follow-up ($n=4$).

Conclusions and key recommendations: Tracing infants and young children who are contacts of infectious TB cases and offering them chemoprophylaxis was feasible in the Ethiopian setting. Contact screening among adult index cases served as a key entry point for identification childhood TB cases. The IPT completion rate was good but the remaining gap should be addressed.

Figure: Contact screening and IPT among under-five children



PC-1277-06 Close contact tracing of children in urban slums of Delhi, India

D Kundu,¹ S Chandra,¹ K Chopra,² A Khanna³ ¹World Health Organization Country Office for India, Delhi, ²New Delhi Tuberculosis Centre, Delhi, ³Directorate of Health Services, Delhi, India. e-mail: debashishkundu@yahoo.com

Background and challenges to implementation: As per the WHO recommendations on contact investigation, all household contacts and other persons who are in close contact with TB patients are to be screened for TB. In India, under the Revised National Tuberculosis Control Programme (RNTCP) all children less than 6 years of age, who are household contacts of the family member suffering with active TB are screened for TB and provided with Isoniazid chemoprophylaxis once active TB is ruled out. However, there are constraints observed in the state of Delhi while screening household contacts, especially close contact for TB in the urban community due to social, cultural and behavioural factors.

Intervention or response: We reviewed contact tracing efforts in the state of Delhi from interviews of sputum positive patients living in urban slums during various internal evaluations conducted between the periods from October 2012 to November 2013. The proportion of contacts screened for TB above and below 6 years of age; and proportion of eligible children contacts (below six years of age) prophylactically provided with Isoniazid preventive therapy were found.

Results and lessons learnt: During the study period, there were 131 contacts (85 household+ 46 close) of the index cases, interviewed during internal evaluation exercise. Of the household contacts, 48 were children, of which 83% (39) received isoniazid chemoprophylaxis and 2% (1) was detected with TB, while 65% (24/37 adult household contacts) were evaluated for TB.

Conclusions and key recommendations: None of the 46 close contacts, living in adjoining slum household, could be evaluated due to unclear operational guidelines to screen them and social causes. RNTCP could consider in close contact tracing and evaluation of TB with chest symptoms of all members living in adjoining households in urban slums as a policy.

PC-1278-06 TB disease prevalence among children exposed to drug-susceptible TB patients: the Indus Hospital TB program

F Amanullah,¹ A Malik,^{1,2} K Asif,¹ M Jaswal,¹ R Jafri,¹ H Hussain^{1,2} ¹Indus Hospital, Karachi, ²Interactive Research and Development, Karachi, Pakistan. e-mail: amyn.malik@irdresearch.org

Background: Children in contact with patients with pulmonary tuberculosis (TB) are a known high risk group for TB disease. Investigation of child TB contacts allows for early TB case detection and effective treatment including isoniazid preventive therapy (IPT). Children particularly 0-4 year olds are more likely to acquire TB infection and progress to TB disease compared to adults. The objective of this study was to assess the prevalence of TB disease among 0-4 year old children exposed to infectious pulmonary TB patients.

Design/Methods: We retrospectively analyzed the findings and outcomes of our TB screening and IPT program for 0-4 year old children exposed at home to newly diagnosed bacteriologic positive TB patients from 2011 to 2014. All 0-4 year old household contacts who presented for evaluation, underwent a history, clinical examination, CXR and TST to rule out TB disease prior to initiating Isoniazid preventive therapy.

Results: A total of 256, 0-4 year olds were evaluated for TB disease, 27% of whom were <1 year olds. We found that 90/256 (35%) children evaluated were severely underweight. We found TB infection (TST= $\geq$ 10 mm) in 5% children at initial evaluation. TB disease was diagnosed in 18/256 (7%) children, 10/18 (55.5%) of the children who developed disease were either never initiated on IPT or did not complete IPT. The remainder 16% (3/18) developed disease during IPT treatment and 28% (5/18) were diagnosed at initial evaluation. None of the children who completed IPT developed TB disease during a one year follow-up period.

Conclusion: Our findings highlight the need for an effective IPT program. Children 0-4 year old who completed 6 months of IPT did not develop disease, whereas children in whom Isoniazid preventive therapy was either not started or not completed were more likely to develop disease. IPT programs need strengthening to ensure treatment adherence and completion.

PC-1279-06 Lessons learned from conducting clinical trials for new TB drugs in children

M T Gler,¹ M Frias,² R Reyes,¹ J Hafkin¹ ¹Otsuka Manila Research Center, Makati, ²De La Salle Health Sciences Institute, Dasmarias, Philippines. Fax: (+632) 754 1450. e-mail: maricelle-tc-gler@otsuka.us.com

Background: Delamanid is a new anti-tuberculosis agent recently endorsed by the World Health Organization for the treatment of multi-drug resistant tuberculosis (MDR-TB) in adults. In order to accurately characterize the safety and define the dose of delamanid in children, Otsuka pharmaceuticals launched a phase 1 PK study (Trial 232) in the Philippines at De La Salle Health Sciences Institute (DLSHSI) in Cavite Province. Study

Design: Trial 232 is an 18-day phase 1 open-label trial in which children with MDR-TB received delamanid for 10 days combined with an optimized background regimen (OBR) followed by OBR alone prescribed according to the national guidelines of the Philippines. This trial requires a total enrollment of at least 36 children from ages 0-17. Older children were enrolled first and progressively younger children will subsequently be enrolled as safety and pharmacokinetics are established among the older children.

Challenges: A number of challenges were encountered both before and during the implementation of the trial. The key challenges prior to the start of the study revolved around recruitment, regulatory approval, and logistical issues. Although the Philippines has a high prevalence of TB disease (12.8%) and TB infection (65.6%) among household contacts of MDR-TB patients, the program historically has only focused on treating bacteriologically confirmed disease. Indeed, since the treatment program's inception, there have been only a handful of children treated for MDR-TB out of the total population of children thought to actually have the disease. In order to implement this trial, DLSHSI had to undertake significant capacity building which included educating study staff and regional clinicians, networking with the NTP for identification of suspected cases, and performing recruitment activities in MDR-TB centers in the Metro Manila and the Luzon areas. Active case finding via contact tracing of the adult MDR-TB patients in the MDR-TB unit was also done. Other challenges encountered were ensuring the acceptability of frequent venipuncture for PK determination, creating retention materials for each cohort to maintain interest in study participation, confirming that schooling would not be affected during the course of the trial, and reducing the daily burdens on the broader family caring for the child. **Lessons learned:** With our experience for the first 2 cohorts, we have learned that clinical trials for novel TB drugs in children are feasible.

PC-1280-06 What can visual methods contribute to paediatric TB treatment experience?

K Abney¹ ¹University of Cape Town, Cape Town, South Africa. e-mail: kate.abney@uct.ac.za

Background: There is a move to document and convey the experiences of people being treated for severe forms of TB within inpatient treatment facilities. However, children's experiences do not feature as prominently as those of adults within clinical settings. One reason is that children are minors and have very little authority or say in their individual treatment and living situations. A second reason is that research methods employed are not always appropriate when working with children. The study was premised on trying to apprehend and understand a 'child's eye view' of inpatient treatment for TB.

Design/Methods: The larger project comprised of one year of qualitative research facilitated within a children's ward in a sub-acute long term stay TB hospital. Data was collected alongside child patients living and being treated at Brooklyn Chest Hospital, located in Cape Town, South Africa. The data presented here was based on qualitative methods used in research alongside 50 child patients. Child-centred visual methods included; drawing, photography and sculpting clay. Visual methods were used to engage child patients in discussion of their experiences of hospital life, individual treatment and their subjective understanding of their TB.

Results: Visual methods were a productive means to generate data in four areas: 1) individual conceptions of TB, 2) treatment challenges, 3) hospital life and 4) educational challenges during duration of treatment.

Conclusion: Visual methods are beneficial to research with paediatric TB patients, and provide a more nuanced perspective on the challenges children face during inpatient treatment. Findings are useful and allow for the development of evidence-based child-centred hospitalisation policy and practice in sub-acute long term stay hospitals.

PC-1281-06 Outcomes of IPT usage among children < 5 years old in a TB Reach contact tracing project in Swaziland

R Golin,^{1,2} P Ustero,^{1,2} P Swamy,² J Glickman,¹ K Ngo,² S Dlamini,¹ M Hlatshwayo,¹ A Mandalakas² ¹Baylor College of Medicine Children's Foundation - Swaziland, Mbabane, Swaziland; ²Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. Fax: (+268) 2404 0214. e-mail: golin@bcm.edu

Background: Swaziland is the epicenter of the HIV and TB pandemics. Despite national policy recommending Isoniazid Preventive Therapy (IPT) for all pulmonary tuberculosis contacts who are under age 5 years (U5) or HIV-infected there is no data regarding IPT uptake in Swazi U5 contacts and IPT usage is recognized as sub-optimal. Perceived barriers to IPT delivery include transport fees to healthcare facilities, facility and radiology fees, frequent drug shortages, and a broad lack of recognition regarding the importance of IPT. In concert with our WHO sponsored TB REACH contact tracing

program, Baylor College of Medicine Children's Foundation – Swaziland (BCMCF-SD) promoted and monitored IPT uptake among contacts of index cases starting anti TB treatment (ATT) at 7 local TB clinics (TBC).

Intervention/Response: BCMCF-SD's contact tracing enabled cough monitors to identify all contacts eligible for IPT and make referrals for evaluation and management at the TBC. Barriers to healthcare access were addressed through home visits, transport reimbursement, and vouchers for chest X-rays. Analysis of IPT uptake was limited to U5 contacts as the validity of reported HIV-status was unknown.

Results and lessons learnt: Of the 4171 index cases enrolled, 2589 (62%) underwent contact tracing, yielding 9803 reported contacts. 16.4% (1608) of contacts were U5, including 3.4% (55) HIV-infected, 51.7% (828) HIV-uninfected, 44.8% (718) HIV unknown. Despite systematic referral of all eligible U5 contacts, IPT uptake was low (16% for all 7 TBC; range 1% - 36%). Contacts were more likely to initiate IPT if they were younger ($P = 0.0012$), HIV-negative ($P < 0.001$), slept in the same room as the index case ($P < 0.001$), and were the child of the index case ($P < 0.001$). IPT uptake was not associated with contacts' gender, recent household death, completion of a home visit, or presence of a miner in the household.

Table 1: Comparison of U5 contacts who did and did not initiate IPT

CHARACTERISTIC	CONTACTS ON IPT	CONTACTS NOT ON IPT	P-VALUE*
OVERALL [n (%)]	162 (10%)	1446 (90%)	N/A
MEAN AGE [years $\pm$ SD]	2.26 $\pm$ 1.49	2.65 $\pm$ 1.44	0.0012
SEX			
Male [n (%)]	69 (42.6%)	707 (48.9%)	0.13
Female [n (%)]	93 (57.4%)	740 (51.1%)	
HIV STATUS			
Positive [n (%)]	7 (4.2%)	48 (3.3%)	< 0.001
Negative [n (%)]	106 (65.4%)	722 (49.9%)	
Unknown [n (%)]	48 (29.6%)	670 (46.3%)	
DEATH IN HOUSE IN LAST 2 YEARS			
Yes [n (%)]	39 (24.1%)	417 (28.8%)	0.22
No [n (%)]	118 (72.8%)	993 (68.7%)	
SLEEP LOCATIONS			
Different House [n (%)]	35 (21.6%)	565 (39.1%)	< 0.001
Same House [n (%)]	38 (23.5%)	400 (27.7%)	
Same Room [n (%)]	67 (41.4%)	355 (24.6%)	
Same Bed [n (%)]	22 (13.6%)	125 (8.64%)	
RELATIONSHIP TO INDEX CASE			
Child [n (%)]	94 (58%)	480 (33.2%)	< 0.001
Other [n (%)]	68 (42%)	966 (66.8%)	
HOME VISIT DONE			
Yes [n (%)]	73 (45.1%)	630 (43.6%)	0.72
No [n (%)]	89 (54.9%)	816 (56.4%)	
FAMILY MEMBER EMPLOYED AS MINER			
Yes [n (%)]	48 (29.6%)	404 (27.9%)	0.65
No [n (%)]	114 (70.4%)	1042 (72.1%)	

* Test of significance comparing U5 contacts who did and did not initiate IPT

Conclusions and key recommendations: Uptake of IPT among U5 contacts is critically low in Swaziland. Although we identified an association between IPT uptake and some important factors such as HIV status and sleep location, there remains much uncertainty regarding factors limiting IPT uptake that might inform focused interventions to increase IPT uptake and adherence. BCMCF-SD's experience emphasizes the ongoing need to prioritize a national approach for evaluation and implementation of IPT for this vulnerable population.

PC-1282-06 Feasibility and yield of hospital-based screening of household child contacts of newly diagnosed adult tuberculosis patients

J Kiwanuka,^{1,2} C Kyakwera,² N Kyomugasho,³

D Atwine,³ M Nansumba,³ Y Boum li,^{1,3}

J Mwanga-Amumpaire,^{1,3} M Bonnet^{3,4} ¹Mbarara

University of Science and Technology, Mbarara, ²Mbarara

Regional Reference Hospital, Mbarara, ³Epicentre, Mbarara,

Uganda ; ⁴Institut de Recherche pour le Développement

(IRD), Montpellier, France. e-mail:

maryline.bonnet@geneva.msf.org

Background: Contact investigations of infectious tuberculosis (TB) patients can be an efficient method of finding new child TB cases and identifying at-risk children for preventive therapy. However, despite recommendations this is rarely practiced in most low-resource countries. We assessed the feasibility and yield of hospital-based contact investigation and treatment of children in household contact with newly diagnosed adult TB case in south-western Uganda.

Methods: Over a 24-month period, adults newly diagnosed with smear- and/or culture-positive pulmonary TB were invited to bring children <5 years in their households to hospital for assessment. Children were assessed for active TB or latent TB infection (LTBI) using a standardised symptom screen, tuberculin skin test (TST) and chest radiography. Children with suspected active TB were referred for further evaluation and treatment. The rest, classified as LTBI or uninfected were started on a 6-month regimen of isoniazid preventive therapy (IPT) and followed for 9 months, with repeat TST at 3 months for initially TST-negative contacts.

Results: A total of 162 adult index cases were diagnosed and 133 enrolled. A total of 281 out of 339 (82.4%) eligible children (median of 2 child contacts per index case) identified were assessed; 53% female, median age 33 months, 4.5% HIV infected. The median interval between diagnosis of index cases and screening of contacts was 17 days (IQR 6, 53 days). Forty three children (15.3%) were referred for TB treatment. Three children did not return for TST reading, 102 (36.3%) were classified as LTBI and 133 (47.3%) as uninfected. Of 235 children classified as LTBI or uninfected 8 did not receive IPT; 227 started and 185 (81.5 %) completed 6 months of IPT. Children with low level exposure (a few hours during the day) to the index case were less likely to complete IPT (aOR 0.4, 95%CI 0.2-0.9). Two children

on IPT were reclassified as active TB during follow-up, and 10 out of 133 (7.5%) non-infected children converted to TST positive on IPT.

Conclusion Hospital-based tuberculosis contact investigation was feasible, and yielded a high number of new cases of active TB and LTBI among children in household contact with adult TB cases. IPT was effective and well accepted by the majority of contacts. Repeat TST during follow-up is important to identify additional LTBI cases. Home-based follow-up could help to optimize uptake and completion of investigation and IPT.

PC-1283-06 Symptom-based screening of child contacts of tuberculosis cases: a prospective cohort study in Uganda

M Bonnet,^{1,2} C Kyakwera,³ N Kyomugasho,² D Atwine,² M Nansumba,² Y Boum li,^{2,4} J Mwanga-Amumpaire,^{2,4} J Kiwanuka^{3,4} ¹Institut de Recherche pour le Développement (IRD), Montpellier, France; ²Epicentre, Mbarara, ³Mbarara Regional Reference Hospital, Mbarara, ⁴Mbarara University of Science and Technology, Mbarara, Uganda. e-mail: maryline.bonnet@geneva.msf.org

Background: Tuberculosis (TB) screening and isoniazid preventive therapy (IPT) of young child contacts of adult TB cases can reduce the risk of active TB in children. However, this is poorly implemented in high burden countries partially due to difficulties in screening children for active TB at lower level health facilities. We assessed the performance of symptom-based screening to facilitate the routine implementation of TB screening for paediatric contacts.

Methods: Children younger than 5 years, in contact with TB confirmed adult index cases were assessed with standardized symptom screening, chest X-ray and tuberculin skin test (TST). Children diagnosed as active TB disease based on clinical, radiological and bacteriological investigations were referred for treatment; the rest who were either uninfected or with latent TB infection (LTBI) were systematically treated with 6 months IPT and followed for 9 months. The accuracy of symptom-based screening for the diagnosis of active TB was estimated against a reference definition of active TB based on chest X-ray findings independent of clinical findings.

Results: Of 281 child contacts (median age 33 months; 53% female and 4.5% HIV infected), 43 (15.3%) were initially classified as active TB, 102 (36.3%) as LTBI and 136 (48.4%) as non-infected cases. Two additional patients were diagnosed as active TB during follow-up on IPT. Active TB was initially diagnosed in 33/69 (47.8%) of symptomatic children vs. 10/212 (4.7%) of non-symptomatic children, $P < 0.001$. Chest X-ray was highly suggestive of active TB in 35/280 (12.5%) patients. After adjustment on age, HIV and sex, cough (aOR 3.2, 95%CI 1.4-7.6), reduced playfulness (aOR 9.7, 95%CI 2.5-37.7) and moderate to severe malnutrition based on weight-for-height z-score (aOR 13.0, 95%CI 1.8-91.9) were associated with radiological active TB. Screening based on the presence of one of these 3 signs showed 71.4% (25/35, 95%CI 53.7-85.4)

sensitivity, 63.1% (154/244, 95%CI 56.7-69.2) specificity and 93.9% (154/164, 95%CI 89.1-97.1) negative predictive value. Of 10 patients with negative screening and radiological active TB, 9 were started on TB treatment and 1 on IPT.

Conclusion Symptom-based screening could be an effective and easy tool to identify paediatric TB contacts requiring further evaluation for active TB. However, our symptom-based screening needs to be optimised to reduce the risk of initiating IPT in children with potentially active TB. Further evaluation using a more accurate reference standard for active TB is required.

69. Paediatric TB: epidemiology - II

PC-1284-06 Systematic review of the epidemiology of and programmatic response to TB in children in South Africa

A Garcia-Prats,¹ F Adeniyi,¹ S Nicol,¹ K Du Preez,¹ H Rabie¹ ¹Stellenbosch University, Cape Town, South Africa. e-mail: liesl.nicol@gmail.com

Background: Tuberculosis (TB) causes substantial morbidity and mortality in children. Challenges in diagnosis, a focus on smear-positive disease which is uncommon in children, and an underestimate of the morbidity and mortality from childhood TB, has resulted in a lack of attention to children (i.e. <15 years of age) in TB programmes. Age-related differences in TB epidemiology, pathophysiology, disease manifestations, diagnosis, prevention and treatment require children be considered specifically in TB programmes. With the aim of contributing to evidence-informed TB policy development in South Africa this systematic review collated all relevant research on the epidemiology of and programmatic response to TB in children in South Africa.

Design/Methods: A comprehensive search for published and unpublished research was conducted. Based on specific inclusion criteria research investigating TB incidence, prevalence, risk factors, prevention, treatment, clinical outcomes and care in children in South Africa were included in this systematic review.

Results: 190 studies were included in the review and reported on one or more of the review outcomes. Table 1 indicates the number of studies reporting on each of the main outcomes as well as information on where the studies were conducted.

Conclusion: This review demonstrated a high burden of childhood TB, suggesting a failure of existing TB control. There was little health systems and services research and the available studies reported serious problems with implementation of key programs, such as delivery of isoniazid preventive therapy. Other important findings were a paucity of community-based research and a lack of geographic distribution, with most studies being from the Western Cape. Renewed efforts to address key research and implementation gaps will be needed to improve the programmatic response to childhood TB in South Africa.

Table 1: Characteristics of included studies

Incidence of TB disease and infection	15 studies	Public health facilities KZN, WC, MP, SA
Prevalence of TB disease and infection	21 studies	Public health facilities WC, Gauteng
Risk factors for TB and TB transmission dynamics	18 studies	Public health facilities SA, WC, Limpopo
TB case finding	8 studies	Public health facilities KZN, WC, Limpopo, Gauteng
TB diagnostics	59 studies	Public health facilities KZN, WC, SA
TB prevention	19 studies	Public health facilities KZN, WC, SA
TB treatment	24 studies	Public health facilities WC, MP, KZN
Clinical outcomes of TB	26 study	Public health facilities KZN, Gauteng, WC
TB health systems and services	1 studies	Public health facilities Limpopo, KZN, SA

PC-1285-06 Childhood tuberculosis in Mbarara National Referral Hospital, Uganda: a description of patients and diagnosis

E Kumbakumba,^{1,2} M Nansumba,³ J Kiwanuka,^{1,2} M Bastard,⁴ P Orikiriza,³ D Nansera,^{1,2} Y Boum li,^{1,3} M Bonnet^{3,5} ¹Mbarara University of Science and Technology, Mbarara, ²Mbarara National Referral Hospital, Mbarara, Uganda, ³Epicentre, Mbarara, Uganda ; ⁴Epicentre, Paris, ⁵Institut de Recherche pour le Développement (IRD), Montpellier, France. e-mail: maryline.bonnet@geneva.msf.org

Background: Tuberculosis (TB) is common in young children with HIV infection and malnutrition. We investigated a cohort of children for active tuberculosis by age, HIV co-infection and nutrition status. Methodology: Children < 14 years old with at least one of the following symptoms (unexplained weight loss, persistent respiratory symptoms, fever, fatigue or reduced playfulness) were investigated with chest X-ray, sputum microscopy, XpertMTB/RIF and culture and stool XpertMTB/RIF and culture on a subset of patients started on treatment. Decision to initiate treatment was based on clinical, mycobacterial and radiological findings.

Results: Of the 396 children enrolled, 217 (54.8%) were male and 123 (31.1%) were HIV positive. The median age was 4 years (IQR 1.4-7.5) and 79 (20.3%) children had moderate or severe acute malnutrition (weight for height Z- score). Seventy-six (19.2%) children had a TB contact history and 144 (36.4%) were started on TB treatment. These children were significantly younger than those who were classified as 'not TB', with a median age of 2.5 (IQR 1.1-5.4) years versus 5 (IQR 2.1-8.3) years ($P < 0.001$). A significantly higher proportion of these children had moderate or severe acute malnutrition (33.8% versus 12.5%, $P < 0.001$) but there were no differences in HIV co-infection rates. Overall, TB was confirmed in 20 (5.0%) children: 13 had a positive Xpert MTB/RIF on sputum and 7 on stool and 13 had positive culture. Of 351 children tested with both culture and Xpert MTB/RIF on sputum, sensitivity of Xpert MTB/RIF was 90.9% (10/11) and specificity was 98.8% (336/340). Sixty-four children started on TB treatment had XpertMTB/RIF done on both sputum and stool: 8 (12.5%) were positive; 4 (6.3%) on both, 3 (4.7%) on sputum only and 1 on stool only (1.6%). Two children

with confirmed TB died before treatment initiation. Of the remaining 126 children started on treatment, 103 (81.7%) had a chest X-ray suggestive of TB.

Conclusions: The prevalence of HIV infection and malnutrition was high in this cohort. Despite high sensitivity of the Xpert MTB/RIF as compared to culture, very few patients started on treatment had confirmed TB and majority were treated based on chest X-ray. There is need to routinely and systematically evaluate malnourished and HIV infected children for TB. More robust diagnostic tests are required to increase the proportion of children treated on the basis of confirmed TB.

PC-1286-06 High burden of tuberculosis and delayed initiation of treatment among children in a resource restricted setting

S Kizito,¹ A Katamba,¹ C Atuhaire,¹ G Amany, ¹ E Obuku¹ ¹Makerere University, Kampala, Uganda. e-mail: somekizito@yahoo.com

Background: In Uganda, childhood TB is neglected. Contact tracing lags, no disaggregation of reported data for children, limited diagnostic capacity. With high HIV and adult TB burden, and 51.4% of population being children, child TB burden is expected to be high. Use of "Desk Guide" is limited. TB diagnosis is mainly based on smear results. There is paucity of data and uncertainty in prevalence of childhood TB in Uganda. We aimed at determining prevalence; factors associated with PTB in children attending PHC facilities in Kampala and missed opportunity to initiate treatment within a month of diagnosis.

Design/Methods: Cross-sectional study among 255 children 5 – 15 years, in 6 health facilities in Kampala, March 2015. Socio-demographic, clinical, and laboratory data were collected using questionnaire. TB diagnosed using "Desk Guide" algorithms. Sputum based on ZN/FM and/or Gene-xpert. Logistic regression used to assess associations with outcome.

Results: Prevalence of all-forms, smear positive, smear negative TB were respectively: 13.7% (2.6 – 24.8), 6.3% (0.9 – 11.6) and 7.5% (2.8 – 14.6). Among HIV positive: 41.7%, 33.3%, and 8.3%. Among malnourished; 21.7%, 8.3%, and 5.3% respectively. Among contacts, all-form 89.3% and smear positive 78.6%. Factors associated with smear positive PTB; windows/room (OR = 0.1, 95%CI: 0.01 – 0.48), contact (OR = 8.3, 95%CI: 2.02 – 33.70), malnutrition (OR = 3.6, 95%CI: 1.28 – 9.99). Factors for smear negative PTB: tobacco smoker at home (OR 8.1, 95 % CI: 2.72 – 24.14), 5 Km or more from hospital (OR 3.1, 95 % CI: 1.02 – 9.66), use of firewood as fuel (OR 15.7, 95 % CI: 2.30 – 106.56). Factors for all-form PTB: tobacco smoker at home (OR = 1.6, 95 % CI: 1.07 – 6.86), stunting (OR = 2.2, 95 % CI: 1.01 – 4.15). Only 5.3% of smear-negative, 81.3% of smear-positive, overall 40% of diagnosed children were initiated on treatment within a month of diagnosis.

Conclusion: We found high pediatric TB burden more-so in HIV positive, malnourished, contacts. Delayed initi-

ation of TB treatment. There is need to intensify screening HIV positive and malnourished for TB, intensify contact tracing, and need to follow up diagnosed children to ensure timely treatment initiation.

Variable	Categories	All form TB	Smear positive TB	Smear negative TB
		Prevalence	Prevalence	Prevalence
Overall	255	13.7 (2.6 – 24.8)	6.3 (0.9 – 11.6)	7.5 (2.8 – 14.6)
HIV	Negative (236)	12.7 (0.6 – 24.8)	5.1 (0.9 – 10.3)	7.6 (0.4 – 15.7)
	Positive (12)	41.7 (12.0 – 71.3)	33.3 (4.0 – 62.6)	8.3 (0.1 – 31.0)
Nutrition	Good (194)	11.3 (4.5 – 18.2)	4.1 (0.1 – 13.2)	7.2 (1.2 – 13.2)
	Poor (60)	21.7 (0.1 – 53.1)	13.3 (0.5 – 22.0)	5.3 (0.5 – 13.0)
Sex	Female (145)	9.7 (1.2 – 18.1)	3.4 (1.1 – 5.8)	6.2 (1.0 – 13.5)
	Male (110)	19.1 (0.7 – 34.5)	10.0 (0.8 – 20.8)	9.1 (0.3 – 18.6)
Contact	No contact	10.7 (1.0 – 22.5)	21.4 (1.4 – 43.0)	
	Had contact	89.3 (77.5 – 99.9)	78.6 (57.0 – 99.9)	
Education	Not enrolled (17)	17.6 (4.1 – 31.2)	5.8 (0.2 – 9.5)	11.8 (0.4 – 28.5)
	Pre-primary (26)	11.5 (4.2 – 27.3)	11.5 (0.4 – 27.3)	No observation
	Primary	12.8 (1.5 – 24.1)	3.7 (0.1 – 8.5)	9.1 (0.8 – 19.1)
	Secondary (48)	16.7 (0.1 – 38.1)	12.5 (3.7 – 28.7)	4.2 (0.2 – 9.9)

Table showing the prevalence of TB among children 5 to 15 years with features suggestive of tuberculosis, Kampala Uganda 2015

PC-1287-06 Capacity of health facilities to diagnose and manage childhood TB in Uganda

M Sekadde,¹ R Asimwe,¹ B Ngwatu,² P Bakkabulindi,² E Namusoke-Magongo,¹ E Quinto,¹ S Okokwu,³ F Mugabe¹ ¹Ministry of Health, Kampala, ²Clinton Health Access Initiative, Kampala, ³UNICEF, Kampala, Uganda. e-mail: moorine.sekadde@gmail.com

Background and challenges to implementation: With a childhood TB case notification of 3% among bacteriologically confirmed incident TB cases, the TB Program in Uganda conducted an assessment to determine the capacity for childhood TB diagnosis and management.

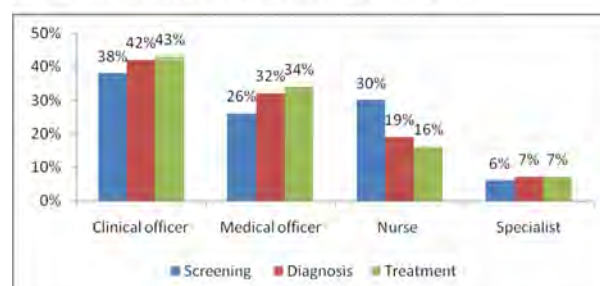
Intervention or response: A cross sectional study. 112 public and private health facilities were randomly selected from the 12 regions. Capacity was defined as practices and resources for childhood TB screening, diagnosis, treatment, prevention, and recording and reporting. A pretested tool was used to collect data from key facility personnel. Univariate and bivariate analysis was done using SPSS version 16.

Results and lessons learnt: Of the facilities assessed 29 (26%), 38 (33%), 31 (28%), and 14 (12%) were Health Center (HC) III, IV, district and referral hospitals respectively and 87% were public sector facilities. Childhood TB case notification was highest in the

district hospitals (14.8% of 4428), referral hospitals (12.2% of 9315) compared to HCIII (7.8% of 743) and HCIV (6.2% of 2427). Treatment success was better in the lower level facilities (referral hospitals (46%), district hospitals (56%), HCIV (80%), HCIII (78%)). Deaths were higher in HC III (13%) and referral hospitals (8%) while LTFU was higher in referral (20%) and district hospitals (16%). While 48% of the facilities had the national TB guidelines available, only 24% of them were conducting contact tracing. Screening for TB in children using the recommended tool was evident in 80% of the facilities. There was limited involvement of specialists in childhood TB management as shown below. Persistent cough (30%), weight loss (29%), and persistent fevers (16%) were the most identified childhood TB symptoms. Microscopy (37%), CXR (29%), and Xpert (14%) were the most listed appropriate childhood TB diagnostic tests. Clinical symptoms (26%) and smear microscopy (25%) were the most commonly used diagnostics. Sputum (27%) and gastric aspirate s(21%) were the most collected samples. Only 21% of the facilities had access to onsite Xpert test. 91% of the facilities were providing anti-TB medicines. Most of the facilities manage TB-HIV co-infected children in the TB (43%) and HIV (25%) clinics.

Conclusions and key recommendations: Findings indicate minimal involvement of specialists in child TB management, limited access to recommended diagnostics hence an urgent need to streamline and strengthen national capacity for the diagnosis and management of TB in children.

Cadre of health workers involved in child TB management



PC-1288-06 DETECT Child TB: increasing access to TB services for children in Uganda

S Muyanja,¹ A Detjen,² F Mugabe,³ M Sekadde,^{3,4} J Nakaweesi,⁵ M Murungi,⁴ S M Graham,²

A Nakanwagi-Mukwaya¹ ¹International Union Against Tuberculosis and Lung Disease (The Union), Kampala, Uganda; ²The Union, Paris, France; ³The Uganda National TB and Leprosy Program, Kampala, ⁴Baylor College of Medicine Children's Foundation Uganda, Kampala, ⁵The Mild May Hospital Uganda, Kampala, Uganda. e-mail: szmuyanja@yahoo.com

Background: The Decentralize TB services and Engage Communities to Transform lives of children with TB (DETECT Child TB) project aims to develop a district-wide health systems model for routine childhood TB care

in two districts in Uganda. The Project will train and mentor facility-based health care workers in prevention, diagnosis and management of childhood TB and engage village health teams (VHTs) to perform contact screening and treatment support.

Objective: To determine baseline data on child TB case finding, treatment and prevention services in Wakiso and Kabarole districts.

Methods: A cross sectional survey was conducted in all hospitals, level IV health facilities and a selection of level III health facilities. Information was obtained on current practices concerning the prevention, diagnosis and treatment of TB in children. In addition, information on VHTs and their existing linkages to facilities and roles in TB care was collected. Document reviews of NTLP Facility Registers were done to verify the number and disease category of children notified to the NTLP.

Results: A total of 58 health facilities were included in the survey, covering 60% of all facilities down to level III in the two participating districts. From January 2013 to December 2014, 404 children 0-14 years were notified with TB from these health facilities, representing 9% of all TB cases notified during this time period. Of these only 4% (18) were under 5 years and 10% (43) were bacteriologically confirmed. The majority of children (60%, $n=241$) were diagnosed at hospitals, which made up only 14% (8) of all health facilities sampled. ZN Microscopy and CXR were the main diagnostic tools to aid TB diagnosis in children. 42% of health facilities reported doing routine contact tracing although only 10% ($n=6$) had a record of this. IPT was routinely provided at only 18% (10) health facilities while only 19% (11) facilities utilized VHTs for TB Services.

Conclusion: Provision of child TB services in Uganda is still highly centralized and should be decentralized to lower health facilities. At these health facilities, contact screening and IPT should be integrated into routine care and healthcare workers should be trained to confidently make a clinical diagnosis of TB in children.

PC-1289-06 "Looking where the light is bad": engagement in care among individuals with LTBI in the United States

J Mancuso¹ ¹Uniformed Services University of the Health Sciences, Bethesda, MD, USA. e-mail: james.mancuso@usuhs.edu

Background: An estimated 12 million people (4.2%) in the U.S. had LTBI in 2000, and prevalence was higher among the foreign born and certain ethnic groups and races. However, the proportion of these infected persons who have been diagnosed or appropriately treated is unknown. The objective of this study was to estimate engagement in LTBI care in the United States and examine risk factors for lack of engagement.

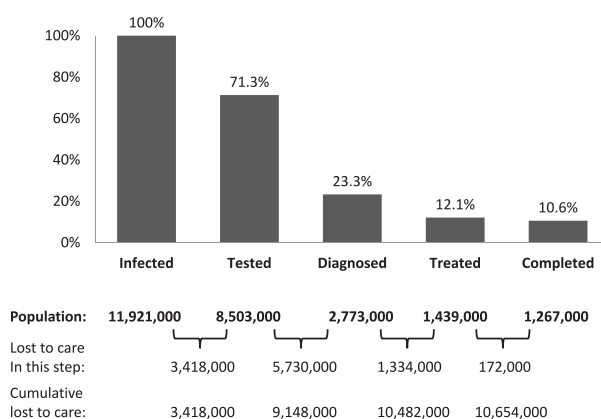
Design/Methods: We used the demographic and TB components of the National Health and Nutrition Examination Survey (NHANES) from 2011-2012. The population at risk was all those with LTBI, as determined by a TB skin test induration of 10 mm or larger. Those

with a history of active TB were excluded from this study. Engagement in care was measured by self-reported history of testing, diagnosis, treatment, and completion of therapy. Prevalence estimates for the U.S. population were calculated using NHANES 2011-2012 Medical Examination Center 2-year weights to adjust for probability of selection and nonresponse to the survey, with additional reweighting to account for nonresponse to TB testing.

Results: There were a total of 11.9 million people infected with LTBI in the United States in 2011-2012. Of these, 71% had been tested for TB, but only 23% reported a history of a diagnosis of TB (Figure). Only 12% had a history of treatment and 11% a history of completion of therapy. Thus, 10.6 million people (89%) infected with LTBI never completed a course of therapy and remain at higher risk for developing TB disease. Infected people who were older or were contacts of a case of TB disease were more likely to be aware of the diagnosis of LTBI. Foreign born and members of higher risk racial and ethnic groups were not more likely to be aware of their LTBI than people who were US-born or Caucasian.

Conclusion: As seen in the cascade of LTBI care shown in the Figure, most persons in the USA with LTBI had been tested previously, but few recalled a history of diagnosis and almost 90% never completed a course of treatment. Although those who start therapy for LTBI in the USA are likely to complete it, this is a poor measure of TB control program effectiveness. To contribute meaningfully towards TB elimination, efforts should be directed towards looking "where the light is bad"—that is, identifying those with LTBI and ensuring that they are diagnosed and engaged in treatment.

Figure 1. Cascade of Engagement in Care of Latent Tuberculosis Infection



PC-1290-06 Association between latent tuberculous infection and indoor air pollution among household contacts of pulmonary tuberculosis cases

S K Sahu,¹ D Reddy,⁴ A Mcintosh,³ R Kubiak,² G Roy,¹ J Ellner,² S Sarkar,¹ N Hochberg,² ¹Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; ²Boston University, School of Medicine, Boston, MA, ³Boston University, School of Public Health, Boston, MA, ⁴Albert Einstein College of Medicine, Bronx, NY, USA. Fax: (+1) 718 678 1020. e-mail: divya.reddy@einstein.yu.edu

Background: One component of the effort to control tuberculosis disease (TB) is to identify modifiable factors associated with latent tuberculosis infection (LTBI). Approximately half the world's population uses unprocessed solid fuels such as coal and biomass (e.g. wood, dung, crop residues) for household cooking that cause indoor air pollution (IAP). Limited data suggest an increased risk for TB due to IAP, but its association with LTBI has not been evaluated. This study aims to assess the association between use of biomass cooking fuels and LTBI.

Methods: We analyzed data from culture-confirmed pulmonary TB cases and their household contacts (>6 years) recruited into the Regional Prospective Observational Research for TB (RePORT) cohort in Pondicherry and Tamil Nadu, India. Demographic, clinical, and household data were collected and tuberculin skin tests (TST) administered for household contacts. LTBI was defined as a TST induration of ≥ 10 mm. Univariate associations were calculated using logistic generalized estimating equations to account for household-level clustering effects.

Results: Of the 242 household contacts in the 74 households with environmental data, 144 (60%) were female, and the median age was 22 years (IQR 24). Among household contacts, 223 (92%) had never smoked tobacco, but 109 (45%) lived in households where smoking was allowed, including 58 (53%) on a daily basis. 75 (31%) household contacts had LTBI. Household contacts with LTBI were more likely to live in households where tobacco smoking was allowed (OR 1.9; 95%CI 0.9-3.6; $P = 0.07$). The primary cooking fuels were liquid petroleum gas (52; 70%), wood (18; 24.3%) and kerosene (2; 2.7%); 1 (1.3%) household used electricity. Among those using wood as the primary fuel, 11 (61%) had an outdoor kitchen. Compared to households using electricity for cooking, those using wood were more likely to have household contacts with LTBI (OR 2.9) but the difference was not statistically significant (95%CI 0.7-12.5; $P = 0.16$).

Conclusion: About one-quarter of the studied households use wood for cooking, which is a known contributor of IAP, however the majority use an outdoor kitchen. While our data do not show a statistically significant association between biomass fuel use and LTBI, the effect estimate is substantially larger than 1, despite the small sample size. Additional analyses are ongoing to assess the role of potential socioeconomic confounders including tobacco use and ventilation.

PC-1291-06 Clinical and immunologic profile of TB-HIV co-infected children at a paediatric HIV clinic in Uganda

H Lukolyo,^{1,2} M Murungi,¹ A Mandalakas,^{2,3} D Damba,¹ K Ngo,³ A Kekitiinwa^{1,2} ¹Baylor College of Medicine-Bristol Myers Squibb Children's Clinical Center of Excellence at Mulago Hospital, Kampala, Uganda; ²Baylor College of Medicine, Houston, TX, ³The Global TB Program, Texas Children's Hospital, Houston, Texas, USA. e-mail: heather.lukolyo@bcm.edu

Background: Tuberculosis (TB) is one of the most common and deadliest opportunistic infections among people living with human immunodeficiency virus (HIV) in resource-limited settings. However studies describing the clinical characteristics and outcomes of children with TB-HIV co-infection are lacking.

Design/Methods: This is a retrospective cohort analysis of all new cases of active TB disease among children 0-15 years diagnosed in 2013 at the Baylor College of Medicine Children's Foundation of Uganda. Data were extracted from the electronic medical record. Descriptive statistical analysis was performed to describe clinical characteristics of cases.

Results: There were 4036 HIV-positive and HIV-exposed children ages 0-15 years active in care at the end of 2013. During 2013, 90 children were diagnosed with TB and started on anti-TB treatment (ATT); three were found to be HIV-negative and excluded from analysis. Of the 87 remaining cases, 43 (49.4%) were male with median age at TB diagnosis of 4.3 years (interquartile range (IQR) 6.5 years). Forty-six (52.9%) cases were diagnosed among children already on antiretroviral therapy (ART) while 41 (47.1%) cases were in ART-naive patients. There were 82 (94.3%) pulmonary TB (PTB) and five (5.7%) extrapulmonary TB cases. The majority of PTB cases were diagnosed clinically. For children 0-5 years old, the mean CD4 percent was 15.1% (IQR 13%) at TB diagnosis and increased to 28.0% (IQR 15%) after completion of ATT. For children 5-15 years old, the median CD4 was 293/mm³ (IQR 694/mm³) at TB diagnosis and increased to 776/mm³ (IQR 565/mm³) by completion of ATT. The majority (60.8%) of children were malnourished at the time of TB diagnosis; by ATT completion 88.7% had adequate nutrition, demonstrating a decreased odds of malnutrition (OR 0.057, 95%CI 0.023-0.14). Sixty-two (71.3%) patients completed ATT, while 21 (24.1%) died, one (1.1%) was lost to follow up and three (3.4%) transferred out prior to ATT completion.

Conclusion: In this population of HIV-positive and HIV-exposed children, the incidence of new TB cases was 22 per 1,000 children. This study demonstrated a high mortality rate of 24.1% among TB-HIV co-infected children. Most children were immunosuppressed and malnourished at time of TB diagnosis; those completing ATT demonstrated improvements in both immunologic and nutritional status. The few patients with bacteriologically confirmed TB highlights the challenge of accurate TB diagnosis in children.

Change in immunologic and nutritional status after anti-tuberculosis therapy (ATT)

		Pre ATT (n=87)		Post ATT (n=62)	
		Number	%	Number	%
Severity of immunosuppression*	Normal	23	26.4%	39	62.9%
	Mild	12	13.8%	8	12.9%
	Advanced	13	14.9%	1	1.6%
	Severe	36	41.4%	7	11.3%
	CD4 data not available	3	3.4%	7	11.3%
Acute nutritional status**	Adequate nutrition	31	35.6%	55	88.7%
	Mildly malnourished	13	14.9%	4	6.5%
	Moderately malnourished	23	26.4%	1	1.6%
	Severely malnourished	17	19.5%	0	0.0%
	Data not available	3	3.4%	2	3.2%

* Immunologic status defined for children <5 years as: normal = >25%, mild = 20-24%, advanced = 15-19%, severe = <15%; and for children >5 years as: normal >500/mm³, mild = 350-499/mm³, advanced = 200-349/mm³, and severe = <200/mm³.

** Nutritional status defined based on weight-for-height Z-scores (age <5 years) and BMI Z-scores (age >5 years). Adequate = >-1 SD, mild = -1 - -2 SDs, moderate = -2 - -3 SDs, and severe = <-3 SDs from mean.

PC-1292-06 Adolescent TB treatment outcomes in Gaborone, Botswana

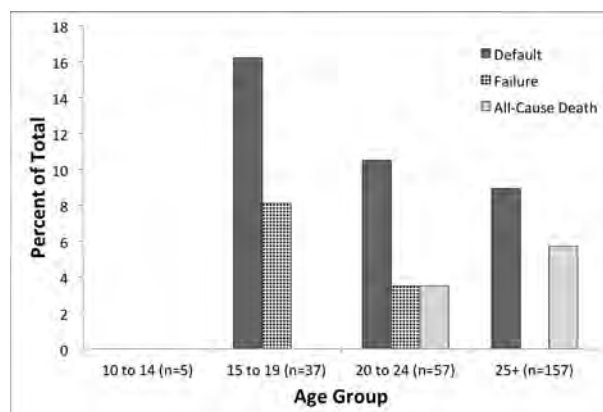
L Enane,¹ E Lowenthal,^{1,2} T Arscott-Mills,^{1,2,3} B Kgwaadira,⁴ S Coffin,^{1,2} A Steenhoff^{1,2,3} ¹Children's Hospital of Philadelphia, Philadelphia, PA, ²University of Pennsylvania, Philadelphia, PA, USA; ³Botswana-UPenn Partnership, Gaborone, ⁴Botswana National TB Programme, Gaborone, Botswana. e-mail: leslie.enane@gmail.com

Background: Adolescents are at high risk for TB, particularly if they are HIV-infected. HIV is the leading cause of death among adolescents in Africa; the impact of TB in hastening these deaths is unknown. Furthermore, there has been very little research on adolescent TB treatment outcomes. The neglect of adolescent TB patients is an impediment to their care, and to global TB control. We sought to describe TB treatment outcomes among adolescents and young adults (10-24 years) in Gaborone, Botswana, and to compare the rates of poor outcomes with those of older adults (>25 years). **Design/Methods:** This was a retrospective cohort study of standardized TB patient register data at three clinics in Gaborone, Botswana, from January 2012-January 2014. Using a paper data abstraction form, we sampled every adolescent and young adult case, and every third older adult as a comparison group. Rates of poor treatment outcomes were calculated for 5-year age groups: 10-14, 15-19, 20-24, and for all 10-24 year-olds, and compared with those of older adults (>25).

Results: We enrolled 99 adolescent and young adult patients and 157 older adults. Median ages (interquartile range) were 21 (18; 23) and 37 (31; 45), respectively. The adolescent and young adult group, when compared to older adults, was predominantly female (56% vs. 36%, $P < 0.01$); less likely to be HIV-positive (19% vs. 75%, $P < 0.001$); and less likely to have a documented HIV test result (8% vs. 2%, $P < 0.04$). Adolescents and young adults had higher default rates (12% vs. 9%), though this was not statistically significant. The 15-19 year old group had the highest default rate (16%) (Figure). All of the treatment failures were in the adolescent and young-adult age groups (5%). The 15-19 year-old group had the highest rate of treatment failure (8%). Seventeen patients (7%) did not have a treatment outcome recorded as they transferred out to receive care at another site.

Conclusion: While adolescent and young adult TB patients were less likely to be HIV-positive, they were

also less likely to have a documented HIV result. There is a missed opportunity for adolescent HIV testing at the time of TB diagnosis in this setting. Future studies of larger cohorts should explore default and failure rates among 10-24 year-olds treated for TB, particularly among 15-19 year-olds. Poor outcomes should be further characterized, and treatment challenges should be explored, in order to optimize TB treatment in this age group.



70. The two 'Ts': linking TB and tobacco

PC-1293-06 Tobacco smoking and recurrent pulmonary tuberculosis in Armenia

A Harutyunyan,¹ V Petrosyan,¹ N Truzyan¹ ¹American University of Armenia, Yerevan, Armenia. e-mail: aharutyunyan@aau.am

Background: Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease. Poverty, HIV infection and tobacco smoking are the main determinants for TB. This cross-sectional study evaluated smoking behavior of TB patients and the role of smoking for the recurrence of TB.

Design/Methods: All the patients with drug sensitive pulmonary TB that started continuation phase of TB treatment in March-December 2014 were recruited through 52 outpatient TB offices in Armenia. Data were collected through interviewer administered surveys using a structured questionnaire. The wealth score was calculated based on the weighted values of self-reported families' general standard of living, household monthly expenditure, employment and migrant statuses of the TB patients. The level of depression was assessed using the Center for Epidemiological Studies Depression (CES-D) scale. The study used descriptive statistics and logistic regression for data analysis.

Results: Overall, 395 TB patients participated in the study. The mean age of participants was 46.7 years (SD=15.4), 78.0% were male. Smoking prevalence was significantly higher among males compared to females

(67.5% vs. 5.8%; $P < 0.001$). The mean number of cigarettes smoked per day was 19.5 (SD=12.5). About 80% of current non-smoking males reported to be past smokers which resulted in 75.4% lifetime smoking prevalence with average smoking history of 28.0 years (SD=14.7). One-fifth (19.8%) of TB patients were recurrent cases. The odds of having recurrent TB was higher among current smokers (OR=1.93, $P = 0.014$), males (OR=1.72, $P = 0.117$), older (OR=1.03, $P < 0.001$) and depressed (OR=1.78, $P = 0.046$) patients and those who had lower wealth score (OR=0.82, $P = 0.006$). Multiple logistic regression revealed that after adjusting for age, wealth score and depression status, the odds of having recurrent TB was 1.90 times statistically significantly higher among current smokers compared to non-smokers ($P = 0.032$).

Conclusion: Smoking is very prevalent among drug sensitive pulmonary TB patients in Armenia and it is a statistically significant risk factor for recurrence of pulmonary TB. Joint efforts should be made to coordinate national tobacco and TB control programs to raise awareness about the TB and smoking association and to provide assistance for quitting to smoking TB patients.

PC-1294-06 Incorporating tobacco control with community-based TB services in improving TB cure rates and tobacco quit rates in urban centers in Bangladesh

M Basher,¹ S Islam,¹ S Reza,¹ S Alam,¹ M Siddiqui,¹ M Akramul Islam,¹ M Haque² ¹BRAC, Dhaka, ²NTP, Dhaka, Bangladesh. e-mail: basher.ak@brac.net

Background and challenges to implementation: Last few decades, tobacco consumption through inhalation has increased substantially especially in developing countries like Bangladesh. BRAC started integration of smoking cessation intervention into Directly Observed Therapy (DOT) programs in 17 DOTS centers of Dhaka since 2011 as tobacco smoking is associated with tuberculosis (TB) and decrease the effectiveness of TB treatment. Main aim of the initiative is to explore current smokers among TB patients and see the effectiveness of smoking cessation and prevention on TB treatment outcomes.

Intervention or response: BRAC TB programme staff was trained on tobacco control with precise focus on harmful effect of smoking and its effect on treatment outcome. All tools were developed in Bengali based on the guideline "Smoking Cessation and Smoke-free environment for TB patients" of the Union. Counseling is given to patients for smoking cessation during initiation of treatment and subsequent visits to TB centre.

Results and lessons learnt: From 2011 to 2014, a total of 14 202 TB patients were enrolled in the intervention areas. Among them, 23% patients were smokers of whom 98% were male and 2% female. The level of addiction was high in 31% cases and low in 69% cases. Among registered patients between 2011 and 2013, 73% people quit smoking among smokers (22%). Treatment outcome 91% which is much better among the TB

patients and quit rate was 80% among the successfully treated TB patients

Conclusions and key recommendations: Tobacco cessation counselling within TB Patients is found more effective which may replicate within community based DOTS programme.

PC-1295-06 Does smoking during tuberculosis treatment affect outcomes? A cross-sectional study in Chandigarh, India

S Goel,¹ J Kathiresan,¹ A Garg,² R J Singh³ ¹Post Graduate Institute of Medical Education and Research, Chandigarh, ²Health & Family Welfare, U T Chandigarh, Chandigarh, ³International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India. Fax: (+91) 17 2274 4993. e-mail: sonugoel007@yahoo.co.in

Background: World Health Organization (2014) reported that Tuberculosis (TB) is one of the world's deadliest communicable diseases, with an estimated 9 million developing T.B and 1.5 million succumb from illness. In year 2013, a total of 240 000 deaths occurred due to TB in India, with a prevalence rate of 19/100 000 population. A WHO/The Union monograph on TB and tobacco control has confirmed a strong link between active and passive tobacco smoking and a range of TB outcomes including infection, response to treatment, relapse rates and mortality and had strongly recommended co-ordination between National TB and tobacco control programmes. There is a lack of data from India on the direct effects of smoking on TB treatment outcomes. The study aim to analyze smoking pattern among T.B patients and the effect of smoking on treatment outcome of TB patients.

Methods: The study used cross-sectional design among pulmonary tuberculosis patients over 15 years of age in Union Territory (UT) of Chandigarh, located in north India. All the TB patients who enrolled themselves for DOTS in two quarters (January till June 2013) in total 17 Designated Microscopy Centres (DMCs) of Chandigarh were target population in the study and were followed up till their final outcomes. The data was analyzed using SPSS version 16.0. The study was ethically approved by Institute Ethics Committee, PGIMER, Chandigarh.

Results: Out of 686 T.B patients enrolled, 78.4% fall in category 1 of treatment category. Around 12.6% ($n = 87$) were daily smokers, 10% ($n = 69$) occasional smokers and almost similar number ($n = 72$, 10.4%) were quitters. 46.3% ($n = 318$) were smokeless tobacco users. Over two third (68.6%) initiated their smoking habit before 20 years of age and almost all smokers take their first puff within 30 minutes of their wake-up in morning. Half (57.5%) of the smokers made at least one quit attempt in their lifetime. The cure rate was significant higher in non-smokers as compared to smokers. Transfer out rate and death cases was also found less in non-smokers, however not statistically significant. The defaulters and failure cases were significantly more in smokers as compared to non-smokers.

Conclusions: The TB patients who smoke have higher chance of poor treatment outcomes as compared to non-

smokers. The tobacco control interventions should especially focus on tuberculosis patients as they are the captive and receptive audience during their treatment.

PC-1296-06 Assessment of pulmonary tuberculosis and its association with smoking habits in Paniya tribes of India

S Palliyal¹ ¹DM Wayanad Institute of Medical Sciences, Kalpetta, India. e-mail: shanupalliyal@gmail.com

Background and challenges to implementation: The tribal populations throughout India have remained socially and culturally alienated from mainstream Indian society until developmental and conservation activities in tribal areas forced interactions between the *M. tuberculosis* (TB) is a major public health problem among Paniya tribes, a marginalized tribal group in Kerala state, South India. Previous studies have documented a high prevalence of tobacco use among Paniya Tribals in Wayanad. However, little is known about their correlation exists between tobacco habit and pulmonary tuberculosis. The aim of this study was to evaluate the pulmonary tuberculosis among nonsmoking and smoking Paniya tribes.

Intervention or response: A cross sectional survey was done among 688 nonsmoking and 483 smoking Paniya tribal populations of Wayanad District, India from January 2013 to June 2013 after approval from the Institutional ethical committee. Information on smoking status, type of tobacco smoked, quantity of tobacco smoked, and duration of tobacco smoking was collected from cases and controls using a questionnaire.

Results and lessons learnt: In this study pulmonary tuberculosis was found to be far more prevalent among smoking Paniya tribes than among the non smoking Paniya tribes. ($P < 0.0001$). The prevalence of severe tuberculosis was found to be 32% amongst smokers. This was much higher than the 2% found among the non smokers. Among the Smokers a statistically significant relationship was observed between pulmonary tuberculosis and poor access to health care ($P < 0.001$).

Conclusions and key recommendations: There is a positive association between tobacco smoking and pulmonary tuberculosis. The present study demonstrates gross disparities in pulmonary tuberculosis among smoking and nonsmoking Paniya tribes. There is an urgent need to develop and implement culturally appropriate awareness raising activities to target smoking to support the efforts to control TB in this community.

PC-1297-06 Tobacco and tuberculosis free India

S Gupta¹ ¹Individual, Shimla, India. e-mail: smshellyhp@yahoo.co.in

Background and challenges to implementation: The Health Department's target is to make the state "TB free by 2035". This target seems to be a tough task. About 14 000 new TB patients have been detected last year. The state continues to report increased lung cancer cases due

to smoking. A study at IGMCM, Shimla revealed weak immune system in people of HP, leading to diseases like TB. The presence of heavy metals like chromium in soil & water in industrial area leading to lung ailments. Education on TB prevention, cure and treatment, sustainability of smoke free public places and more initiatives by Govt. is required. Non participation of community in TB Control, unavailability of treatment up to remote areas, discontinuation of treatment by the patients, tobacco usage, increased pollution are a few identified threats and challenges.

Intervention or response: According to health officials there is a gap in the access to the DOTS centre and treatment of patients and patients suffer from malnutrition. ASHA workers are helping detect patients and monitor the treatment for six to eight months. Migrant laborers and workers exposed to hazards of pollution and dust from mines are being focused. HP is a smoke free state and progressing towards Tobacco free state. Appointment of nodal officers, strong advocacy, frequent raids, seizure of Gutka, liaising with administration, discussions in steering and monitoring committee meetings, monthly meetings, Gram Sabhas, involvement of media, serving of notices to public place managers for violations, removal of promotional boards under sec 5 of COTPA are few activities done to enforce law. More than 20 000 challans were done during the year 2012-2013 with a fine collection of more than Rs. 20 lakh. Similar aggressive drives are required by each state for preventable epidemics like TB, HIV and for TAT Free India.

COMPARATIVE ANALYSIS :
TOTAL NUMBER OF PATIENTS REGD. FOR TREATMENT IN HIMACHAL PRADESH (DISTRICT WISE)

S.NO.	DISTRICT	TOTAL NUMBER OF PATIENTS REGISTERED FOR TB TREATMENT YEAR 2010	TOTAL NUMBER OF PATIENTS REGISTERED TB FOR TREATMENT YEAR 2013
1.	BILASPUR	757	649
2.	CHAMBA	1155	1156
3.	HAMIRPUR	906	761
4.	KANGRA	2759	2613
5.	KINNAUR	216	189
6.	KULLU	1387	1332
7.	LAHAUL SPITI	91	63
8.	MANDI	2170	2157
9.	SHIMLA	1557	1766
10.	SIRMOUR	1146	1014
11.	SOLAN	1289	1285
12.	UNA	746	706
	TOTAL (Negligible Improvement)	14179	13691

Results and lessons learnt: Tobacco related Lung diseases can be reduced by formulation, implementation & Evaluation of TB Control Strategies; Ensuring Smoke

Free Public Places , reaching the unreached & Pollution free environment.

Conclusions and key recommendations: Sustainability Monitoring , Evaluation Public Private Partnership Prevention , Education & In time Quality Treatment to reduce morbidity & mortality . Research & Development Effective Enforcement of smoke free laws.

PC-1298-06 Smoking among tuberculosis patients in India: proactive cessation efforts are urgently needed

S Nayak,¹ P Sharma¹ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, India. Fax: (+91) 11 4605 4429. e-mail: SNayak.HR@theunion.org

Background and challenges to implementation: The new Stop TB strategy recognizes prevention of most frequent risk factors as an important contributor to the sustainability of a case management intervention for TB control. Available evidences show that tobacco smoking is one of the key risk factors that favour the progression from latent TB infection to pulmonary disease. The comorbidity of TB and Tobacco has been well established. However, the effort to help TB patients, quitting tobacco by explaining the harmful effects/ dangers, especially during the treatment should be an absolute must. Simultaneously, required essential support system like accessibility of cessation centres to the patients either in their communities or in the hospitals must be established. As Tobacco creates addiction, hence, cessation can occur only at moments when an individual finds both a reason and desire to stop smoking. Smoking substantially increases the risk of TB and death from TB.

Intervention or response: A cross sectional community-based knowledge, attitude and practices (KAP) survey was conducted in 30 districts of India by The Union. The respondents, including general population, TB patients, health service providers, opinion leaders and representatives of NGOs interviewed (November 2012 to April 2013) through door-to-door survey conducted by using a semi-structured questionnaire on tobacco use/control.

Results and lessons learnt: All the respondents were asked about using tobacco in any form, to which 175 (35%) responded affirmatively. Among those respondents who used tobacco, 24% smoke, 36% smokeless tobacco and 5% were dual users. Noticeably, 49% tobacco users have been using tobacco for < 10 years. A majority of the smokers use beedi and among those using smokeless tobacco, 55% chew tobacco. Though, there was fair knowledge about TB and tobacco linkages in general, 73% were advised to quit using tobacco during their hospital visits. Over and above first hand smokers, 32% are further exposed to secondhand smoke, 38% knew the consequences, 35% use tobacco despite being a TB patient, 38% knew the association between TB and tobacco, 56% knew smoking can increase the risk of developing TB disease and 48% knew the consequences of smoking during TB treatment.

Conclusions and key recommendations: Not to smoke warning messages often go unheeded among TB patients. Proactive efforts are needed to encourage health staff and DOTS providers to give strong cessation messages.

PC-1299-06 Integrating smoking management and TB control program: a way forward

I Pangaribuan,¹ B Dwihardiani,² D Perwitasari,¹ T Tejayanti,¹ J Irianto,¹ M Farid,³ A V Siagian⁴ ¹Ministry of Health Republic Indonesia, Jakarta Pusat, ²World Health Organization, Indonesia Country Office, Jakarta Pusat, ³Tuberculosis Operational Research Group, Jakarta Pusat, ⁴Ministry of Health Republic Indonesia, Jakarta Pusat, Indonesia. e-mail: bintari_dwihardiani@yahoo.com

Background: The relation of smoking and TB has been proven in many literatures. Because both cause lung problem, the collaboration of TB control program and smoking cessation project may help control the two problems. Based on Indonesian national TB prevalence survey results, we propose findings to support the integration of the two control programs.

Design/Methods: National TB prevalence survey (NPS) which was conducted in 2013-2014 applied smoking history question in its questionnaire. NPS was conducted as a cross sectional survey with multi staged cluster sampling among population aged 15 years old and above. Eligible participants were invited to attend interview and chest X-ray screening. Those with positive screening symptoms or chest X-ray were requested to submit sputum specimen, in which LJ culture and smear microscopy were conducted. Bacteriologically confirmed TB case was defined by panel team based on laboratory results supported by chest X-ray and clinical information. Positively screened individuals and 10% of negatively screened individuals were interviewed for TB knowledge, attitude, and practice.

Results: Among NPS participants, 33.9% admitted that they were smoking at the time of interview. Smoker is significantly higher in the male population. The proportion of TB cases is higher among smoker even though the association is not significant. As TB prevalence is higher among male, male sex can be a confounder of the association of smoking and TB cases. Among TB cases, smokers had slightly higher proportion of infiltrates and cavities shown in chest X-ray. Among the participants of KAP interview, there is no difference in knowledge about TB symptoms, transmission, and the access of TB treatment between smoker and non smoker.

Conclusion: Considering high smoker prevalence in Indonesia, focus on smoker to detect TB may open the opportunity to manage smoking problem. Moreover, most of the smoker are men and TB prevalence is higher among men, therefore integration of TB and smoking management which focus on male population may work. Further research is needed to evaluate the yield, cost effectiveness on TB control and smoking control, and feasibility of integrating the two programs.

PC-1300-06 Deaths due to respiratory neoplasms and the trend of tobacco use in Sri Lanka, 1960–2010

L Athauda¹ ¹Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka. e-mail: lathika@kln.ac.lk

Background: The prevalence of current tobacco smoking among adults in Sri Lanka in 2012 was estimated as 15.0%, the prevalence being 29.9% for males and 0.4% for females. Deaths due to neoplasms of the respiratory tract have been on the rise over time. This study aimed at describing the tobacco use trends from 1960–2010 and its influence on deaths due to respiratory disease neoplasms.

Intervention or response: Tobacco consumption data was obtained from the Food and Agricultural Organization database, population data from the UN database and deaths data on respiratory disease from the department of census and statistics Sri Lanka. Deaths due to respiratory neoplasms included, neoplasms of the larynx, trachea bronchus and lungs, as well as neoplasms of intra thoracic organs. Correlation and regression analysis were carried out.

Results and lessons learnt: The average tobacco use from 1960–2010 was 560.87+223.43kg/capita/year. The trend of tobacco use displayed an increment from 1960–1978, and a declining trend thereafter. The average death rate due to neoplasms of the respiratory tract from 1960–2009 were 1.47+1.04. There was a decrease in mortality due to respiratory neoplasms beginning in 1995; this decrease corresponds to the decrease in smoking since 1978 having a lag period of about 15 years ($r=0.002$ $P=0.021$, $R^2=0.151$). Tobacco control policy was implemented at a national legislature only in the year 2006, though execution has been problematic.

Conclusions and key recommendations: The rise in deaths due to neoplasms of the respiratory tract in Sri Lanka shows a clear association with tobacco use of a lag of 15 years. The trends of respiratory neoplasm deaths are yet on the rise. The future may be predicted to be a downward trend, as Sri Lanka follows a global trend of reduction in tobacco use. However, the reduction of deaths can be influenced by the improving health care and technology of the country.

71. From old to new: chicha to e-cigarettes

PC-1301-06 The emerging E-cigarette in China

C Wang,¹ J Wang,¹ L Zhao,^{1,2} Y Yang,¹ Y Jiang¹ ¹Chinese Center for Disease Control and Prevention, Beijing, China; ²U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: wangcongxiiao@163.com

Background: E-cigarette was first invented and sold in China in the 2000s. However, it was not widely used in China but well recognized in the western. As it is more and more popular worldwide, the situation also changes

in China. When a survey was conducted in 14 Chinese cities, questions related to E-cigarette were also included. **Design/Methods:** An urban representative population of individuals age 15 or above was selected with PPS method in 14 cities. A target sample size of 2000 respondents was required for each city. The adjusted sample size was 2500 after taking into account the potential loss due to ineligibility and non-response (assuming an 80% final response rate). In Beijing, the adjusted sample size was 4,800 in the urban areas. In-house interview was conducted using handheld devices from October 2013 to August 2014. Questions of “Have you ever heard of e-cigarette?” “Do you currently use e-cigarette?” were asked to the subjects. SPSS was used for data cleaning and data management; SAS-callable SUDAAN was used in data analysis. Sample weights were calculated for each respondent, and were also post-stratified to the total adult population of each city respectively, by gender and age groups, using population counts from the 2010 China National Population Census.

Results: 31 151 of 37 300 respondents completed the survey, representing a population of 52.8 million. In the current survey, more than 40.0% of adults reported having heard of e-cigarettes in each of the 14 cities. However, in all 14 cities, the percentage of adults who currently used e-cigarettes was low, with the highest found in Luoyang at 1.7%. The survey showed that the majority of the current e-cigarette users were also current cigarette smokers (80.0% or more in all cities). However, some e-cigarette users reported that they were not current or occasional tobacco smokers, including some who never smoked tobacco before.

Conclusion: E-cigarettes attained a high degree of awareness in the 14 participating cities, while a small percentage of adults reported using the products. It is worth noting that current e-cigarette users consisted of current tobacco smokers and adults who were not current tobacco smokers, some of whom had never smoked tobacco before. Additional research and regulation are needed to be conducted on multiple areas of e-cigarette use.

PC-1302-06 End of ‘ENDS’ (Electronic Nicotine Delivery System) in state of Punjab, India

R Gupta,¹ V Mahajan,¹ K Singh,¹ A Singla,¹ S Goel²

¹Tobacco Control Cell Punjab, Chandigarh, ²Post Graduate Institute of Medical Education and Research, Chandigarh, India. Fax: (+91) 1725 012 356. e-mail: rakesh60.mahajan@gmail.com

Background and challenges to implementation: Electronic Nicotine Delivery System (ENDS) popularly known as e-cigarettes are highly addicting and potentially lethal products. It is mostly being used by children and youth because these are glamorised by the tobacco industry. Though not generally available in stores, they are widely promoted through social media, email marketing with discount offers. Sales are increasing sharply all over the world. Currently, these are not regulated by any national authority in India. Punjab

became the first state in India to declare Electronic Nicotine Delivery System (ENDS) as illegal in 2013.

Intervention or response: Various steps were undertaken during the process to institutionalise the monitoring mechanism for abuse of ENDS. These included sensitization of political leadership and bureaucracy at state level; advocacy meetings of all Deputy Commissioners (administrative head of district) and Civil Surgeons (administrative head of health department of district); meetings with tobacco wholesalers to make them aware about the violation of Drugs and Cosmetics Act, which allows nicotine (2 mg and 4 mg) only as gum and lozenges to be manufactured and sold and sensitization of media about the importance of making e-cigarettes unavailable for sale.

Results and lessons learnt: A circular was issued by Government of Punjab regarding declaration of manufacture and sale of ENDS as illegal. District level Task Force effectively implements the ban through conducting raids at suspected point of sale, which is being monitored monthly by Deputy Commissioners. At state level, Health Minister and Principal Secretary regularly monitor the implementation with Civil Surgeons. The media sensitises the public through regular news-articles/stories/talk-shows etc. about the importance of making e-cigarettes unavailable for sale. Violators are being booked under Drugs and Cosmetics Act. Court cases have been filed against violators. In a special 3 day campaign in March 2015, 1050 Points of sale were checked all over Punjab and no sale of ENDS/E-Cigarettes was found.

Conclusions and key recommendations: The declaration by the Government of Punjab opens the way for other states to follow suit and prevent ENDS becoming an additional marketing strategy for tobacco companies.

PC-1303-06 E-cigarettes: prevalence of use and perceptions among adolescent college students of Mangalore city

E Aluckal¹ ¹A J Institute of Dental Sciences, Mangalore, India. Fax: (+91) 824 222 4968. e-mail: draluckal@gmail.com

Background: Tobacco usage is the largest, preventable cause of premature mortality in the world. E-Cigarettes are battery-powered devices that deliver vaporized nicotine without the tobacco combustion of regular cigarettes. Tobacco control advocates and researchers are concerned that e-cigarettes could act as "gateway" devices, getting novice users, particularly the young people, addicted to nicotine and encouraging future tobacco use. The adolescent college students are a group that is at risk for smoking initiation and may use e-cigarettes as an experimentation to start smoking. These products are gaining popularity in many countries but little is known about their use among college students in India.

Design/Methods: A descriptive cross sectional study was conducted on 1074 adolescent college going students of different pre-university colleges of Mangalore city using cluster sampling. Information was elicited on their socio-

demographic characteristics, usage of e-cigarettes, perceptions and practices related to that. Statistical analysis was done using SPSS version 21.

Results: The mean age of study population was 16.4 years with 59% males. Around half of respondents (46.4%) had seen e-cigarettes advertised. A total of 16.1% reported trying an e-cigarette (5.1% nonsmokers, 18.4% former smokers, and 34.5% current smokers), and 5.9% reported use in the past 30 days. Compared to non-smokers, former smokers and current smokers were more likely to have tried e-cigarettes (OR 4.15 and OR 9.84 respectively), and current smokers were more likely to have tried e-cigarettes than former smokers (OR 2.37). Current smokers were also more likely to be current users of e-cigarettes than both former smokers (OR 15.24) and non-smokers (OR 4.83). Smokers were interested in trying e-cigarettes to help them quit smoking (80.4%), as a long-term replacement for cigarettes (74.8%), or to use in places where they cannot smoke (82.1%).

Conclusion: Most adolescent college students were aware of e-cigarettes, and a substantial minority reported trying them, with evidence of use among nonsmokers. Given that even experimentation with e-cigarettes could lead to nicotine dependence and subsequent tobacco usage, regulatory and behavioral interventions are needed to prevent 'gateway' use by adolescent college students. Education about e-cigarettes could help providers deliver comprehensive preventive services to adolescents at risk of tobacco use.

PC-1304-06 Hookah smoking and lung cancer in Kashmir valley, Indian subcontinent

M Dar¹ ¹Directorate of Health Services Kashmir, Srinagar, India. e-mail: uberaltaf@yahoo.co.in

Background: The literature about the causal relationship between lung cancer and tobacco smoking mostly concerns cigarettes. Hookah smoking is popular in the Kashmir valley of the Indian subcontinent, and is generally believed to be innocuous because of the passage of the smoke through water before inhalation. **Objective:** To determine the relationship of hookah smoking to lung cancer in Kashmir. Hookah smoking is widely practiced in Kashmir and was found to be the commonest form of smoking amongst the patients with lung cancer.

Design/Methods: The study was conducted in the SheriKashmir Institute of Medical Sciences, Srinagar, Kashmir (India), a 650 bedded tertiary care university hospital that serves as the main referral center for the Pulmonary and Oncology cases of the Kashmir valley of the Indian subcontinent. Hookah (locally called 'Jajeer') in Kashmir is traditionally made of an earthen-ware water bowl or base (made in current times of tinned copper or brass with exquisite surface carvings) that is half filled with water and connects to a separable earthenware head (or Chillam) by a cane wood conduit or body, the lower end of which stays submerged in the water of the base. Another inverted

Results: The cases included 209 males and 42 females whereas the controls included 328 male and 72 female

subjects. The mean age in males was 58.4 years and in females 56.51 years. Seventy seven percent of the cases and 44.6% of the controls were ever smokers. Table 1 shows distribution of the smoking patterns in the cases and the controls. Smoking was strongly associated with the presence of lung cancer, with 194 cases being ever smokers (178 current smokers, 16 ex smokers) as compared to 173 controls hookah smoking was the commonest pattern of smoking either exclusively or with cigarettes.

Conclusion: Our hospital based study provides evidence that hookah smoking is associated with an increased risk of lung cancer in ethnic Kashmiri population with the risk being 6 times more as compared to non smokers. The study reaffirms the previous report by Nafae et al in the sixties who found hookah smoking as the commonest form of smoking in a cohort of 25 patients of lung cancer, seen in 20 of the 25, being exclusive in 17.

PC-1306-06 Water-pipe tobacco (shisha) use among undergraduate health professional students, College of Health Sciences, Nairobi University, Kenya, 2014

A Maina,^{1,2} D Kiptui,² W Arvelo^{1,3}

¹Field Epidemiology and Laboratory Training Programme, Nairobi, ²Division of Non-Communicable Diseases, Ministry of Health, Nairobi, ³Centres for Disease Control and Prevention, Nairobi, Kenya. e-mail: akmaina@yahoo.com

Background: Tobacco use contributes to more than 6 million annual deaths globally. A growing body of knowledge shows a rise in the use of water pipe tobacco (shisha), spreading from the traditional Eastern Mediterranean and Northern African regions to other parts of the world. In Kenya, anecdotal reports from the media and observations made in social places have shown a rise in shisha use among the youth who perceive it as a safer alternative to cigarette use. We assessed the prevalence of and factors associated with shisha smoking among undergraduate health profession students in the College of Health Sciences, University of Nairobi, Kenya.

Design/Methods: We conducted a cross-sectional study among final year undergraduate students enrolled in the medicine, nursing, pharmacy and dentistry programmes in August 2014. Students completed a questionnaire adapted from the Global Tobacco Surveillance System. Information on ever and current use of shisha, social demographic variables, alcohol and cigarette use was obtained. Data was analyzed using Epi Info 3.5.1.

Results: A total of 246 students were interviewed with a mean age of 23 years. Majority were female 145 (59%) and in the Medicine program 128 (52%). Fifty three (21.5%) of the respondents were current shisha users, 84 (34.1%) had ever used shisha in their lifetime and 11 (4.5%) were current cigarette smokers. Current shisha use was more commonly reported among males 24 (23.8%), medical students 37 (28.9%), self-sponsored students 33 (25%) and students residing in a rented

house 14 (37.8%). Majority 36 (69%) smoked weekly; mainly at entertainment spots 47 (89%). Concurrent alcohol and cigarette use among current shisha users was 47 (90%) and 8 (15.4%) respectively. Factors associated with current shisha use were catholic faith (OR= 2.03; 95%CI 1.04, 3.96), residence in a rented house (OR=2.65; 95%CI 1.25, 5.61), alcohol use (OR=13.46; 95%CI 5.47-33.06) and family member who smokes shisha (OR= 6.43 95%CI 3.32-12.43).

Conclusion: The use of shisha as an alternative form of tobacco is high among university students undertaking health professional courses. There is need for initiatives geared towards behavior change among these students to boost tobacco control efforts among the youth in Kenya.

PC-1307-06 An evidence-based public campaign against waterpipe / hookah smoking in Turkey

T Durgut¹ ¹Turkish Green Crescent, Istanbul, Turkey. e-mail: erdebirtuba@hotmail.com

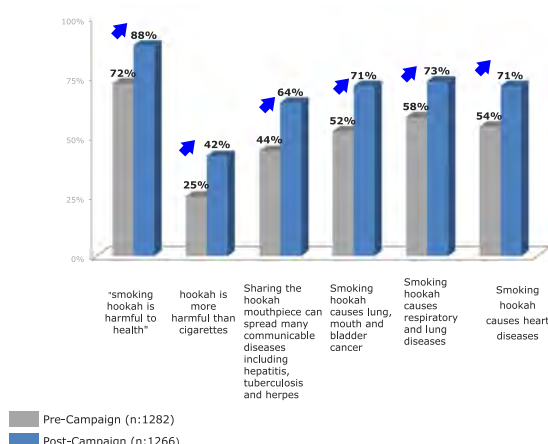
Background: Hookah use has been spreading rapidly in epidemic proportions in Turkey, especially among teenagers and youth. For this reason the Turkish Green Crescent Society has developed a hookah awareness campaign. Both qualitative and quantitative pre-campaign research has been conducted in order to define the perception, attitudes and behaviors of the target population regarding hookah. In this stage we conducted focus group studies and a baseline survey encompassing interviews with 1288 people. As a result of the pre-campaign analyses, we observed that the level of awareness on the dangers of hookah was very low compared to that of cigarettes, that hookah was not perceived as a tobacco product, that it was preferred due to its scents and flavors and that many false beliefs were propagated such as its smoke being less dangerous due to passing from water.

Intervention: Measurable objectives of our campaign, campaign strategies and concepts were defined according to the data collected through the pre-campaign analyses. We applied our campaign in four phases. In each phase we delivered different messages and the public was gradually informed of hookah facts through the use of TV and radio ads, outdoor materials, brochures, PR studies as well as the use of internet and social media

Results and lessons learnt: Following the campaign we surveyed 1266 people in order to analyze the effectiveness of the campaign. The recall rate of the campaign is high by 72.7%, in total group. TV ads recalled are evaluated "believable" (83%) and "effective since it would discourage people from smoking hookah" (77%) and also "taught persons something new" (75%). The awareness level about the negative health effects of smoking hookah significantly increased in post-campaign period. More than half of the people, who "recall the campaign say that "their interest to try smoking hookah diminished" and also "ads made them to advise people nearby to quit smoking hookah".

Conclusions and key recommendations: Legal and environmental regulations and restrictions are necessary in order to prevent the hookah epidemic, in addition to the social marketing and awareness campaigns. Restrictions on the production of flavored hookah tobacco would positively impact our struggle against prevalent hookah use, since the analyses of target population showed that 88% of users preferred flavored hookah. Legal restrictions on the fast spreading hookah cafes would also reduce the prevalence of hookah use.

AWARENESS ABOUT THE DISEASES RELATED TO HOOKAH SMOKING



PC-1308-06 Lung health and e-cigarettes: a review of recent government actions on e-cigarettes and electronic nicotine delivery devices

M Wisotzky¹ ¹International Union Against Tuberculosis and Lung Disease, Edinburgh, UK. e-mail: mwisotzky@theunion.org

Background and challenges to implementation: Research on e-cigarettes safety and efficacy as a cessation aid continues to emerge. A single new study shows that e-cigarettes compromise the immune system in the lungs of mice and make their lungs more vulnerable to infection. Human population studies show that, while the chemicals in e-cigarettes are at much lower levels than traditional cigarettes, the long-term effects are still unknown. Studies indicate that youth are taking up e-cigarettes with some evidence that they may be more likely to begin using traditional cigarettes. The huge surge in marketing/promotion, investment by transnational tobacco companies, increased awareness and use of ENDS, lack of long-term data on safety or effectiveness for cessation creates challenges for governments making policy decisions to protect lung health.

Intervention or response: In response to the quickly growing e-cigarette market, national and international public health organizations, including The Union, have assessed existing literature and research and developed specific policy recommendations for governments. Public

health and government responses range from cautious acknowledgement of potential cessation benefits to calling for product bans. Current literature shows that key areas of governments' regulation include sale, use, advertising, promotion, taxation and product classification. Many countries have bans or laws that prohibit or restrict the sale of e-cigarettes. Some regulate e-cigarettes as medicinal products. Others regulate e-cigarettes as tobacco products (or tobacco-related products). A very small number regulate nicotine-containing e-cigarettes as poisons.

Results and lessons learnt: One size does not fit all. However, there are common objectives which should guide governments' policy on e-cigarettes, e.g. Minimize health risk to consumers; Ensure control over nicotine/ other substances; Prohibit unproven health claims and marketing that prevents smokers from quitting, promotes uptake by non-smokers, youth and pregnant women; Protect tobacco control policies from interference. They can be adapted to specific national situation and modified as the science on e-cigarettes evolves.

Conclusions: Public health and governments must continue to conduct/use credible scientific evidence with the objective of protecting lung health. This session provides an overview of current government regulatory responses and related issues.

72. Holding hands: high-level cooperation on tobacco control

PC-1309-06 SmokeHaz: an example of a scientific society-led advocacy tool for tobacco control

C Vardavas,¹ C Jimenez-Ruiz,² J I De Granda,³ C Gratzou⁴ ¹University of Crete, Rethymnon, Greece; ²Sociedad Madrileña de Neumología y Cirugía Torácica, Madrid, ³Hospital 12 de Octubre, Madrid, Spain; ⁴Athens University, Athens, Greece. e-mail: maeve.barry@ersnet.org

Background and challenges to implementation: Smoking is the leading preventable cause of morbidity and mortality worldwide. At European level, approximately 700 000 EU citizens die prematurely every year because of tobacco consumption and 13 millions are affected by smoking related diseases. A large number of non smokers are victims of passive smoke exposure.

Intervention or response: As a medical society, the European Respiratory Society (ERS) is highly involved in activities for Tobacco Control since 1990. Most recently its Tobacco Control Committee created a new website the SMOKEHAZ.eu to provide a one-stop web platform that intended as an easily accessible and usable source of information regarding the impact of active and passive smoking on lung health in adults and children.

Results and lessons learnt: SMOKEHAZ.eu presents the results of systematic reviews and meta-analysis of a large number of studies selected by strict criteria, to assess the effects of active and passive smoking on adults and children respiratory health. This is a collaboration project between ERS the University of Nottingham, the

UK Centre of Excellence for Tobacco and Alcohol Studies and the European Lung Foundation (ELF). The new ERS site contains health messages based on scientific evidence with specific figures and sources of the information, so that all points can be easily traced to the source and examined in detail.

Conclusions and key recommendations: The SMOKE-HAZ website is a valuable and unique advocacy tool for tobacco control targeted at policymakers, but also serves as an educational tool for health professionals and other researchers including relevant recommendation based on scientific evidence.

PC-1310-06 Partner network consolidation for national policy on tobacco control in Brazil

E Rangel,¹ T Cavalcante,¹ A P Teixeira¹ ¹Ministry of Health, Rio De Janeiro, RJ, Brazil. e-mail: ecavalcanti@inca.gov.br

Background and challenges to implementation: The network construction process was initiated in 1989 by the National Programme for Tobacco Control articulated by the National Cancer Institute with the state and municipal health departments. In 2001, this process has become systematic and strengthened by the need to ratify the WHO Framework Convention for Tobacco Control and to combat the tobacco industry strategies trying to delay the accession of Brazil. The Executive Secretariat of the National Commission for Implementation of the FCTC was created to support and expand the construction of the network partnership between Ministries, Universities, Medical Societies, Congress and NGOs.

Intervention or response: The articulation of the network is to monitor and establish contacts with organizations that converge to strengthen the National Tobacco Control Policy. The interaction is established by telephone, narrowed by technical visits, technical training and seminars for the empowerment of organizations referenced to become spokespersons of common interests.

Results and lessons learnt: The partnership allowed the Brazilian State to ratify the WHO FCTC and implement several measures of this treaty. As a result of the partnership, in 2013 Brazil, as a key facilitator of the Working Group of Articles 17 & 18 (Provision of support for economically viable alternative activities & Protection of the environment and the health of persons) established by the Conference of the Parties to the FCTC, received in the city of Pelotas, Rio Grande do Sul (federal state with predominance of tobacco growing), 18 countries to demonstrate the implementation methodology of National Programme of Production Diversification on Tobacco Growing Áreas coordinated by the Ministry of Agrarian Development. There was also the commitment agreement signed between the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA), through Attorney General's Office (AGU), and the Interstate Association of Tobacco Industry to establish ways of combating deforestation in the Atlantic Forest for tobacco plantation.

Conclusions and key recommendations: The Brazilian experience has enabled, empowered and legitimized

several organizations to position themselves in favor of Tobacco Control Policies and provided great social adherence to the advancement and strengthening actions. The partnership has been a powerful strategy for strengthening the National Policy on Tobacco Control.

PC-1311-06 Tobacco control in social networks: the Brazilian experience with the virtual health library prevention and cancer control

L Casado Costa,¹ R Feijo,¹ L Labrego¹ ¹Instituto Nacional de Câncer José Alencar Gomes da Silva, Rio De Janeiro, RJ, Brazil. Fax: (+55) 21 3207 6068. e-mail: leticiac@inca.gov.br

Introduction: Social networking is an important media strategy for the dissemination of information in virtual environments with interactivity and sharing of information in real time and dynamically. Lately it has been used by large companies and institutions. One way of inserting tobacco control issues on social network in Brazil was through the development of a fan page of the Virtual Health Library Prevention and Cancer Control on Facebook. The focus of this fan page is to promote, through posts, issues related to cancer control. Smoking, known as a risk factor for several types of cancer, occupies a prominent place on this page which allows the interested public to access quality information in a friendly language.

Methodology: Posts are selected through a search on Facebook and other websites, of issues which could be interesting for the fan page public. Videos, papers, information on legislation and other publications are prioritized.

Results: The Facebook page became public in July 2013 and until the end of April, 1,925 people had liked it and consequently became fans. Of this total, 81 % are women and 19 % men. By sex and age group, 25 % are women between 25 and 34 years old, 21 % between 35 and 44 years and 13 % are between 45 and 54 years. Among males, 6 % of the fans of the page are between 25 and 34 years and 3 % between 45 and 54 years. Most fans are Brazilians (1,841). Actually, there are fans in 24 countries around the world. Among Brazilians, 381 are from Rio de Janeiro and 143 from São Paulo. This distribution is related to the fact that INCA, leader of VHL, is located in Rio de Janeiro. The most visualized posts were, in first place, a video of a choir of 12 people with laryngectomy, victims of tobacco and patients of AC Camargo Cancer Center, which occupied a museum in São Paulo performing Beatles songs. The post was visualized by 3410 people and shared 41 times. In second place, a news article regarding the World Conference on Tobacco or Health on which the World Health Organization highlights the harms of waterpipes. The post was visualized by 516 people and shared 20 times.

Conclusion: The Library page on Facebook has become an important means of mobilizing people interested in the topic. The disclosure of matters related to smoking on the page represents a strong strategy for publicizing the issue, in addition to attracting users to the library where they have access to the publications available in its collection.

PC-1312-06 The role of Bloomberg Initiative grants in tobacco control in India and Bangladesh

B Gopalan,¹ R J Singh,¹ R Thakur,² S S Mahbubul Alam,^{3,4} I Chowdhury⁴ ¹International International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Office, New Delhi, New Delhi, ²Consultant, Shimla, India; ³The Union, Dhaka, Bangladesh. Fax: (+91)11 4605 4430. e-mail: bgopalan@theunion.org

Background: Studies have proved that the health outcomes of India and Bangladesh were highly affected due to tobacco use. Both Countries have legislations in place but implementations of activities are sub optimal at grass root level. To support tobacco control policy development & implementation, total grant of US\$12.987 million (59 grants in 16 rounds) have been received. These grants are managed by The Union with population coverage of 652 million in both these countries since 2007.

Intervention: The project team designed and implemented customized interventions as per the policy changes of India and Bangladesh at par with MPOWER strategy. The interventions focused on administrative framework and infrastructure, Capacity Building, Enforcement, coalition building and network, Public Education, Stop Tobacco Industry Interferences and Policy focused research, monitoring and evaluation. Grants were analyzed in terms of population coverage, funding support, capacity building, smoke free jurisdictions, building coalition and partnerships, inter-sectoral involvement.

Results: The activities under MPOWER implementation are progressing towards achieving the objectives in both countries. Grants have built the capacity of National and sub national Governments and local public Health institutions, civil societies and law makers who directly and indirectly associated with tobacco control in the region.

Description

	India	Bangladesh
Population coverage under BI	539 million	113 million
Legislation	2003	2005
Amendment/ strengthening of Legislation	2008–2014	2013
Population protected from secondhand smoke	196 million (36%)	12 million (11%)
No. of BI Grants	41	18
Human capital under existing BI project	93	71
BI grants obligated	US\$9.617 million	US\$3.370 million
Mean utilization	78%	85%
Outcomes: Building of stake holders		
No. of persons trained	0.250 million	0.100 million
No. of network institutions	35	6
Rate of compliance (SF) in project area	90%	85%
No. of smokefree jurisdictions	90 (districts/cities)	16 854 (Public Places)

Conclusion: The BI Grants contributed significantly in prioritising tobacco control in India and Bangladesh. National and sub national governments have benefited from the BI resulting in overall implementation of the MPOWER strategy in India and Bangladesh. BI's continued support is the need of the hour till national/ sub national Governments takes complete lead in Tobacco Control Activities.

PC-1313-06 WHO engagement with Ministry of Finance in South-East Region

N N Kyaing,¹ M Goodchild,² A M Perucic,² M Huq,³ V Munish,⁴ F Qureshi,⁵ D Kania⁵ ¹World Health Organization South-East Asia Regional Office, New Delhi, India; ²World Health Organization, Geneva, Switzerland; ³World Health Organization Bangladesh, Dhaka, Bangladesh; ⁴World Health Organization India, New Delhi, India; ⁵World Health Organization Indonesia, Jakarta, Indonesia. Fax: (+91) 112 337 0197. e-mail: kyaingn@who.int

Background and challenges to implementation: Bangladesh, Sri Lanka and Thailand were the only countries in the Region where the share exceeded 70% of the retail price in 2012. While some countries in the Region employ simple structures of tobacco taxation, others have very complicated structures combining import tariff, excise tax (specific and/or ad valorem), surcharge, local tax and value-added tax. In most countries, the policies have been targeted at cigarettes and have made them more expensive; whereas other tobacco products are subject to lower tax rates, and are allowed to be sold at lower prices. These structures encourage smokers, especially the poor, to switch from the more expensive cigarettes to cheaper products such as hand-rolled cigarettes, bidis and smokeless tobacco. Consequently, tobacco control policies have become less effective.

Intervention or response: World Health Organization had engaged with the Ministry of Finance (MOF) in Member States of WHO South-East Asia Region including Bangladesh, India, Indonesia, Myanmar, Nepal, and Thailand since 2009. MOF personnel get engaged with WHO through courtesy calls, briefings, advocacy workshops, symposia, trainings, study tours and secondment of MOF personnel at WHO, Geneva. WHO tax simulation was applied in the trainings and symposia using country data to estimate increase in tax revenues after raising taxes and simplifying tax systems.

Results and lessons learnt: Bangladesh, India and Indonesia had removed some tiers from the tax system and simplify it. After series of meetings with MOF in India, Ministry of Finance raised the taxes significantly in 2014. Bangladesh and India raised taxes on bidis too and Myanmar has increased the taxes on non-cigarette tobacco products and chewing tobacco twice. Thailand introduced minimum specific floor and increased taxes on roll your own products.

Conclusions and key recommendations: Engaging with Ministry of Finance has brought significant increases in tobacco taxes increasing government revenues and reducing tobacco consumption. The engagement should

be further enhancement and the same measures should be applied in all Member States of WHO.

PC-1314-06 Government and community established model of high compliance of smoke-free provisions of legislation in Tehri, a difficult hilly jurisdiction of India

G Tripathi,¹ R J Singh,¹ Y Pant,² P Tripathi³ ¹International Union Against Tuberculosis and Lung Disease South-East Asia Office, Delhi, ²Government of Uttarakhand, Tehri, ³University of Delhi, Delhi, India. e-mail: tripathi.govind@gmail.com

Background: Indian tobacco control legislation (Cigarette and Other Tobacco Product Act-2003) prohibits smoking in public places. The law mandates that a specific signage informs people about smoke free status of a public place must be displayed at prominent places. Under the law, violators of the smoke free provisions will be fined up to INR 200/- . Tehri (population 6 16 409), a hilly district of Indian state of Uttarakhand, implemented various steps for enforcing smoke free legislation through massive awareness activities, series of capacity building programmes followed by effective law enforcement .This study conducted with an objective to assess the current level of compliance to the smoke free provisions of the law.

Design/Methods: Smokefree compliance surveys are important tools to validate levels of compliance. An unobtrusive cross sectional survey of randomly selected 405 public places in nine administrative blocks of Tehri district was done in the month of January, 2015 by trained investigators using pretested checklist. The five core parameters of evaluation were: Presence of signage, absence of active smoking, absence of smoking aids, absence of tobacco litter and absence of tobacco smell.

Results: The “No smoking signage” informing general public and tourists about smoke free provisions were observed at 86 % of public places; While 95% of public places were found without active smoking. 96.21% public places were observed free from Smoking aids like ashtrays, match boxes & lighters. More than 91% of sampled public places didn't have any tobacco litter (cigarette butts and bidi ends). Over 95% of public places dint have evidence of recent smoking as evident of absence of tobacco smell.

Conclusion: Tehri district has achieved high level of compliance to smoke free provisions of the legislation as a result of increased awareness among general public and custodians of public places. Robust enforcement mechanism established. Pro-active district administration involved all important stakeholders led to this historic achievement. The administration has declared Tehri as first smoke free district of the state. This model has motivated and speeds up the Implementation mechanism of tobacco control in entire hilly and difficult state.

PC-1315-06 Government's pro-public health policies and effective coordination is key for success in tobacco control: a case study from Himachal Pradesh, India

K Thakur,¹ R Thakur² ¹Government of Himachal Pradesh, Shimla, ²World Health Organization-Randstad, Shimla, India. e-mail: healthmin-hp@nic.in

Background and challenges of implementation: Himachal Pradesh (Pop: 7 million, Area: 55 673 km²) is a state in northern part of India. Despite the Indian tobacco control legislation (COTPA), the state was been facing huge tobacco burden. More than one-fifth of adult population in the State is tobacco user. State is not covered under India's National Tobacco Control Programme; as a result the state had major resource constraints in terms of manpower, finance and technical expertise. However, an effective collaboration between the state government, network of local NGOs (HPVHA) and The Union- an International organization worked very well and state became a model for tobacco control in India.

Intervention or response: HPVHA generated massive awareness among general public about the issue, strategically carried out political advocacy with policy makers. The Union provided funding and technical assistance. Government issued relevant circulars, notified squads and simplified the enforcement procedures.

Results and lessons learnt: Collaborated efforts resulted in setting up of an institutional framework for implementation of tobacco control policies. Stringent enforcement was carried out across the state. Till May 2014, more than 80 000 violations has been reported and near Rs 9 million has been collected as fine amount which is further utilized for tobacco control activities. TAPS violations at points of sale are nearly rooted out from the state. First conviction in the country under for TAPS violations, pictorial health warnings on tobacco packs and gutkha ban was carried out in the State. Based upon the findings of compliance survey on an International protocol, the state of Himachal Pradesh was declared “smoke free” in July 2013 by Health Minister. WHO awarded HPVHA and State government in the year 2011 and 2012 respectively for implementing tobacco control policies effectively.

Conclusion and key recommendations: State Government's pro-public health policies formulation and implementation and strategic collaboration between Government and NGOs are always vital for successful implementation of any public health initiative as demonstrated in State of Himachal Pradesh. This model can be replicated in other states in India or other developing countries with similar settings. State Government is currently working on the plan to regulate the to ban the single cigarette sale and mandatory licensing of tobacco vendors.

PC-1316-06 How a standardized capacity building program scaled up National Tobacco Control Program implementation in India

G Tripathi,¹ R J Singh¹ ¹International Union Against Tuberculosis and Lung Disease, South-East Asia, New Delhi, India. e-mail: tripathi.govind@gmail.com

Background: India launched its National Tobacco Control Programme (NTCP) in 2007-08 in 9 states (18 districts) and 12 states (24 districts) in 2008-09. Currently in 53 districts of 29 states. Under the BI initiative The Union provide technical and financial support in 40 districts of 20 states with the objective to build supportive political and administrative environment, establish and strengthen the system, institutionalise enforcement of provisions of National legislation. An analysis conducted to understand that how effectively standardised Capacity building program enhances the pace of Tobacco control implementation.

Intervention: Analysis conducted of 8 state level, 20 district level, 11 law enforcement, 5 municipal corporations, 38 piggy back, 18 WNTD, 68 state and district level training and review programs. In all 168 training/reviews conducted and trained 2550 officials and stakeholders under 8 types of different training programs during Oct-2013 to Mar 2015. Efforts shown good results and capacitated various state and district level authorities, administrative heads, department heads, local bodies, PRI members, media personals, civil society members, Tax authorities, tourism authorities and others. The core parameters of impact evaluation were: Establishment of system, availability of IEC material, establishment of enforcement mechanism, convergence with other stakeholders, Active involvement for issuance of directives/policy notifications, increased level of engagement of Media and civil society organizations

Results: Tobacco control infrastructure established at 85% jurisdictions, availability of awareness related material found at 90% places. Enforcement mechanism is established at 60% places. Multi-stakeholders engagement initiated at 50% places of intervention areas. Issuance of directives/policy notifications increased at 85% places. Increased level of engagement of Media and civil society organizations at 95% places of the all intervention areas.

Conclusions and recommendations: Despite many constraints, a standardised capacity building program under NTCP project has resulted considerable rise in terms of enhancing the capacity of stakeholders. The analysis shows that standardised capacity building programme can have substantial positive effects to implement the NTCP programme in country. While the other tools such as policy level intervention and related to the same, can be readdressed to analyse further strategy for getting good results.

PC-1317-06 Potential of Institute for Global Tobacco Control's online course for health professionals' capacity building: an evaluation

T Ahmad¹ ¹Doctors' Network for the Eradication of Tobacco (DOCNET), Moradabad, India. e-mail: combatobacco@gmail.com

Background: Capacity building of health professionals is one of priority areas in the global fight against tobacco. Institute for Global Tobacco Control (IGTC) at Johns Hopkins Bloomberg School of Public Health, which is a global leader in tobacco-control education and training, has recently launched a short online course aimed at health professionals (http://hp.globaltobaccocontrol.org/online_training). This course entitled, 'Learning from the Experts: A Course for Healthcare Professionals' is available internationally free of cost. Keeping in mind the broader picture of capacity building in low-resource settings, we have undertaken an evaluation of this online course based on the structured feedback received from MBBS students and interns enrolled in a medical college in India.

Design/Methods: Kirkpatrick's four-level evaluation model for training programs was utilised for formulating the design of this evaluation. This pre-, post-, follow-up study was administered to a cohort of 121 final year medical students and interns of Teerthanker Mahaveer Medical College and Research Center, Moradabad. After the baseline survey and briefing about the online course, the participants were required to complete the online course and report to the investigators. A pre-structured questionnaire was used to collect the data in the baseline as well as the post-course survey. Parameters assessed included the feedback of study subjects on various aspects of the course module design and perceived utility. By comparing with the baseline response a change in knowledge and attitude in relation to tobacco-control was also assessed.

Results: Of the 121 students included in the study 97 students completed the post-course survey. 91% of these rated the course as 'Excellent', while 9% of the subjects rated it as 'Good'. 93% believed that the course would be 'Very much useful' in their career as doctors, while 7% believed it to be 'Somewhat useful'. All the subjects (100%) responded that they would 'Recommend' this course to their peers. In the baseline survey only 18% expressed an interest in participating in a research related to tobacco-control while in the post-course survey this rose to 64% ($P < 0.001$). 98% of the students found the course 'Easy' to follow. 27% of the subjects in the baseline survey responded with 'Strongly Agree' to the statement that tobacco-control ought to be taught in greater detail in the medical curriculum, while in the post-survey this rose to 72% ($P < 0.001$).

Conclusion: The online course Learning from the Experts: A Course for Healthcare Professionals can help fill the tobacco control curricular gap in medical schools in a cost-effective way. The slide lecture with audio format employed in the course delivery can work in technologically compromised settings also. Innovative marketing strategies may be applied with designated

funding to promote this course amongst healthcare professionals worldwide.

73. IPT: attitudes, application and adherence

PC-1318-06 Predicting development of active tuberculosis in dialysis patients by serial follow-up of latent tuberculous infection

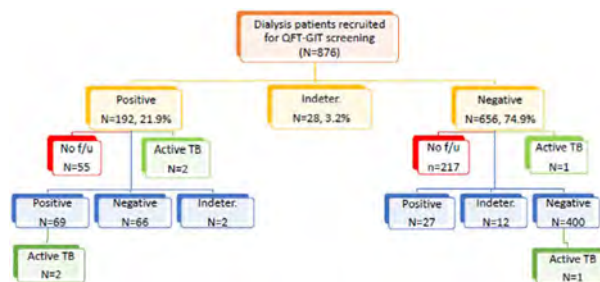
C-C Shu,^{1,2} J-Y Wang,^{1,2} V-C Wu,^{1,2} F-J Yang,³ C-J Yu,^{1,2} L-N Lee,^{1,2} ¹National Taiwan University, Taipei, ²National Taiwan University Hospital, Taipei, ³National Taiwan University Hospital, Yun-Lin Branch, Yun-lin County, Taiwan. e-mail: stree139@yahoo.com.tw

Background: Tuberculosis (TB) is still one of the most common infectious diseases. In preventing transmission of TB, early screening and treating patients with latent TB infection (LTBI) will be a milestone to eliminate TB, especially in TB closely contacts, HIV-infected patients, and patients using immunosuppressants. However, the efficacy for predicting active TB by LTBI is unclear in patients requiring dialysis, who actually have 10~25 fold risk of active TB. Therefore, we conducted the present study following dialysis patients' LTBI status and analyze the performance predicting active TB. **Design:** Patients received long-term dialysis (≥ 3 months) in multiple medical centers in Taiwan were screened from April 2011 to March 2013 under approval of institutional review board. We excluded patients with past history of active tuberculosis, recent exposure to pulmonary TB, and HIV infection or recent use of immunosuppressant. Finally, 876 were enrolled and received Quantiferon-TB Gold In-tube (QFT-GIT) test, used for defining the status of latent TB infection. Among them, 589 patients received QFT-GIT follow up after six months. Primary outcome was active TB, defined by mycobacterial culture positive for *Mycobacterium tuberculosis* or typical histology finding plus treatment response.

Results: The enrolled 876 dialysis patients were at average age of 62.3 years (SD: 13.2) and had male proportion of 53% and hemodialysis at 84.2%. The first time of QFT-GIT was positive in 192 patients (21.9%), negative in 656 (74.9%) and indeterminate in 28 (3.2%). The QFT-GIT six months later reported 98 (16.7%) positive and 474 (80.6%) negative. Among them, there was 69 patients with persistent positive QFT-GIT. In the following up, six (0.68% of 876) patients had been diagnosed as active TB including 3 plueral TB, 1 pericarditis, 1 disseminated type and 1 pulmonary TB. Only 3 (0.51% of 589) of them was diagnosed after 6 months. Two of them had initial positive QFT-GIT (1% of 192) and persistent positivity of QFT-GIT (2.9% of 69). In Kaplan Meier curve, the persistent positive QFT-GIT results was significant associated with active TB development ($P = 0.004$, log rank test).

Conclusion: In dialysis patients, LTBI defined by QFT-GIT test, especially persistent positive in six months later,

can significantly predict active TB and may suggest preventive therapy if no contraindication.



PC-1319-06 Perceptions and knowledge of health care workers plays a role in increasing isoniazid preventive therapy uptake amongst people living with HIV

M Calnan,¹ M Pasipamire,² S Mazibuko,² S Haumba,¹ N Shongwe¹ ¹University Research Co. Mbabane, ²Swaziland National AIDS Programme, Mbabane, Swaziland. Fax: (+268) 2404 7199. e-mail: maricalnan@yahoo.co.uk

Background and challenges to implementation: In 2007, Swaziland implemented the TB-HIV policy guidelines but only in 2011 were the 3T's guidelines produced emphasizing provision of Isoniazid Preventative Therapy (IPT) to reduce the risk of active tuberculosis among people living with HIV. Health care workers (HCWs) received orientation to the 3T's guidelines and facilities supported to initiate IPT. However, the uptake for IPT has remained low (9% nationally). This study aimed to determine HCWs' perceived role in IPT uptake.

Intervention or response: Mixed methods approach including focus group discussion (FGD) for HCWs stationed in HIV clinics and a collection of retrospective data on IPT initiations, adherence and outcomes from electronic medical record and pharmacy databases, patient files and IPT log books in 4 high volume HIV clinics. Data was from patients initiated on isoniazid from January 2012 through to December 2013 and analysed using StatsDirect

Results and lessons learnt: The FGD revealed that 50% (8/16) of HCWs were aware of IPT but are reluctant to provide it due to fears of creating isoniazid resistance or Isoniazid side effects. The other 50% were not knowledgeable about IPT and thus could not talk to patients about it. Documentation by the HCWs in patient files and IPT log book was poor with 45% of patients not being assigned an outcome. Outcomes were retrieved from the electronic database and pharmacy database. Between January 2012 and December 2013, only 1.1% (445/38 756) of eligible patients were initiated on IPT across the four facilities. Of the 350 records reviewed, 67% were female and 95% were aged 20 to 60 years. Only 32% (112) completed treatment, while 56% (196) defaulted their IPT, 5% were LTFU and 2% (7) transferred out. Of patients who had a documented default date, 30% adhered through 4 months of IPT and

28% defaulted after 1 month. Among the defaulters, 88% adhered to ART treatment for 22 months after the default.

Conclusions and key recommendations: The data suggests that patient adherence or clinic attendance and accessibility are not the major problems; rather Health-care worker perceptions and knowledge affect IPT service delivery negatively and need to be addressed as a priority through training and ongoing mentoring.

PC-1320-06 Predictors of isoniazid preventive therapy completion among adults newly diagnosed with HIV in rural Malawi

K Little,¹ G Barnes,² M Khundi,³ L G Ngwira,³ R E Chaisson,² A Nkhoma,³ L Corbett,^{3,4} D Dowdy¹ ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²Johns Hopkins University School of Medicine, Baltimore, MD, USA; ³Malawi-Liverpool Wellcome Research Trust, Blantyre, Malawi; ⁴London School of Hygiene & Tropical Medicine, London, UK. e-mail: klittle@jhsph.edu

Background: As a part of comprehensive HIV care, the WHO recommends that people living with HIV (PLHIV) receive at least 6 months of isoniazid preventive therapy (IPT) once tuberculosis (TB) disease has been excluded. IPT reduces the risk of TB disease in PLHIV, both before and during antiretroviral therapy (ART). However, completion of IPT remains a major challenge in resource-limited settings.

Design/Methods: We evaluated predictors of IPT completion (defined as receipt of ≥ 150 doses of isoniazid) in newly diagnosed PLHIV recruited from 8 rural primary clinics in Malawi, as part of a cluster-randomized trial of TB screening. Participants who presented for antenatal care or symptomatic diagnosis were screened for TB and offered IPT on the same day as their HIV test. Individuals reporting one or more symptoms of TB (cough, fever, night sweats, and/or weight loss) received further microbiological evaluation via sputum smear microscopy or Xpert MTB/RIF before initiating IPT in order to rule out active TB disease. ART initiation criteria included WHO Stage 3 or 4, CD4 cell count < 350 , or pregnancy/breastfeeding. Our analysis includes all participants who started IPT by June 1, 2014. Predictors of IPT completion were evaluated using a multilevel logistic regression model with patient- and clinic-level characteristics.

Results: Of 828 trial participants screened negative for active TB and started on IPT, median (interquartile range, IQR) age was 34 years (26-40), and 67% were women (551/828, 66.6%) (Table 1). Overall, 612 (73.9%) completed ≥ 150 doses of IPT, although 8% of these individuals reported treatment interruptions of ≥ 2 months before completion. The mean duration of IPT taken was 190.3 days (IQR: 167-202) in completers and 90.3 days (IQR: 28-139) in non-completers ($P < 0.001$). On univariate analysis in a multi-level model, older age (OR: 1.21, 95%CI: 1.10-1.32), and receipt of ART (OR: 3.26, 95%CI: 2.00-5.31) were significantly associated with IPT completion. After controlling for potential confounders, concomitant ART (aOR: 3.85,

95%CI: 2.27-6.52) and older age (aOR: 1.16, 95%CI: 1.03-1.30) significantly increased the odds of IPT completion, while WHO stage III/IV at baseline was significantly associated with decreased odds of completion (aOR: 0.51, 95%CI: 0.31-0.85).

Conclusion: In this population of rural Malawian adults recently diagnosed with HIV, completion of IPT was associated with concomitant receipt of ART, older age, and WHO stage. Our findings highlight the importance of additional efforts to ensure IPT completion among younger HIV patients, those with clinically advanced HIV, and those not immediately eligible for ART.

PC-1321-06 Population-level impact of different durations of isoniazid preventive therapy among people living with HIV

A Kunkel,^{1,2} F Crawford,² T Cohen² ¹Harvard School of Public Health, Boston, MA, ²Yale School of Public Health, New Haven, CT, USA. e-mail: agkunkel@gmail.com

Background: The World Health Organization recommends the use of at least 6-9 months of isoniazid preventive therapy (IPT) among people living with HIV (PLHIV) who are deemed unlikely to have active TB on the basis of symptom screening. Longer durations of IPT among PLHIV could further reduce risks of TB at both the individual and community levels. However, extending the duration of IPT could also exacerbate concerns about the risk of side effects and the potential for increased resistance to isoniazid.

Design/Methods: We have created a mathematical model to assess the potential health costs and benefits of varying IPT durations in terms of TB incidence, drug resistance, and mortality. Our model incorporates TB transmission and treatment dynamics as well as HIV incidence and antiretroviral uptake. Unlike previous IPT models, this model simulates IPT on the backdrop of existing isoniazid, rifampicin, and multi-drug resistant TB and includes mixed infections with up to four distinct strain types (pan-sensitive, isoniazid mono-resistant, rifampicin mono-resistant, and multi-drug resistant). We estimated model parameters using data from the joint TB and HIV epidemics in Botswana.

Results: Using this model, we evaluated a range of IPT durations in Botswana, using mortality as the primary outcome measure to evaluate the composite effects of IPT on isoniazid-sensitive and isoniazid-resistant TB. Our results show that changing the duration of IPT would affect the prevalence of both isoniazid-sensitive and isoniazid-resistant TB. The optimal duration of IPT varies depending on the time horizon of interest, with more aggressive IPT strategies supported in some circumstances despite increases in the prevalence of drug resistance.

Conclusion: These results suggest that concerns about increases in isoniazid resistance that could result from longer IPT durations should be balanced against the potential benefit of reductions in drug sensitive TB. The development of novel TB drugs and regimens will play a crucial role in mitigating concerns about future increases

in isoniazid resistance resulting from extended IPT durations among PLHIV.

PC-1322-06 Biologic anti-rheumatoid agents alter interferon-gamma release assay results for detection of latent tuberculous infection

W Thanassi,^{1,2} J Chang,¹ J Sokolove^{1,2} ¹Department of Veterans Affairs, Palo Alto, CA, ²Stanford Medical Center, Palo Alto, CA, USA. e-mail: wendy.thanassi@gmail.com

Background: Since the risk for development of active tuberculosis disease is several-fold greater in individuals taking immunosuppressive medication for rheumatoid arthritis and other autoimmune conditions, screening for tuberculosis (TB) infection is routine practice. Testing for latent TB using interferon-gamma release assays (IGRA) is commonplace. Our objective was to determine the influence of two common biologic anti-rheumatoid agents on the results of the two available interferon-gamma release assays in a known positive test result cohort.

Methods: Whole blood from ten adults in California, United States who had childhood TB exposure risk factors and who had tested positive by IGRA twice previously was exposed in-vitro to a 1:120 dilution (twice therapeutic) of etanercept (Enbrel™) and abatacept (Orencia™). The IGRAs elispot (TB.TSPOT™) and the enzyme-linked immuno-assay (ELISA) (QuantiFERON™) (QFT) were run on the drug-exposed and unexposed samples by Oxford Laboratories, Tennessee and in the Palo Alto Veterans Affairs Hospital, California clinical laboratory, respectively. Control tubes had an equal volume of polyclonal immunoglobulin without biologic agent added. Results of the assays were compared against their nils by paired *t*-test.

Results: One individual was excluded for excessive reactivity at baseline. All nine remaining participants had declines in their QFT result with abatacept ($P < 0.001$) and etanercept ($P < 0.01$). Individual declines varied from 7-60% with abatacept and from 34-81% with etanercept (see Figure). Neither the ESAT-6 nor CFP-10 TB antigen panels on the elispot showed a significant change in response to either drug.

Conclusions: While anti-tumor necrosis factor- α chemotherapy has been associated with decreased IGRA response to tuberculin antigens, such response has not been shown with the CTLA-4 Ig agents abatacept or belatacept. We theorize that the elispot did not show the same response decline as the elisa IGRA because the cells are washed prior to exposure to TB antigen, which may result in a more accurate immunologic response. Such findings have implications for the selection of IGRA used in TB screening of adults being treated by the chemotherapeutic agents and drug classes.

PC-1323-06 Improving implementation of isoniazid preventive therapy through community-based referral in rural South Africa

S Sheno, ¹ A P Moll, ² T Van Der Merwe, ² P Vranken, ³ L Andrews, ¹ R P Brooks, ¹ E K Dokubo, ⁴ G Friedland ¹ ¹Yale University School of Medicine, New Haven, CT, USA; ²Church of Scotland Hospital, Tugela Ferry, ³Centers for Disease Control and Prevention, Pretoria, South Africa; ⁴U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. Fax: (+1) 203 737 4051. e-mail: sheela.sheno@yale.edu

Background: Isoniazid preventive therapy (IPT) is an effective World Health Organization-endorsed strategy to reduce TB incidence among HIV-positive persons. South Africa has among the highest TB incidence rates globally (860/100 000) and more than 5 million people living with HIV. IPT has been slow to be effected and faces obstacles to widespread implementation. New strategies to improve its successful uptake are urgently needed.

Design/Methods: Through a community-based intensive case finding program in rural South Africa, we identified HIV-positive community members without fever, cough, night sweats, or weight loss and referred them to the government health care clinics for IPT. We measured IPT uptake, provided adherence training, and measured monthly monitoring, and six-month treatment completion. Adherence was measured by self report and isoniazid metabolite testing in urine.

Results: Among the first 184 community members enrolled, the median age was 35 (IQR 29-45), 152 (82.6%) were female, and 92 (50%) had CD4 >350 mm³. Subjects made 640 (85%) of 752 scheduled visits; to date, 58 have completed the IPT course, 3 were lost to follow up, and 1 patient died of unrelated causes. Among 640 urine tests conducted, 603 (94%) demonstrated INH metabolites. Self report overwhelmingly (93%) concurred with urine testing results.

Conclusion: Preliminary data suggests that community members in TB and HIV endemic areas are interested in TB prevention and willing to participate in IPT. Community members who are HIV-positive but have not entered treatment can be engaged in care through IPT, and even if not yet qualifying for ART by CD4 criteria can successfully adhere to IPT alone. Self report may be a successful predictor of adherence. Offering IPT to those not yet engaged in HIV care may be a viable method of expanding IPT and reducing TB incidence.

PC-1324-06 Impact of pregnancy on latent tuberculous infection diagnostics in HIV-infected pregnant women in western Kenya

S Lacourse, ¹ L Cranmer, ^{1,2} D Matemo, ^{1,3} J Kinuthia, ^{1,3} D Horne, ¹ G John-Stewart ¹ ¹University of Washington, Seattle, WA, ²Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, USA; ³Kenyatta National Hospital, Nairobi, Kenya. e-mail: smlacourse@gmail.com

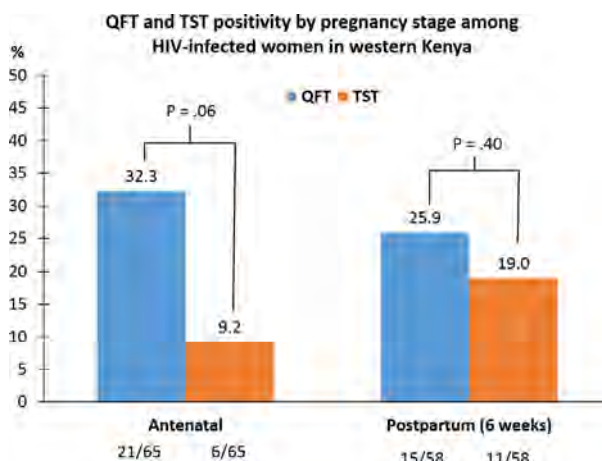
Background: Maternal TB-HIV co-infection is associated with poor maternal and infant outcomes. Pregnancy provides a unique opportunity for TB prevention efforts.

Latent TB infection (LTBI) treatment benefit is most clearly demonstrated in those with evidence of *M. tuberculosis* infection by tuberculin skin tests (TST) or interferon-gamma release assays (IGRA). The impact of pregnancy on LTBI diagnostics in HIV-infected women in sub-Saharan Africa is unknown.

Design/Methods: In this ongoing longitudinal study, LTBI testing was performed on HIV-infected pregnant women in two antenatal clinics in western Kenya. TST and IGRA [QuantiFERON (QFT)] were performed at enrollment during pregnancy. Sputum culture was performed irrespective of symptoms. Women with negative or discordant QFT/TST were retested 6 weeks postpartum.

Results: Of the 100 women enrolled between August 2014-January 2015 with negative sputum culture, 65 have completed post-partum follow-up with median age of 27 years (IQR 22-32), CD4 of 563 cells/ μ l (IQR 315-780), and gestational age of 30 weeks (IQR 24-32). The majority (95%) were taking combination antiretroviral therapy. More women had positive QFT vs. TST at baseline (21/65 [32.3%] vs. 6/65 [9.2%], $P=0.06$); 6.2% were concordant positive (QFT+/TST+) and 50.8% were concordant negative. Ten (15.4%) women had indeterminate QFT (9 TST-, 1 TST+). IGRA/TST agreement in pregnancy was 56.9% ($\kappa=0.13$, 95%CI -0.02-0.21). Between pregnancy and 6 weeks postpartum, 9 (16.1%) had TST conversion; 1 had QFT conversion. LTBI test reversion occurred in 3 women (1 TST, 2 QFT). The majority of women with indeterminate pregnancy QFTs (9/10) were negative at postpartum. Postpartum IGRA/TST had higher agreement (86.2%, $\kappa=0.61$ 95%CI 0.36-0.85), with 15/58 (25.9%) and 11/58 (19.0%) positive QFT and TST, respectively ($P=0.40$). Overall mean QFT IFN- γ was higher in postpartum (.96 vs. 2.43 IU/ml, $P=0.04$). Baseline report of TB contact was associated with postpartum positive QFT but not TST (QFT+ OR 3.8, 95% CI 1.1-13.7 vs. TST+ OR 1.7 95%CI 0.4-6.7).

Conclusion: LTBI testing performance varies by pregnancy stage among HIV-infected pregnant women in western Kenya, with more QFT positive women compared to TST during pregnancy. TST conversion in the early postpartum period in the setting of relatively consistent IGRA positivity may reflect pregnancy associated TST anergy. A reliance on TST could miss a considerable number of women potentially benefiting from LTBI treatment.



PC-1325-06 Tuberculosis screening and isoniazid Preventive therapy provision among patients initiating antiretroviral therapy, Nigeria, 2004–2012

I Pathmanathan,¹ E K Dokubo,¹ S Ray,¹ D Onotu,² S Odafe,² I Dalhatu,² H Debem,² S Agolory¹ ¹U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Centers for Disease Control and Prevention, Abuja, Nigeria. e-mail: ydi6@cdc.gov

Background: Tuberculosis (TB) is the leading cause of mortality among people living with HIV (PLHIV), and often goes undiagnosed. Nigeria had the most AIDS-related deaths worldwide in 2013 (210 000), of which 39% were associated with TB. Since 2004, the World Health Organization (WHO) has recommended collaborative TB and HIV activities, including routine screening of all adult PLHIV for TB using a four-symptom screen, and the offer of isoniazid preventative therapy (IPT) to those unlikely to have active TB. We assessed TB screening and IPT provision among adults initiating ART in Nigeria between 2004 and 2012 to identify missed opportunities for TB diagnosis and prevention.

Design/Methods: We analyzed retrospective cohort data from a nationally representative sample of ART patients ≥ 15 years old who were enrolled in U.S. President's Emergency Plan for AIDS Relief (PEPFAR)-supported care and treatment programs from 2004 to 2012. Data were abstracted from 3,496 patient records at 35 sites selected using probability-proportional-to-size (PPS) sampling. Analyses were weighted and controlled for the complex survey design. Logistic regression was used to assess if ART start year was associated with TB screening among PLHIV initiating ART.

Results: Ninety-two percent (95%CI 91.1-92.9%) of patients initiating ART were screened for TB. Of those, 4.2% (95%CI 3.2-5.4%) were already on TB treatment, 1.2% (95%CI 0.6-2.3%) reported prior TB, and 6.7% (95%CI 4.7-9.6%) were documented as having "suspected TB", indicating a positive TB symptom screen. There was no statistically significant association between year of ART enrollment and TB screening, with those enrolled in 2010-2012 having an odds of being screened only 1.1 times greater than those enrolled in 2004-2006 (OR: 1.1; 95%CI 0.5-2.7). Only 0.5% (95%CI 0.2-1.1%) of patients eligible for IPT (without suspected or prior TB and not on TB treatment) were on IPT at ART initiation.

Conclusion: A high proportion of PLHIV initiating ART are screened for TB in Nigeria; HIV facilities should continue to screen these patients at every clinical encounter to facilitate timely TB diagnosis and treatment for co-infected patients. IPT uptake in Nigeria for eligible PLHIV is poor. An effective implementation system is required to increase provision of IPT for PLHIV with a negative TB symptom screen, in accordance with WHO and national guidelines, in order to reduce their risk of developing active TB.

PC-1326-06 Modelling the post-treatment effect of isoniazid plus antiretroviral therapy on tuberculosis incidence

T Sumner,¹ R Houben,¹ G Maartens,² M Rangaka,³ R White¹ ¹London School of Hygiene & Tropical Medicine, London, UK; ²University of Cape Town, Cape Town, South Africa; ³University College London, London, UK. e-mail: tom.sumner@lshtm.ac.uk

Background: Trials of isoniazid preventive therapy (IPT) for people living with HIV in high tuberculosis (TB) incidence settings in the absence of antiretroviral therapy (ART) have shown limited duration of protection against TB disease following completion of therapy. This may be due to reinfection or reactivation of existing infections which were insufficiently treated. Recently published data from a pragmatic trial of IPT among people on ART in Khayelitsha, Cape Town, South Africa (Rangaka et al, 2014) suggested that the effect of IPT persisted in the first year after completion of IPT, longer than observed in trials in ART-naïve individuals. We used mathematical modelling to explore if this increased duration of protection may be due to an increased curative ability of IPT when given in combination with ART.

Methods: A mathematical model describing *Mycobacterium tuberculosis* transmission in a cohort of HIV-infected individuals after completion of IPT was used to analyse data from the Khayelitsha trial to estimate the annual risk of infection (ARI) and the proportion of individuals whose latent TB infection (LTBI) was "cured" by IPT.

Results: The model captures the trends in TB incidence in the placebo and interventions arms observed during the trial. The estimated ARI was 4.0% (2.6-5.8) and the estimated proportion of individuals whose LTBI was cured following IPT was 35.4% (2.4-76.4%). The proportion cured was sensitive to assumptions about isoniazid resistance; if all infections were assumed to be susceptible the proportion cured was lower at 23.2% (0.1-61.5%). Immediately following completion of IPT the majority of disease in the model was due to reactivation of uncured infection, however over time the proportion of disease due to recent infection increased. The cumulative proportion of disease that occurred in individuals cured by IPT was estimated to be 7.8% (0.4-32.1).

Conclusions: Our results suggest that IPT can cure LTBI in approximately 35% of HIV positive individuals also taking ART, and therefore provide protection beyond the period of IPT. In low incidence settings, 12 months of IPT in combination with ART may provide additional long term benefit to HIV-positive individuals. However the durability of this protection will be limited in high incidence settings where there is a continued risk of exposure to re-infection and continuous preventive therapy together with improved infection control efforts would be required to provide long-term protection against TB.

SHORT ORAL ABSTRACT SESSIONS

01. Across the spectrum of TB management

SOA-600-06 New strategy for the treatment of tuberculosis with hepatotoxicity free anti-tuberculosis drug

C-Y Tsai,¹ T-Y Shih,¹ H-T Ho,¹ W-J Su,² Y-W Huang,³ W-C Perng,⁴ F-Y Chang,⁴ O Y-P Hu¹ ¹National Defense Medical Center, Taipei, ²Taipei Veterans General Hospital, Taipei, ³Chang Hua Hospital, Chang Hua, ⁴Tri-Service General Hospital, Taipei, Taiwan. e-mail: chanyentw@gmail.com

Background: Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) reported that one-third of the world's population has latent TB, and roughly 9 million cases of active TB emerge annually, resulting in 2-3 million deaths. These data exemplify the importance of the problem, especially as most new cases occur in populated nations, including India and China. Currently available anti-TB drugs (isoniazid [INH], rifampin [RIF], and pyrazinamide [PZA]) cause serious hepatic side effects, especially in patients with liver dysfunction. Cytochrome P450 2E1 (CYP2E1) and amidase synergistically contribute to RIF- and INH-induced hepatotoxicity. To prevent anti-TB drug-induced hepatotoxicity, a new, hepatotoxicity-free formulation of traditional anti-TB drugs was developed by inhibiting CYP2E1 and amidase activity.

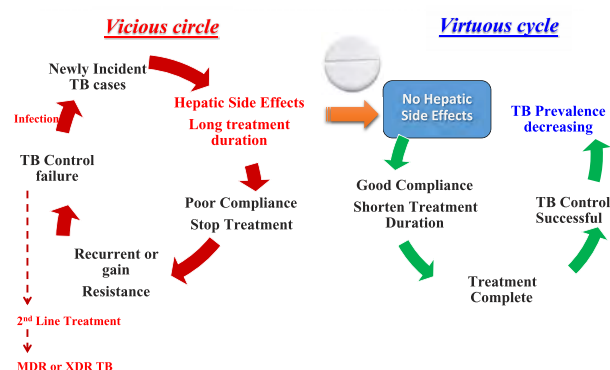
Methods: Numerous known pharmaceutical excipients were screened as CYP2E1 or amidase inhibitors in vitro and in vivo. The most active inhibitor was used to develop a hepatotoxicity-free formulation with INH, RIF, and PZA.

Results: An FDA-approved, classified as "Generally Recognized As Safe (GRAS)", excipient was shown to be a CYP2E1 inhibitor. This excipient can also inhibit amidase activity at similar concentrations. In both animal and human studies, the selected agent significantly inhibited the activity of CYP2E1 (up to 58%) and amidase (up to 70%) in vivo. Pathology data revealed that drug-induced hepatotoxicity was nearly eradicated. Furthermore, the inhibitor did not affect the area under the curve (AUC)_∞, maximum concentration (C_{max}), and anti-TB effects of active ingredients (INH, RIF and PZA). A randomized, double-blind, active drug controlled, multi-center phase III clinical study is currently underway in 15 medical centers to assess the efficacy of the new anti-TB formulation to reduce anti-TB drug-induced liver injury.

Conclusion: We have developed a new, hepatotoxicity-free formulation of traditional anti-TB drugs, which has successfully entered phase III study. We expect this hepatotoxicity-free anti-TB drug at high doses will both shorten TB treatment time and improve compliance in TB patients. Consequently, this may decrease the incidence of multi-drug resistant (MDR)-TB. Thus, this

hepatotoxicity-free anti-TB drug will dramatically change TB prevention and treatment.

Unmet Medical Needs for TB Treatment



SOA-601-06 High transfer-out affecting hospitals' performance in tuberculosis treatment outcomes

S Gebreyes,¹ D Habte,¹ Z Dememew,¹ I Jemal Abdulahi,² D J Dare,¹ M Nigussie,³ M Aseresa Melese,¹ P G Suarez⁴
¹Management Sciences for Health, Help Ethiopia Address the Low TB Performance (HEAL TB), Addis Ababa, ²Oromia Regional Health Bureau, Addis Ababa, ³Amhara Regional Health Bureau, Bahar Dar, Ethiopia; ⁴Management Sciences for Health, Center for Health Services, Arlington, VA, USA.
 Fax: (+25) 111 661 6824. e-mail: solomon_ngsh@yahoo.com

Background and challenges to implementation: Directly Observed Treatment for TB patients is implemented at hospital and primary health care unit levels. The USAID-funded Help Ethiopia Address the Low Performance of TB (HEAL TB) project in collaboration with the national TB program (NTP) has been providing technical and material support to all the Hospitals and Health Centers (HCs) in Amhara and Oromia Regions since 2011.

Intervention or response: NTP with support from HEAL TB provided capacity building for TB program managers at different levels, training of health professionals at hospital and HC levels, laboratory capacity building including quality assurance, mentoring and supportive supervision. In this report, we compared the TB treatment outcomes between Hospital and HC registered TB patients in the 10 zones of the initial phase of project implementation.

Results and lessons learnt: The project supported treatment of 18 874 new smear positive pulmonary TB (SS+) patients in the hospitals (1208) and HCs (17 666) between October 2011 and June 2014. Treatment success rate (TSR) among hospital enrolled patients improved from 59.6% at baseline to 80.2% at the end of the third year and from 85.7% to 90.9% in the HCs. The improvement in cure rate (CR) over three years in the hospitals was from 51.6% to 74.2% whereas the corresponding progress in the HCs was from 69.1% to 85.3% (Figure 1). The average rate of annual decline in unfavorable outcomes (transfer out (TO), default, death

and treatment failure) was higher in the hospital group as compared to the HC counterpart (19.1% vs. 4.0%, $P < 0.05$). The baseline and latest TO in the hospital were 28.7% and 10.3 % in contrast with the 6.4% and 2.5% at the HCs ($P < 0.05$). Default and death showed decreasing trend in both hospitals and HCs with the latest rate for the hospital and HCs being 2.8% and 1.5% default ($P > 0.05$) respectively; and 2.8% and 2.6% deaths ($P > 0.05$) respectively. Treatment failure at the end of the third year was 4% and 2.4% ($P > 0.05$) at hospitals and HCs respectively.

Conclusions and key recommendations: The relatively higher TO in the hospitals and failure of the hospitals to trace the final outcome underestimated their TSR and CR as compared to the HCs. In the hospitals, the TO rate has declined significantly in three years because of the referral of hospital diagnosed TB patients to the patients' nearest health center for DOT. Further effort is required to reduce the TO in hospitals and trace the outcome from the receiving health facilities.

SOA-602-06 Thrice-weekly dose of anti-tuberculosis drugs: efficacy under India's program conditions

R Kakar¹ ¹RNTCP, District TB Center, Faridabad, State Haryana, India. e-mail: raman24march@yahoo.com

Background: When discovered, anti tuberculosis drugs were always administered in Daily-doses. That worked wonders! Later, some studies claimed that drugs were equally effective even if given as thrice-weekly doses (intermittently). Not everyone believed that. Three Reviews (Cochrane, Thorax, Azhar) appear unconvinced! Most nations worldwide (including 20 High TB Burden Countries) remain skeptic and continue to practice time-tested Daily dosing! However, India is exception. In 2000, India adopted a unique thrice-weekly regimen. During 14 years, under national program, Thrice-weekly doses have been administered to 14.2 million TB patients, self-claiming 85% success. Objective: To revisit long-term fate of all registered patients; identify the ones, who clearly didn't achieve lasting cure with a single course of thrice-weekly treatment, were later re-registered for a second innings; thus, their names figure twice in national registry (nicknamed herein as Repeaters). Setting: Author heads District Tuberculosis Center, Faridabad, India; his job has been to monitor thousands of current / ex-patients on Thrice-weekly regimen, by providence, offering him unique access to patients, data and entire network of TB workers of district.

Design/Methods: Two methods of data collection: Retrospective Record Review: Author motivated district work-force; jointly conducted systematic review of hand-written registers of past 14 years, one at a time – thus identified 1575 Repeaters. Clinical Audit: Author conducted exhaustive clinical audit in his busy TB OPD, cherry-picked (on an average) one repeater per day; thus tracked 1600 Repeaters in 42 months (Of these, 800 were referred in for Re-treatment, duly diagnosed at

Delhi's premier TB institutes and needed local registration).

Results: Long-term fate of 27 120 registered TB patients was analyzed. 3175 patients noticed to have returned – sick, meriting Re-treatment; thus over 11.7 % identified as Repeaters - registered twice/thrice (names, unique govt. ID's, irrefutable evidence enclosed) – revealing an unfavorable outcome, unreported anywhere thus far - a bubble within. Besides, study found 1282 (5.4%) Deaths; 2271 (9.6%) Defaulters – recorded similarly with clinching details.

Conclusion: Under India's routine program conditions, thrice- weekly regimen is ineffective. Too many (11.7%) patients come back sick, which may promote drug-resistance on industrial scale!

SOA-603-06 Assessing the quality of diagnosis, treatment service and adherence monitoring by private practioners to TB patients in India: a case study from Himachal

A Singh¹ ¹Office of the CMO, Solan, India. Fax: (+91) 179 222 4151. e-mail: dpo3solan@gmail.com

Background: Private Practioners in India treats more than half of tuberculosis patients; infact are the first point of contact. Private sector often has been blamed for non-standardized diagnosis, irrational treatment and biggest contributor to spreading drug resistance. Present study was conducted with an objective to assess quality of diagnosis, treatment service and adherence monitoring provided by private practioners in Himachal Pradesh in India.

Design/Methods: In April 2015, a list of TB patients diagnosed, initiated on treatment and notified by private sector from third quarter 2012 to 1st quarter 2015 in Solan district in Himachal Pradesh was extracted from the web based system called Nikshay. After obtaining consent from patients, each one of them were contacted and interviewed; responses were recorded in a case record form. Medical records were also studied in details.

Results: Out of total 126 patients notified by the private sector, 90 patients and attendants of four deceased patients were interviewed. Cough (85%) was the most common symptoms reported by the patients. Near one-third patients also reported fever along with cough. Few patients (16%) also reported loss of weight. X-ray examination (79%) was the most common investigation followed by blood investigation (74%), sputum smear examination (55%), pleural fluid cytology (22%), and FNAC (1%). Patient also reported a variable treatment history; 11% patients were on single drug, 28% patients were on two drugs, whereas near half of the patients were on three drugs regimen. Near one-fourth of patients were also given injections. No INH prophylaxis was given to children lesser than six years of age who were in contact of 13% of cases. Treatment duration ranged from three months in 13% patients to >1 year in 8%. All doses were self-administered. 12 cases opted for taking DOTS in the public hospital. None of the patients were monitored by the PP. Total 22 (23%) cases were cured, 46 (48%)

relapsed, 17 (18%) defaulted, 5 (5%) were failure and 4 (4%) died.

Conclusion: There are major limitations in the quality of diagnostic and treatment services by the private practioners, which is reflected as a poor treatment outcome. Non-standardized diagnostics and inappropriate treatment regimen by PP are a major challenge for tuberculosis control and a cause for impending drug resistance. Each private practioner must be provided training on Standard for TB care in India.

SOA-604-06 Factors for diagnostic delay in smear-positive tuberculosis patients: Patna, India

S Mannan,¹ S Dhawan,² S Upadhyay,³ K Sahai,³ K Rade,¹ A Sreenivas,¹ N Kulshreshta⁴ ¹World Health Organization Country Office, New Delhi, ²International Union Against Tuberculosis and Lung Disease South-East Asia Office, New Delhi, ³State Health Services, Bihar, Patna, ⁴Central TB Division, New Delhi, India. e-mail: alitangni@gmail.com

Setting: East Indian District of Patna with a population of 5.6 million (urban 43% and rural 57%).

Objective: To estimate the duration between onset of symptoms and diagnosis of smear positive TB patient in the Microscopy Centres of Patna and assess whether age, gender, literacy, knowledge on TB and the source of first health care provider are associated with delay from onset of symptoms to diagnosis of TB.

Method: A community based cross-sectional study was conducted with structured questionnaire, which included data from the laboratory register for smear positive diagnosed.

Results *: During the study period (December 2012-February 2013), 311 Smear-positive tuberculosis patients were diagnosed, of whom 164 were enrolled, 140 (85%) were successfully interviewed, 18 (11%) could not be traced, 4 (2%) refused and 2 (1%) died. The median age was 27 years (range: 14-70), 51% lived in rural and 49% in urban areas. The reason for approaching government health provider were "Proximity" (40/61, 66%) and for private provider were "Faith in the provider" (27/38, 71%). The delay was longer if the patient, was a male (75 days vs. 30 days), unemployed (135 vs. 60) and contacted providers other than the government (150 days vs. 60 days $P < 0.001$). Awareness about DOTS had shorter delays and the odds were 0.9 (0.4-1.8) compared to participants not aware. Participants having knowledge about tuberculosis before being diagnosed had an odd of 1.8 (.9-3.6) to delay to those who had no knowledge of tuberculosis. The median delay for patients with cough 74 (53%) was 60 days while it was 30 days for those with fever 40 (29%).

Conclusions and key recommendations: After 14 years of NTP in the district, there is median delay of 53 days in diagnosing smear positive TB. Dissemination of information regarding the signs/symptoms of TB and the availability of free services under NTP is to be re-examined considering the delay in patients with cough more than that with fever. Though the patients are reaching the diagnostic facility, ensuring laboratory

examination is done on the same day will reduce delay within the system. Also delay is less if the first care provider is government though 56% first sought medical services from non-government providers. The policy of the state with regards to the rural health providers need to be reassessed considering the proportion of patients for whom they are the first health care provider.

SOA-605-06 Major delays in the diagnosis and management of tuberculosis patients in Nepal

R Mahato,¹ W Laohasiriwong,¹ R Koju,² K Biraj,² K Vaeteewootacharn¹ ¹Khon Kaen University, Khon Kaen, Thailand; ²Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel, Nepal. Fax: (+977) 011 490 707. e-mail: mahatoroshank@gmail.com

Background: Early diagnosis is determining factor for spread of this lethal disease as delay in diagnosis and treatment of tuberculosis geometrically increases spread and infectivity of the disease and is associated with higher risk of mortality. The present study aimed to investigate the delays associated with diagnosis and treatment among new pulmonary tuberculosis patient in central development region of Nepal.

Design/Methods: An analytical cross-sectional study was conducted by administration structured questionnaire interview and reviewing the medical record of the new sputum smear positive pulmonary tuberculosis cases during January – April 2015. Simple random sampling was applied to select 5 districts from 19 districts of all 3 ecological regions of Nepal. Delay in diagnosis is collective term for patient delay and health system delay. The patient delay refers to the time interval between onset of disease till patients approaches the formal health facilities. Similarly, health system delay is the time for complete diagnosis of the disease after patient approaches for formal health care provider. An acceptable patient and health system delay was 30days and 7 days respectively.

Results: A total of 374 new sputum smear positive pulmonary tuberculosis cases were included in the study. The mean age of participants was 39.67 years $\pm$ 18.56 years. The majority (62.57%) of the patients were male and married (66.58%). A total of 33.16% were from the rural part of Nepal and 30.75 % were illiterate. The median patient delay, health system delay, and total delay was 32days, 3 days and 39.5days respectively. An unacceptably high patient and health system delays were observed in 52.83% and 23.89% patients respectively.

Conclusion: Nepal has still a significant problem of TB diagnosis and treatment. Most of the delay was caused by patients because of the accessibility. Identifying major delays and developing evidence-based approaches to address those delays will help in advancing tuberculosis prevention and management in low-income settings. This will also be the key to success for reducing TB burden.

SOA-606-06 The impact of the duration of clofazimine administration with first-line drugs in a mouse model of tuberculosis chemotherapy

N Ammerman,^{1,2} R Swanson,^{1,3} B Ngcobo,¹ C Moodley,¹ A Dorasamy,¹ S Modley,¹ S Singh,⁴ J Grosset^{1,2}

¹KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, South Africa; ²Johns Hopkins University School of Medicine, Baltimore, MD, USA; ³University of KwaZulu-Natal, Durban, ⁴University of KwaZulu-Natal, Westville, South Africa. e-mail: nicole.ammerman@gmail.com

Background: The addition of the anti-leprosy drug clofazimine to the first-line drug regimen for tuberculosis (TB) decreased the duration of treatment (from 6 months to 3 months) necessary to achieve relapse-free cure in the mouse model of TB chemotherapy. Because clofazimine accumulates to extremely high levels in the tissues and has a very long half-life (weeks to months), we hypothesized that clofazimine may not need to be administered with the first-line regimen for the entire duration of TB treatment to exert its potent bactericidal and treatment-shortening activity.

Design/Methods: To address our hypothesis, we used the mouse model of TB chemotherapy to evaluate the activity of first-line regimens in which clofazimine has been incorporated in different administration schemes. *Mycobacterium tuberculosis*-infected BALB/c mice were treated for 4 months with one of the following regimens: (i) no drug control; (ii) standard regimen control, 2RHZE/2RH (2 months of rifampicin [R], isoniazid [H], pyrazinamide [Z] and ethambutol [E] followed by 2 months of R and H); (iii) 2RHZC/2RHC (previously tested clofazimine [C]-containing first-line regimen); 2RHZC/2RH (clofazimine only administered during the first 2 months); and (iv) 2RHZC/2C (only clofazimine administered after the first 2 months). Treatment outcomes were bacterial counts in the lungs during treatment and the proportion of culture-positive relapses 6 months after stopping treatment.

Results: After 3 months of treatment, mice receiving any clofazimine-containing regimen had significantly lower bacterial burdens in the lungs compared to mice receiving the standard regimen; however, after 4 months of treatment, only mice receiving the 2RHZC/2C remained culture-positive. Six months after stopping treatment, mice that received the clofazimine-containing regimens had significantly less culture-positive relapse compared to mice receiving the standard regimen: 2RHZE/2RH, 2RHZC/2RHC, 2RHZC/2RH, and 2RHZC/2C had relapse-free cure rates of 53%, 87%, 93% and 80%, respectively.

Conclusion: As part of a first-line regimen, clofazimine might equally contribute to the overall antimicrobial activity when included only in the intensive phase (first 2 months) of TB treatment. Further studies are needed to optimize the dosing of clofazimine, especially considering the role of the sustained release of the drug from the tissues after stopping treatment, to maximize its therapeutic potential for TB.

SOA-607-06 Hepatotoxicity of a high-dose rifampicin treatment regimen among HIV-infected tuberculosis patients in West Africa: findings from the RAFA trial

C Merle,¹ S Floyd,² D Affolabi,³ B Bah,⁴ A Ndiaye,⁵ I Mbaye,⁵ M Sarr,⁵ O Bah-Sow⁴ ¹World Health Organization, Geneva, Switzerland; ²London School of Hygiene & Tropical Medicine, London, UK; ³Centre National Hospitalier de Pneumo-Phtisiologie, Cotonou, Benin; ⁴Ignace Deen Hospital, Conakry, Guinea; ⁵Programme National de Lutte Contre le Paludisme, Dakar, Senegal. e-mail: merlec@who.int

Background: Around 30% of HIV-TB patients die by 12 months after starting TB treatment and the early mortality appears to be TB-related, rather than HIV-related. More aggressive TB treatment might improve treatment outcomes and reduce mortality.

Design/Methods: The RAFA trial is an open label, 3 parallel arms, randomised controlled trial, and includes a nested pharmacokinetic study. TB-HIV patients, who are ARV-naïve and with a CD4 cell-count >50 cells/mm³, are recruited in Benin, Guinea and Senegal. The 3 trial arms are 1) ARV initiation at week 2 combined with standard TB treatment (Arm A); 2) ARV initiation at week 8 combined with standard TB treatment (Arm B); 3) ARV initiation at week 8 with high-dose of rifampicin (15mg/kg) during the intensive treatment phase and standard dose during the continuation phase (Arm C). The primary endpoint is 12-month mortality. Treatment hepatotoxicity is monitored at weeks 2, 4, 6, 8 and 24 of treatment, with ALAT, ASAT, phosphatase alkaline and bilirubin measurements.

Results: 599 patients with pulmonary TB were included in the analysis, with follow-up to at least the end of the intensive phase. Baseline CD4 count was >200 cell-count/mm³ for 46%. Among patients with the high-dose rifampicin regimen, 20% experienced liver injury based on ALAT measurements (40/201); 1.0% (2/201) with grade 3 or 4. Corresponding figures from Arms A and B combined were 23% (92/398) and 0.3% (1/398) with grade 3 or 4, with no statistical evidence of a difference among the 3 treatment arms for the risk of a grade 3 or 4 measurement ($P = 0.26$).

Conclusion: The risk of severe treatment hepatotoxicity is low with a TB treatment regimen using a 15mg/kg dose of rifampicin in TB-HIV patients.

SOA-608-06 Diagnosed but not treated: the problem of untreated diagnosed TB in Uganda

P Kabagambe,¹ J Muhangi,¹ S Orach,¹ J Emuto,¹ C Edemaga¹ ¹Uganda Episcopal Conference, Kampala, Uganda. e-mail: pattkab@gmail.com

Background and challenges to implementation: Coughing patients who have been diagnosed with bacteriologically positive TB detected through Sputum Smear microscopy or GeneXpert testing of their sputum samples are particularly at a high risk of TB transmission to other persons especially if they are not started on TB treatment immediately. Untreated, diagnosed TB is also

hazardous to the patient, leading to poor outcomes like complications of TB as well as high mortality. Without an intervention to ensure that diagnosed bacteriologically positive TB patients are treated immediately, TB control efforts will be futile. Possible causes of delayed or no treatment of diagnosed TB are; drug shortages, delay in receiving TB results hence them returning late when the patient has left the facility, poor documentation, lack of knowledge among laboratory staff and health workers about the urgency of TB treatment, patient factors like transport and long distance problems, poor facility-community linkages and death before initiation of treatment.

Intervention or response: We performed an audit of bacteriologically positive TB patients identified by Sputum-Smear Microscopy and GeneXpert testing in the period from 1st March 2013 to 23rd April 2015 in 11 health facilities in Mpigi district in Central Uganda. Laboratory registers were reviewed to list all B-positive patients in the review period. Names were then cross referenced from the Unit TB register (Treatment register) for documented evidence of treatment. Documented evidence of transfer out or referral was also sought.

Results and lessons learnt: A total of 481 patients were diagnosed with bacteriologically positive TB (172 by GeneXpert (35.8%) and 309 by SS (64.2%)) in the review period. However, 185 (38.5%) patients' TB treatment was unaccounted for.

Conclusions and key recommendations: We propose to conduct focus group discussions with health workers and Village Health Teams in Mpigi to find out why the treatment status of these patients is unaccounted for, on a case by case basis. Follow-up in form of phone calls and visits to the patients will then be instituted. We recommend such audits periodically, not only for TB but also for other infectious diseases like HIV so as to strengthen timely linkage to care and treatment. We recommend a treatment-linkage focal person or team to ensure that all positive results from the laboratory are returned to requesting clinicians and followed by timely initiation of treatment

SOA-609-06 Using electronic data management system leads to improved TB patient monitoring in Kampala, Uganda

A Etwom,¹ D Lukoye,¹ D Kimuli,¹ M Kenneth,¹ M Ruhweza,¹ P G Suarez² ¹Management Sciences for Health, Kampala, Uganda; ²Management Sciences for Health, Medford, MA, USA. e-mail: etwoma@yahoo.com

Background and challenges to implementation: Kampala capital city (KCCA) has an annual TB notification of about 9,000 cases. However, the 2013 treatment completion was about 54.3% and over 20% getting lost to follow up mainly because there was no proper way of identifying treatment interrupters and defaulters. Paper based registers could not support easy retrieval of records during drug refills and tracking of missed appointments. Also at the same time, KCCA had low (20%) timely submission rate of reports to Ministry of Health (MOH)

and affecting timely decision making. We explored benefits of using a computerized data management system for following up patients in Kampala.

Intervention or response: A USAID and PEPFAR funded TRACK TB Project in collaboration with KCCA, developed a database based on TB registers. The project trained 14 health workers on use of the system. Computers (PC) and Internet were given to routinely document patient data that is, physical and phone addresses, diagnosis, refill schedules and HIV services for patients that were started on TB treatment between April 2013 and March 2014 from 60 health facilities. The information was then routed to the central server PC managed by data officers. Data officers routinely generated lists of patients who either missed appointments or interrupted treatment and linked them to Village Health Teams (VHT) who in turn traced these patients from the communities, counseled and linked them back to treatment.

Results and lessons learnt: A total of 9,447 were patient records managed till end of treatment period. As a result of using computerized system to timely inform health workers about patients who are interrupting treatment and using CLFs, quarterly treatment completion improved from 54.3% to 85% over a period of 1 year. The number of treatment interrupters traced and linked back to treatment increased from about 150 to 1594 and hence lost to follow up reduced from 2160 (24%) to 566 (6%). In addition KCCA achieved 100% timeliness and accuracy in reports submitted to MOH because the computerized system generated reports automatically. Also time spent by 12 health workers in compiling quarterly reports was cut from about 24 hours to 2 hours. The data also facilitated numerous decisions.

Conclusions and key recommendations: Results show that use of a computerized system to manage TB patients will improve treatment completion and facilitates quick decision-making.

SOA-610-06 How do patients access the private sector in Chennai, India? An evaluation of delays in tuberculosis diagnosis

L Bronner,^{1,2} R Ananthakrishnan,³ A Swaminathan,³ N Krishnan,³ M Pai,⁴ D Dowdy^{1,2} ¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²Johns Hopkins School of Medicine, Baltimore, MD, USA; ³REACH, Chennai, Tamil Nadu, India; ⁴McGill University, Montreal, QC, Canada. e-mail: lizabronner@gmail.com

Background: Diagnosis and treatment of tuberculosis (TB) in India are characterized by heavy private-sector involvement. Prolonged delays from symptom onset to treatment are important contributors to TB transmission, but these delays remain poorly characterized among patients who seek care in the Indian private sector. We assessed delays in TB diagnosis and treatment initiation among patients in the private sector. Design Cross-sectional survey of 289 consecutive patients who were eventually diagnosed with TB in the private sector and referred to a public-private mix program for TB treatment in Chennai city from January 2014 to February

2015. We conducted interviews using standardized questionnaires to collect data on demographics, TB disease, healthcare providers consulted, and intervals from symptom onset to treatment initiation. We defined formal providers as allopathic and non-allopathic practitioners with formal training in the public or private sector. Informal private providers included traditional healers, unlicensed practitioners, and pharmacists. Total delay was analyzed using multivariable generalized linear and Poisson regression models.

Results: Among 212 patients diagnosed with pulmonary TB in this public-private mix program, 90% first contacted a formal private provider, and 78% were diagnosed by the first or second provider seen. Patients who first consulted the formal private sector experienced longer mean patient delay, but health system delay was longer among patients who first consulted the public and informal sectors (Figure). For patients first seeking care in the informal private sector, mean total delay was longer versus the formal private sector (mean difference: 28 days, 95%CI: 12.5-44.3, $P < 0.001$) or public sector (mean difference: 27 days, 95%CI: 0.6-53.3, $P = 0.05$). After adjusting for potential confounders, consulting an informal provider as the first point of care, compared to a provider with formal training, resulted in a significant increase in total delay (absolute increase: 23 days, 95%CI: 6.2-39.5), and risk of having prolonged delay >90 days (aRR 2.4, 95%CI: 1.3-4.4).

Conclusion: Even among patients seeking care in the private sector in Chennai, delays in TB diagnosis are substantial, often two months or more. Seeking care in the informal private sector is associated with increased diagnostic delay of about one additional month. Novel TB diagnostic strategies are required across all health sectors to reduce the time patients spend seeking diagnosis after onset of infectiousness.

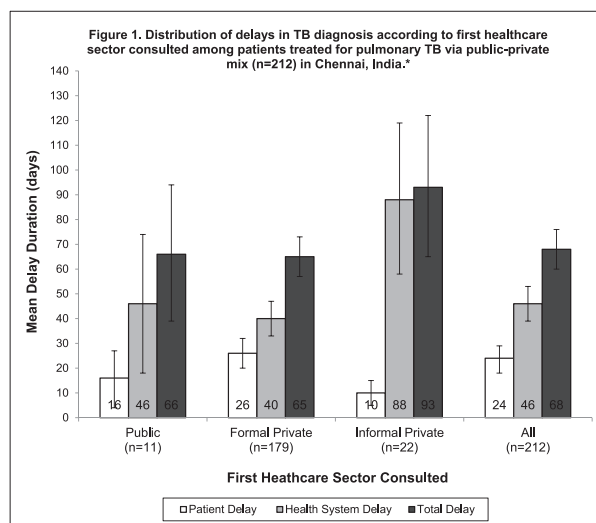


Figure 1.*Patient delay is defined as the interval between onset of symptoms suggestive of pulmonary TB and patient's first contact with a healthcare provider. Health system delay is defined as the time from the patient's first contact with any provider to the initiation of anti-TB treatment, and total delay is defined as time from symptom onset to the initiation of anti-TB treatment. Mean patient and health system delays do not always equal the mean total delay because of occasional incomplete data. Crossbars represent 95% confidence intervals for mean delays.

02. How to reach the END of TB

SOA-611-06 Feasibility of a zero medical burden for pulmonary tuberculosis out-patients through China's new rural cooperative medical system

Z Xu,¹ L Bai¹ ¹TB Control Institution of Hunan Province, Changsha, China. e-mail: evan.xu21@gmail.com

Background: Although China has free TB diagnosis and treatment policy, most patients have to pay additional diagnosis and treatment expenses (such as liver and kidney function test, liver protect medicine), which may lead to treatment interruption due to patients' low affordability. Therefore, Hunan province launched a so-called case-based payment pilot project in fourteen counties successively to cover all patient expenses through China's new rural cooperative medical system. Under this pilot project, patients would not pay any medical fee in whole treatment course. This research is to explore the feasibility of case-based payment (zero medical expense) for pulmonary tuberculosis (PTB) outpatients through new rural cooperative medical system (NRCMS).

Methods: Cross section and qualitative study were applied. All 131 counties of Hunan province were investigated to identify the current situation of medical security in tuberculosis patients by questionnaire and telephone interview. Thirty-six staff of nine pilot counties which already implemented case-based payment were interviewed on their opinions of case-based payment, interviewees were from health bureau, NRCMS sectors and centers for disease control and prevention (CDC) of each county.

Results: Outpatient PTB treatment for rural patients was covered by NRCMS in 118 of all 131 counties. Reimbursement models consist of proportional reimbursement, fixed amount reimbursement and case-based payment. However, the proportion of proportional reimbursement has a range of 30%~80%, the payment of amount reimbursement varies from 200 to 1500 RMB Yuan per case. Patients covered by proportional reimbursement and fixed amount reimbursement need to pay medical expense of 588yuan/case and 463yuan/case respectively, comparing zero expenditure for patients of case-based payment. NRCMS need input about 17.8 million Yuan more per year to reimburse all rural PTB outpatients' medical expenses, which only accounted for 0.12% of total NRCMS fund. In those counties which already implemented case-based payment policy, the number of patients visited CDCs has increased dramatically, follow-up and treatment compliance improved obviously as well.

Conclusion: Zero outpatient medical burden for rural tuberculosis patients is feasible and realizable through case-based payment under China's NRCMS.

SOA-612-06 Innovative social protection mechanism for alleviating catastrophic expenses for multidrug-resistant tuberculosis patients

D Kundu,¹ V Katre,² M Deshpande,³ A Sreenivas,¹ P Parmar¹ ¹World Health Organization Country Office for India, Delhi, ²RSBY and MSBY State Nodal Agency, Directorate of Health Services, Raipur, ³Directorate of Health Services, Raipur, India. e-mail: debashishkundu@yahoo.com

Background and challenges to implementation: Multi-Drug Resistant Tuberculosis (MDR-TB) patients incur huge expenditure for its diagnosis and treatment, which can be reduced through a well designed and implemented social health insurance mechanism. Post-2015 WHO Global TB Strategy Framework, one of the key targets set for 2035 is no affected families face catastrophic costs due to tuberculosis.

Intervention or response: The state of Chhattisgarh in India successfully established partnership between Revised National TB Control Programme (RNTCP) and Health Insurance Programme, a Universal Health Insurance Scheme (UHS) for all, by establishing 'RSBY and MSBY MDR-TB packages' [Table] to absorb catastrophic expenses incurred by MDR- TB patients from diagnosis to treatment completion in public and private sector. Data on uptake of insurance claims through innovative MDR-TB packages from December 2013 to April 2014 was collected to discuss initial experience of linking health insurance programme tailor made to cover catastrophic health expenditure for MDR-TB patients.

Results and lessons learnt: 207 insurance claims of 'RSBY and MSBY MDR-TB Packages' were processed, of which 20 claims were from the private and 187 from the public health establishments, empanelled under the health insurance programme, free of cost. Catastrophic expenditure, ~20000 USD, was saved through RSBY and MSBY insurance mechanism. For the first time in India, national health insurance was successfully linked with the national TB control programme through creation of special packages for the MDR-TB patients. Early finding of implementation of RSBY and MSBY MDR-TB Packages shows that this innovative mechanism is working.

Conclusions and key recommendations: Innovative 'RSBY and MSBY MDR-TB health insurance package' is a step towards reducing catastrophic expenses. Considering that both drug resistant and drug sensitive TB treatment is ambulatory and takes longer time to complete, out-patient care needs to be included into the mainstream health insurance. In order to address the social protection component of post 2015 End TB Strategy, mechanisms emphasizing collaboration with existing social health insurance schemes needs attention in the national policy framework for TB control.

Table Rashtriya Swasthya Bima Yojna (RSBY), Mukhyamantri Swasthya Bima Yojna (MSBY) and Innovative RSBY & MSBY MDR-TB Package Details

RSBY and MSBY – What is the scheme?	Coverage Amount	Financing
RSBY is a cashless, paperless and portable social health insurance scheme through smart cards. RSBY and MSBY, The Chief Minister's Health Insurance Scheme in Chhattisgarh, also managed by RSBY, provides health insurance coverage and protection to people below and above the poverty line ('APL' and 'BPL') to fund medical treatment for packages covered in Round IV of RSBY and MSBY disease list in Chhattisgarh –	Total insurance coverage amount is upto 30000 INR (500 USD*) per annum 17 USD (~2 USD Per Visit)	Beneficiaries need to pay only 0.42 USD as registration fee while Central and State Government pays the premium to the insurer selected by the State Government on the basis of a competitive bidding. Every beneficiary family is issued a biometric enabled smart card containing their fingerprints and photographs.
1. On admission basis 2. For five enrolled members in a family; 3. Covers transportation expenses in a year across all RSBY empanelled network hospitals (both private and public) in the state.		

* 1 USD = 60 INR

Innovative RSBY and MSBY MDR-TB Package Details in Scheme Year 4

Medical/Surgical	MDR – TB Package Name	Package Details	Package Cost	No. of Times/ Days claims can be processed
Medical Conditions	Pre-Treatment Evaluations	Chest X-Ray, relevant haematological and biochemical tests: Complete Blood Count (CBC), Liver Function Test (LFT), Thyroid Function Tests (TFT), Blood Urea Nitrogen (BUN), Creatinine, Urine (Routine & Microscopic), Urinary Pregnancy Tests (UPT)	4000 INR (67 USD)	One Time
Medical Conditions	Follow-up Evaluations	Chest X-Ray, relevant haematological and biochemical tests: Complete Blood Count (CBC), Liver Function Test (LFT), Blood Urea Nitrogen (BUN), Creatinine, Urine (Routine & Microscopic)	3300 INR (55 USD)	Maximum Five Times for Creatinine and rest tests for maximum two times

Medical Conditions	Hospital Stay	Bed Charges, Doctors Consultation Fees and any other additional / ancillary drugs	5600 INR (93 USD @13 USD/Day)	Maximum 7 days stay on pro- rota basis

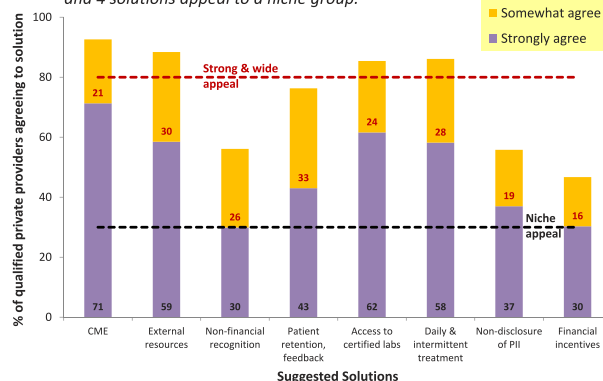
SOA-613-06 Identification of solutions and their levels of acceptance by private health care providers for adoption of key tuberculosis care standards in India

O George,¹ R Ganesan,¹ V Sharma,¹ R Swamickan,² M Benezet³ ¹Abt Associates Inc., New Delhi, ²United States Agency for International Development, New Delhi, India; ³Abt Associates Inc., Bethesda, MD, USA. Fax: (+91) 112 653 5172. e-mail: oommen.geo@gmail.com

Background: Combating tuberculosis (TB) in India and mitigating the growing threat of drug-resistant TB requires adoption of TB care standards by private health care providers (pHCP). Experience suggests that few pHCP utilize sputum tests for diagnosis of pulmonary TB, notify patients or accept intermittent treatment regimens. Treatment monitoring is largely dependent on patient revisits. Engagement of pHCP has hitherto been on the terms of India's National TB Control Program. Solutions influencing pHCP adoption of TB care standards need to be identified and tested.

Design/Methods: A 2-stage study was conducted in 2013-14 with qualified pHCP in Karnataka, India. The objective of stage 1 was to identify possible solutions for pHCP adoption of TB care standards through iterative exploratory interviews using semi-structured questionnaires with 56 doctors. In stage 2, structured interviews with 170 doctors explored potential pHCP behavior change if packages of these solutions were applied.

Private health care provider acceptance of solutions for adoption of TB care standards: 4 solution items have strong and wide appeal and 4 solutions appeal to a niche group.



Results: In stage 1, pHCP identified 8 solutions: (1) continuing medical education, (2) laboratory access through sputum transportation, (3) assured patient retention or feedback on those referred, (4) support for additional documentation and patient monitoring, (5) flexibility to adopt daily drug regimens, (6) non-financial rewards, (7) non-disclosure of personal identifiers (PII) of

patients, and (8) financial incentives. Stage 2 showed that solutions (1), (2), (4) and (5) had strong and wide appeal while solutions (3), (6), (7) and (8) appealed to niche groups. Half the pHCP interviewed reported no concerns with notification, but expressed the lack of means for this. Financial incentives, however, evoked strong negative reactions from some providers. Provider segments and potential value perceived by pHCP to interventions suggest that inputs that create and support a provider network, especially those impacting patient satisfaction of provider services, are valued by a large group of pHCP. A base package offering solutions (1) to (6) had strong effects on utilization of sputum tests (from 27% to 65%), and notification (from 46% to 72%). Incremental effect of adding solutions (7) or (8) or both to the base package were similar, impacting different sub-groups of pHCP.

Conclusion: The study recommends action to support pHCP adoption of key standards for TB care. The base solution package has the potential to substantially improve provider compliance to sputum tests and notification.

SOA-614-06 Retail private pharmacist's knowledge and perceptions about collaborating with the National Tuberculosis Programme: a qualitative study, South India

Y Vijayashree,^{1,2} H Bindu,² N Rao,² N Devadasan²

¹Institute of Tropical Medicine, Antwerp, Belgium; ²Institute of Public Health, Bangalore, India. e-mail: vijayashree@iphindia.org

Background: In India, RPPs are often first and repeated point of contact for patients. NTP is involving RPPs through Indian Pharmaceutical Association by training them to identify and refer chest symptomatics to NTP for TB diagnosis. We conducted this study to assess RPP's (i) knowledge and referral practices (ii) stocking and dispensing of TB drugs (iii) kickbacks to providers.

Methods: Semi-structured interviews were conducted with 40 RPPs in Bangalore (urban = 19) and Tumkur district (rural = 21) during 2013 from Karnataka, India. RPPs were randomly selected from the register maintained with district drug controller.

Results: None of the respondents had received any TB-related training, but majority of them knew about mode of spread of TB. RPPs described the typical profile of TB patients as old and financially weak. Mix of providers, such as allopathic, traditional medicine and quacks referred TB patients to RPPs. Self-referrals were common among the economically poorer sections as they did not see value in paying an additional cost to the doctor as consultation fee and purchased medicines based on the RPP's recommendation. One respondents believed that "pharmacists have experience and that they know what is best for patients". They reported seeing 10-15 chest symptomatic per day and dispensing cough syrups, and antibiotics to such patients. RPPs in rural tend to refer cases to NTP as compared to urban RPPs. They tend to stock TB drugs and their choice was mainly determined by the doctors' prescription patterns, opinions of drug

company representatives and the profit margins associated with drugs. All respondents said that, no patients buy the entire course of drugs at a time "TB patients are mostly daily wage workers. They get money in the evening and buy medicines". Doctors though did not explicitly ask patients to go to a particular RPP, but ensured that they go to the pharmacy attached to their clinic, by writing medicines that were available only there. Pharmacists reported doctors receiving commission upto 40% from pharma companies.

Recommendations: Potential of RPPs has remained untapped in NTP. A policy to systematically involve PRPs should be considered. The PRPs when trained, can create community awareness about TB, help in early case detection/referral and act as DOTS provider and counsel patients. Enforcing regulatory monitoring of sale TB drugs under schedule H1, to check the indiscriminate use is urgent to prevent multi drug resistant TB.

SOA-615-06 Use of voucher schemes: promising higher quality service delivery for early diagnosis and treatment of TB in Mumbai

S Vijayan,¹ P Mhatre,² R Gandhi,¹ R Chopra,¹ J Thakker,¹ P Kandasamay,¹ V Jondhale,¹ Mohu Datta¹ ¹PATH, Mumbai, ²Mumbai Mission for TB Control, Mumbai, India. Fax: (+91) 114 605 4430. e-mail: shibuvij@gmail.com

Background: There is documented evidence of vouchers for offsetting patient costs in Maternal and Child health (MCH) services thus reducing financial constraints amongst the lower socio economic segment. Taking cues from this Private Provider Interface Agency (PPIA) in Mumbai designed and deployed a voucher system for TB suspects and patients who approach private health care providers.

Intervention: The PPIA voucher scheme uses 3 differently colored voucher booklets (20 vouchers) for each of its 3 major services: (i) Free Chest X-ray - availed at networked quality controlled facilities, (ii) Highly subsidized CBNAAT (XpertMTB/RIF) amongst the networked laboratories and (iii) free treatment for the first line drugs availed at the networked chemists. Each voucher has 3 copies (with unique voucher number), for patient, physician and NGO field officer. Two subcontracted NGOs are responsible for voucher stock management and placing as well as replenishment of vouchers at each of the networked facilities. The NGO coordinator forwards the collated details of reimbursable amounts from the service providers with required documents to PPIA - Grant management team. The reimbursement is made against the invoice generated on monthly basis from the NGOs. The reimbursement of every credit note is completed within 7 days of the subsequent month.

Results: In 7 months, 1300 private medical providers, ~100 health facilities, 5 laboratories, 80 X-ray laboratories and ~100 chemists were empanelled with NGO field representatives placing ~25 000 X-ray vouchers at the networked health facilities in Mumbai. ~2000 X-ray vouchers have been issued by Less Than Fully Qualified

(LTFQ) (Utilization – 70%) providers for the suspect patients and ~1400 X-ray vouchers have been issued from networked health facilities (Utilization – 80%) implying a cost of about INR 6 lacs (9500 USD). A total of 1750 gene expert testing vouchers (Utilization – 90%) incurring a cost of ~INR 22.5 lacs (36 000 USD) and about 9000 treatment vouchers (for first line drugs) incurring ~INR 34.5 lacs (55 000 USD) were issued.

Conclusions: The voucher scheme offsets patient costs leading to higher utilization of services and provides private providers with free diagnostic and treatment packages to be directly offered to the patients. An E-voucher mechanism is foreseen for scaling up voucher scheme operations to widen the reach of the program. The future of E vouchers is promising for higher cost effectiveness of the program.

SOA-616-06 Disparities in treatment delay among patients with pulmonary TB in South West Nigeria

M Alagi,¹ O Popoola,² O Uchendu,² E Owoaje² ¹National Agency for Control of AIDS, Abuja, ²University and University College Hospital, Ibadan, Nigeria. e-mail: drpoppee@gmail.com

Background: Nigeria has the highest burden of tuberculosis PTB in Africa. Delays in initiation of DOTS therapy is known to increase the probability of PTB transmission from infected patients to uninfected contacts. This study therefore aimed to estimate the time lapse in initiation of treatment for PTB and explore factors associated with delay including disparities in delay between socioeconomic groups.

Design/Methods: An analytical cross sectional study patients newly initiated on DOTS treatment across was conducted. A multistage sampling technique was used to sample from rural and urban DOTS centres. The WHO EMRO tuberculosis delay survey questionnaire was adopted. Treatment delay was defined as the period between onset of PTB symptoms and initiation of anti-Kochs treatment. The Kaplan-Meier survival analysis technique was used as well as multivariate logistic regression. Level of statistical significance was set at $\alpha = 0.05$.

Results: A total of 403 PTB patients newly initiated on DOTS therapy were studied. 204 respondents were sampled from urban 4 urban DOTS centres while, 199 respondents were sampled from 8 rural DOTS centres. Persistent cough 59.5% and fever 12.7% were the most frequently reported symptoms which prompted care seeking. The median treatment delay was significantly longer among urban PTB patients 49 (range 2 - 363) days compared to rural 40 (range 6 - 344) days. Factors associated with treatment delay in excess of 4 weeks included attempts at concealing ill health OR 3.0 95%CI (1.5 – 5.2); out of pocket expenditure OR 2.5 95%CI (1.1 - 5.5); utilizing more than 2 health care providers OR 2.2 95%CI (1.2 - 4.0; technical unskilled workers (artisans, drivers & traders) OR 2.3 95%CI (1.2 – 4.5 and males OR 1.8 P 0.047 95%CI (1.0 – 3.3).

Conclusion: The study showed unacceptably long delays in initiating PTB in south west Nigeria. Efforts to address disparities in treatment delay should identify that males, unskilled manual workers, individuals without health insurance and with poor health access as being more vulnerable to treatment delay.

SOA-617-06 EXPAND-TB: contribution of an innovative project in increasing global MDR-TB detection

D Orozco,¹ K Kao,¹ J Lemaire,¹ C N Paramasivan,¹ R Mazitov,¹ T Verges,² Y Mundade,³ F Mirzayev⁴ ¹FIND, Geneva, ²STOP TB PARTNERSHIP, Geneva, ³UNITAID, Geneva, ⁴World Health Organization, Geneva, Switzerland. e-mail: kekeletso.kao@finddx.org

Background and challenges to implementation: The EXPAND-TB project is a 7 year (2009-2015) initiative to help countries turn the tide of the TB epidemic by introducing new and faster TB diagnostics in 27 countries, 15 of which are high-burden TB or high MDR-TB burden countries. The EXPAND-TB project aims to address the obstacles to correct diagnosis and treatment of MDR-TB in low-resource settings by improving laboratory capacity to diagnose drug-resistant and HIV-associated TB using WHO endorsed diagnostic tools. The project is focused on establishing or upgrading 103 central and regional reference TB laboratories and 47 Xpert MTB/RIF testing sites.

Intervention or response: 101 central and regional TB reference laboratories and 47 Xpert MTB/RIF testing sites have been established; commodities for MGIT liquid culture and drug susceptibility testing, line probe assay, and rapid speciation are regularly delivered to the countries to meet their testing requirements; comprehensive training packages and SOPs have been developed and training was delivered building the capacity laboratory staff, clinicians and policy makers. Analysis of the EXPAND-TB project's contribution to global MDR-TB notifications was made using data from the latest WHO TB report (2013). The MDR-TB estimates from the 27 EXPAND-TB supported countries were pooled and compared to global estimates.

Results and lessons learnt: The project was implemented in 3 phases: phase 1-laboratory preparedness; phase 2-technology transfer and validation; phase 3- routine testing and monitoring. As the project progressed through the implementation phases its contribution to the global MDR-TB notifications steadily increased. The increase was noticeable in 2012 and 2013 as the majority of countries entered phase 3 (Figure 1). In 2013, from the 299 800 MDR-TB cases estimated globally, only 136 412 (45%) were notified and 63 761 (47%) were notified within the 27 project countries. Amongst those notified within the 27 countries 35 736 (56%) cases were detected directly through EXPAND-TB support and the remainder by other means or in other labs not supported by the project. By the 31st December 2014 a total of 106 983 MDR-TB cases had been diagnosed with EXPAND-TB support since project initiation in 2009.

Conclusions and key recommendations: The EXPAND-TB project has successfully contributed towards the global increase in MDR-TB notifications

SOA-618-06 Customizable economic analysis tools to support evidence-based tuberculosis control decision-making

E Carlson,¹ T Miller,¹ B Naik,² A Vemulapalli¹ ¹University of North Texas Health Science Center, Fort Worth, TX, USA; ²Revised National Tuberculosis Control Programme, Bangalore, India. Fax: (+1) 817 735 0446. e-mail: erin.carlson@unthsc.edu

Background: Tuberculosis (TB) control requires substantial public resources. Effective, sustainable public strategies consider diagnostic and treatment options, as well as associated efficiencies and costs. Economic analysis can bolster effective advocacy for TB programs, identify efficiencies and optimize program efforts. However, such work may be beyond technical capacity of local health authorities. An economic evaluation tool customizable to local, regional, or national circumstances may be a valuable means to provide economic information to facilitate evidence-based decision making by health authorities.

Intervention: We created customizable economic analysis tools to evaluate costs and efficiencies of regional TB programs in the United States and India. These tools combine standard techniques for health care economic analyses with local cost, outcome, and prevalence data in a Microsoft Excel platform. The tools allow health authorities to model potential health and economic effects of proposed programmatic changes and consider how their program may be affected by changes in diagnostics, medications, personnel, food packages, local epidemiology, etc. Outcome measures are customizable and may include case rates, mortality, and money costs or savings in local currency or over time. Two such modeling tools were developed and customized to support TB control activities by the Texas Department of State Health Services (TDSHS) in the United States and the Government of India's Revised National Tuberculosis Control Programme (RNTCP).

Results: The model estimates net monetary costs associated with incidence and other inputs, the number of TB and MDR cases to result from secondary transmission, and the number of deaths caused by index cases during a given time. This baseline data is compared to hypothetical conditions for a newly proposed or modified DOTS or other TB program, assuming conservative observed, published, and estimated cost and outcome differences. Under these assumptions, the model provides information to determine how many dollars, lives, and new cases may potentially be saved under the proposed program compared to the existing program.

Conclusions: A customizable economic analysis tool may support TB program policy through rapid comparisons of costs and outcomes for proposed program changes.

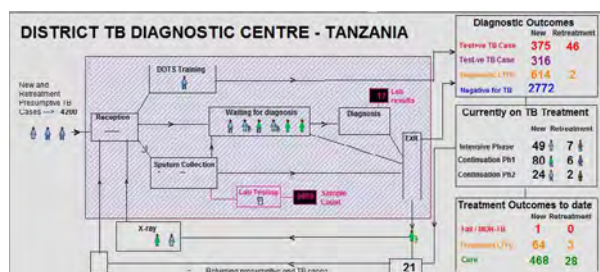
SOA-619-06 Modelling the cost-effectiveness for the health system of Xpert® MTB/RIF scale-up by district profile in Tanzania

I Langley,¹ B Doulla² ¹Liverpool School of Tropical Medicine, Liverpool, UK; ²National TB and Leprosy Programme, Dar Es Salaam, Tanzania. e-mail: ivor.langley@lstm.ac.uk

Background: The computer modelling of patient pathways (known as Virtual Implementation) has been used to assist national policy makers to assess options for the scale-up of new diagnostics (including Xpert MTB/RIF) for pulmonary tuberculosis in Tanzania. This presentation will demonstrate how a new version of the model designed for local staff from the National Tuberculosis Programme to use themselves has been employed to model diagnostic algorithms at district level.

Design/Methods: A model using the Virtual Implementation approach has been developed which is easy to use and contains an Excel user interface for data input and reviewing outputs in a ‘TB diagnostics dashboard’. Individuals in Tanzania have been trained and software installed to enable staff to model for themselves the impact of alternative diagnostic algorithms. The model has been used to assess eight different diagnostic algorithms including those using Xpert MTB/RIF in 10 different diagnostic districts and 5 diagnostic district types. Incremental cost effectiveness ratios have been calculated.

Results: Implementation of Xpert MTB/RIF in all diagnostic districts modelled would be cost effective and have the greatest benefit, measured in DALYs averted and cures, but with highest additional health system costs. Depending on the objective of implementation the priority sequence for implementation of new diagnostic algorithms across the country varies. The projections show that same day LED is particularly effective when funds are tight and reduction in DALYs and increasing cures is top priority. If more funds are available full roll-out of Xpert is the preferred strategy starting with the largest centres and those with high HIV. If MDR-TB detection is the top priority then LED same day will not assist greatly and early roll-out of Xpert is preferred. Similarly if time to start treatment is top priority then reducing high levels of empirically diagnosis becomes the priority so implementing Xpert in districts with a high proportion of smear negative TB should be considered first.



Conclusion: The analysis suggests that an effective policy for pulmonary TB diagnostics in Tanzania would be full

roll-out of Xpert MTB/RIF in larger districts with high HIV first and same day LED microscopy elsewhere. The Virtual Implementation approach is a useful tool that should be retained in Tanzania to model new implementations of Xpert at district level and other new tools as they become available.

SOA-620-06 Future trends in TB epidemiology in China and the potential impact of novel age-targeted TB vaccines: a modelling study

R Harris,¹ T Sumner,¹ G Knight,² R White¹ ¹London School of Hygiene & Tropical Medicine, London, ²Imperial College London, London, UK. e-mail: rebeccaclaireharris@gmail.com

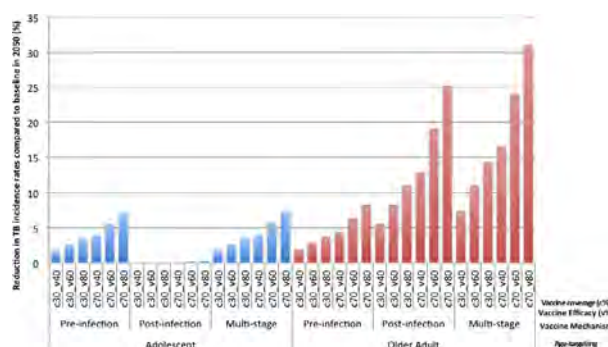
Background: Ageing is an important risk factor for TB in China, with prevalence rates in the elderly 3-times higher than all-age estimates. The impact of population ageing on *Mycobacterium tuberculosis* transmission and the future burden of tuberculosis (TB) disease in China is poorly understood. Furthermore, with a pipeline of new vaccines, understanding the currently unknown benefits of targeting older populations is important for planning development and implementation. These new vaccines are likely to be required for China to reach WHO 2050 elimination targets.

Design/Methods: An *M. tuberculosis* transmission model incorporating Chinese social mixing patterns was calibrated to age-stratified estimates of population size and TB prevalence, notification and mortality rates. The model assessed the elderly (65+years) contribution to *M. tuberculosis* transmission and new cases, and the impact of vaccinating older adults (55-64years) or adolescents (15-24years). Novel vaccines with pre-infection, post-infection and multi-stage mechanisms of action were explored (efficacious in individuals uninfected, latently infected, and regardless of infection status, respectively), at a range of efficacies (40%-80%) and coverages (30%, 70%).

Results: Preliminary results suggest the elderly contribution to *M. tuberculosis* transmission will increase from 18% to 53%, and to new TB cases from 13% to 71%, between 1990-2050. Compared to baseline, vaccination of older adults or adolescents reduced 2050 TB incidence rates by 2%-31% or <1%-7%, respectively, and mortality by 2%-28% or <1%-5%, respectively; thus averting 199 000-3 676 000 or 10 000-963 000 cases, and 7900-152 700 or 300-26 700 deaths 2025-50. Post-infection vaccines provided substantially greater impact than pre-infection vaccines when delivered to older adults, whereas if targeted to adolescents pre-infection vaccines achieved greatest impact. The minimum achievable incidence by 2050 was 22/100 000pop/yr, with 70% coverage of older adults with an 80% efficacious multi-stage vaccine.

Conclusion: Our preliminary results suggest that by 2050 the elderly will be the main contributor to TB burden in China. Strengthening of TB control efforts for the elderly is likely required to achieve WHO 2050 TB elimination goals. Novel TB vaccines targeted to older adults provided consistently higher population level impact

than vaccinating adolescents. The most effective vaccine explored may reduce TB incidence and mortality rates by almost a third by 2050, averting up to 3.7million cases over this time horizon.



SOA-621-06 Comparing the impact of the Global Fund on health systems in Papua New Guinea and Nepal

I Harper,¹ A Street,¹ K Dahal² ¹University of Edinburgh, Edinburgh, UK; ²HERD, Kathmandu, Nepal. e-mail: ian.harper@ed.ac.uk

Background: Both Nepal and Papua New Guinea – with high burdens of tuberculosis – are dependent on GFATM grants for the financing of their TB programmes. Each country also has amongst the remotest, poorest, hardest-to-reach populations in the world, coupled with weak primary health care infrastructure.

Design/Methods: The research questions focused on the impact of GFATM funding structures and evaluation metrics on relationships between health institutions, the distribution of financial and infrastructural resources, and programmatic performance. Independent ethnographic research in both countries was conducted, supplemented with in depth open-ended interviews with government officials and health workers, NGOs project staff, and other stakeholders in GFATM funded projects. Inductive analysis compared data from both countries, to draw up generalizable themes and cross cutting issues.

Results: Both countries have significant resource and programmatic issues facing their TB control linked to geography, weak communication and transportation infrastructure, and a growing number of actors involved in health governance and delivery. The current drive of developing M & E metrics in line with GFATM policy and practice, while generating important data for monitoring performance, has important unintended consequences. A tendency to focus on achieving targets and an increase in bureaucratic procedure has channelled institutional resources into generating these metrics, informants argue, at the expense of broader health service delivery issues. Marginal populations in the hard to reach areas are the most likely to suffer from these unintended consequences.

Conclusion: The current recording and reporting metrics developed for accountability purposes for GFATM funded programmes have unintended effects. While the

development of M & E is a crucial component of health system development, more attention should be focused on the impact these metrics themselves have on the systems. In particular, we show they can reinforce inequalities between infrastructure-dense and infrastructure-sparse areas of the health system. The impact of M & E on access to services for the most marginal and the hardest to reach populations should be a routine part of health system evaluation.

03. HIV and TB: snapshots

SOA-622-06 Blended learning as capacity building option for TB-HIV services: results of a comparative study in Ethiopia

G Tsegaye,¹ T Anteneh,² K Merga,¹ M Abebe,¹ M Behute,¹ M Aseresa Melese,² D J Dare,² P G Suarez³
¹All Africa Leprosy, Tuberculosis, Rehabilitation and Research Training Centre, Addis Ababa, ²Management Sciences for Health, HEAL TB Project, Addis Ababa, Ethiopia; ³Management Sciences for Health, Center for Health Services, Arlington, VA, USA. Fax: (+251) 11 372 4473. e-mail: degujerene@gmail.com

Background: Shortage of trained health workers is a critical barrier to strengthening tuberculosis prevention and control programs. Health workers frequently stay away from routine duty and family for a number of days for off-site workshop trainings. Our objective was to assess if blended learning (BL) approaches which combine distance-based learning with off-site trainings can be implemented without compromising the quality of services.

Methods: We carried out a comparative study using the Kirkpatrick training evaluation model. The BL group received self-reading materials for 3 weeks followed by a 3-day face-to-face off-site training while the traditional group (TD) received a 6-day off-site workshop-style trainings. Training materials were tailored to the specific modality of training but nearly the same content developed and endorsed by the Ministry of Health were used. Health workers with no recent training in the updated national TB-HIV guidelines from two selected zones participated in the study. Health workers with no recent training in the updated national TB-HIV guidelines from two selected zones participated in the study. The evaluation criteria included participant satisfaction, learning, behavioral changes, impact according to the 4-level Kirkpatrick training evaluation model. We compared the level of satisfaction using a 32-item questionnaire between the two groups, and computed pre-test and post-test results between and within the two groups using one way ANOVA test. We also estimated the unit direct cost per trainee for each training modality. This paper presents preliminary results for the first two levels, not inclusive of the behavior change and outcome.

Results: At the time of this analysis, complete data was available for 209 trainees (63 from the TD group and 146 from the BL group). The two groups did not differ in

terms of education and work experience. The two groups had similar level of satisfaction [composite score; 57 in TD vs. 55 in BL]. The mean pre-test result was higher for the TD group (56.2 vs. 51.2) while their post test result was similar (66.7 vs. 63.5; $F=1.73$; $P > 0.1$). Also, the BL group had higher mean (SD) improvement in post-test performance (15.6 vs. 10.1; $F=7.52$; $P < 0.01$). The unit cost per trainee was lower in the BL group [116.8 USD versus 235 dollars].

Conclusion: Both groups had similar level of satisfaction with the training approach and improvement in knowledge level was better in the BL group. The cost and time taken to deliver the BL approach was lower by about a half. This approach could be a more efficient way of delivering in-service trainings but further analysis is needed to compare behavioral and service delivery outcomes between the two groups.

SOA-623-06 Incremental diagnostic yield of incorporating TB-LAM test and Xpert® MTB/RIF into a diagnostic algorithm in HIV-positive patients

H Huerga,¹ G Ferlazzo Natoli,² P Bevilacqua,¹ B Kirubi,³ E Ardizzoni,^{2,4} J K Sitienei,⁵ M Bonnet¹ ¹Epicentre, Paris, ²Médecins Sans Frontières (MSF), Paris, France; ³MSF, Nairobi, Kenya; ⁴Institute of Tropical Medicine, Antwerp, Belgium; ⁵National Tuberculosis Program, Nairobi, Kenya. e-mail: helena.huerga@epicentre.msf.org

Background: The value of LAM test when is incorporated into a diagnostic algorithm has not been elucidated. We aimed to assess the diagnostic yield of an algorithm including LAM test and LAM plus Xpert MTB/RIF in HIV positive patients.

Design/Methods: Prospective observational study conducted in Homa Bay (HIV prevalent area of Kenya). HIV positive patients with suspicion of pulmonary tuberculosis (TB) whether hospitalized, with $CD4 < 200$ cell/ μ l, with $BMI < 17$ Kg/ m^2 or severely ill were eligible. Patients received clinical exam, chest X-ray, LAM test (positive cut-off grade 2), Xpert MTB/RIF test and MTB culture (Thin-Layer-Agar and Löwenstein-Jensen). We used TB treatment initiation as primary end point and MTB culture as reference (positive culture as TB confirmed).

Results: In total 397 patients were included: 201 (50.8%) women; median age 35 years (IQR: 29-44); 308 (77.6%) hospitalized; 270 (69.1%) with $CD4 < 200$ cells/ μ l; 335 (84.4%) severely ill; 169 with $BMI < 17$ (43.4%). A forth of the patients could not produce sputum. Of the 300 patients with laboratory results: 49 (16.3%) were smear positive, 73 (24.3%) Xpert positive, 104 (34.7%) LAM positive and 83 (27.7%) culture positive. LAM test sensitivity and specificity was 54.9% (95%CI: 43.5-65.9) and 72.8% (95%CI: 66.4-78.6). In total, 273/397 (68.8%) patients started TB treatment. The reasons to start TB treatment among the 83 culture positive patients were: 47.0% clinical situation, 16.9% suggestive X-ray, 21.7% positive LAM test, 7.2% positive Xpert, 7.2% positive culture. The addition of the LAM test increased the proportion of confirmed TB cases started on TB treatment from 63.8% to 85.5% compared to the

clinical-radiological algorithm and to 92.8% when Xpert was also included (Table 1).

Conclusion: Despite its low sensitivity, the addition of the urine LAM to the clinical and radiological algorithm allowed TB treatment initiation in more than 80% of confirmed TB patients. This finding is particularly important for patients in severe clinical situation who usually have more difficulties to produce sputum. Although, the low specificity of the LAM test in this study is a concern, it might be partially due to the imperfect reference standard in severely ill patients who are more likely to present negative culture disseminated TB. TB-LAM should be added to the clinical-radiological algorithm in HIV positive patients with TB suspicion not only when CD4 is less than 200 cells/ μ l but also if patients are severely ill or hospitalized.

	Clinical-radiological algorithm	Additional LAM		Additional Xpert
	Diagnostic yield, % (95%CI)	Diagnostic yield, % (95%CI)	Incremental yield, %	Diagnostic yield, % (95%CI)
Overall*	63.8 (52.8-73.6)	85.5 (76.0-91.7)	21.7	92.8 (84.6-96.8)
Hospitalized (N=58)	56.9 (43.6-69.3)	82.8 (70.4-90.6)	25.9	89.7 (78.4-95.4)
CD4<200 cells/ μ l (N=66)	66.7 (54.2-77.2)	90.1 (80.9-95.9)	23.4	95.5 (86.5-98.6)
Severely ill** (N=75)	65.3 (53.7-75.4)	86.7 (76.7-92.8)	21.4	92.0 (83.0- 96.4)
BMI<17 (N=41)	65.9 (49.6-79.1)	82.9 (67.5-91.9)	17.0	92.7 (78.8-97.7)

*Diagnostic yield: proportion of patients started on TB treatment using a diagnostic algorithm among culture positive patients; Incremental yield: increased proportion of patients started on TB treatment among culture positive patients when an additional test is included in the previous algorithm.

**Severely ill: respiratory rate higher than 30 respirations per minute, temperature higher than 39°C, cardiac rate higher than 120 beats/ minute, or unable to walk without help.

SOA-624-06 Pulmonary tuberculosis in HIV-infected patients presenting with normal chest radiograph and negative sputum smear

M Jojula,¹ C Chatla,² S P Chakramahanty,³

A Raghuramreddy,¹ A Mounika,¹ P Mamatha¹ ¹Sri Shivani College of Pharmacy, Warangal; ²World Health Organization, New Delhi; ³State TB Cell, Hyderabad, India. e-mail: chatlac@rntcp.org

Background: Deaths due to tuberculosis (TB) are high among the TB-HIV co-infected patients. Among PLHIV most of the instances the sputum smear is found to be negative for MTb. Chest X-rays also don't yield any diagnostic value mainly due to the advanced immunosuppressed condition. This study makes an attempt to find out the utility of alternate staining methods such as Light Emitting Diode (LED), Fluorescent Microscopy (FM) and solid culture.

Intervention: Two sputum samples were collected from 100 successive presumptive TB cases among PLHIVs

visiting ICTC at MGM hospital, Warangal, Telangana State, India whose smear microscopy and X-ray were negative for *M. tuberculosis*. All the 100 samples were repeated with ZN microscopy and X-ray. Additionally LED and FM microscopy procedures were conducted with the NALC-NAOH concentration method. All the samples were inoculated on LJ medium for solid culture and all the positive cultures were subjected for biochemical test to identify phenotypic appearance, nitrate reduction, niacin and PNB susceptibility test for all the first line anti TB drugs as per standard guidelines. Samples found positive on microscopy were cross checked with Line probe assay (LPA).

Results: All the 100 samples collected showed negative for *M. tuberculosis* on ZN technique and negative for pulmonary TB on chest X-rays. 15 samples were positive for MTb both on LED and FM. LPA reconfirmed the *M. tuberculosis* in all the 15 samples tested with 11 sensitive for both INH and Rif, 3 INH mono resistant and 1 Rif mono resistance patterns. Of the 100 inoculations in LJ medium, 25 culture inoculations were positive for *M. tuberculosis* growth and also were confirmed as *M. tuberculosis* strains based on morphological, biochemical test and growth was seen after 4th week of inoculation. Of the 25 culture positives 20 were sensitive for both INH and Rif, 4 INH mono resistant and 1 resistant to all first line anti TB drugs.

Conclusions: In smear negative and chest X-ray negative presumptive TB cases especially in immune compromised groups such as PLHIV, it is found to be useful to subject the sputum samples to LED and FM methods and solid culture wherever available. These methods clearly demonstrated additional yield over conventional ZN staining which can be recommended especially in the settings where high throughput equipment such as Xpert MTB/RIF is not available. These proactive measures can help in early diagnosis of TB which in turn can reduce mortality due to TB among PLHIV and break the chain of transmission of TB.

Table 1:

Diagnostic Method	Sample size	Results	
		+ve for MTb	-ve for MTb
ZN	100	NIL	100
LED	100	15	85
FM	100	15	85
Chest X-Ray	100	NIL	100
LPA	15	15 INH Resistance = 3 Rifampicin Resistance = 1 INH Sensitive & Rifampicin Sensitive = 11	NIL
Solid Culture	100	25 (positive for MTb growth)	75 (no growth)
Solid Culture DST	25	INH Resistance = 4 Resistance to all first line drugs = 1 Sensitive to all first line drugs = 20	

SOA-625-06 TB mortality measurement: comparing verbal autopsy methods to necropsy in a setting of high HIV prevalence in Siaya County, Kenya

S Murithi,^{1,2} J Sitienei,¹ E Mitchell,^{3,4} H Kipruto,^{1,5} E Amukoye,⁶ C Muturi,⁷ Z Ngan'ga,² K Cain⁸ ¹National Tuberculosis and Lung Disease Program, Nairobi, ²Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; ³KNCV Tuberculosis Foundation, Netherlands, The Hague, ⁴Amsterdam Institute for Global Health & Development, Amsterdam, Netherlands; ⁵World Health Organization, Nairobi, ⁶Kenya Medical Research Institute, Nairobi, ⁷Jaramogi Oginga Odinga Training and Referral Hospital, Kisumu, ⁸Center for Global Health, Centers for Disease Control, Kisumu, Kenya. e-mail: smgacherism@gmail.com

Background and challenges to implementation: Most African countries lack complete vital registration systems. In such settings, verbal autopsy (VA) is recommended to estimate the mortality burden of Tuberculosis (TB). It involves assigning causes of death from interviews with next-of-kin and health record review. Coding is either by trained human coders or computer algorithms. Although widely endorsed as a legitimate method, the performance of VA to detect TB related deaths has never been validated against gold standard. This study sought to assess the accuracy of VA in a sample of deceased individuals above age one presenting with respiratory-related symptoms in a rural Kenyan setting with high TB-HIV co-infection.

Intervention or response: The study was conducted between 2012- 2013. Post-mortems (PM) were done by a pathologist. Tissue and fluid samples from major organs were tested with liquid culture and XpertMTB/RIF. VA interviews were conducted after a median of 50 days mourning period. InterVA4 algorithm was applied to interview data and the probable causes of death were ascertained. If TB appeared as among highest, second or third highest likelihood causes on InterVA4, this was classified as a TB death. VA questionnaires were independently reviewed by two clinicians certified to determine causes of death from VA.

Results and lessons learnt: A total of 156 deaths were notified. Of the eligible cases ($n = 98$), 80% of the families consented to autopsy. PM detected 11 deaths, all bacteriologically-confirmed. All but one was co-morbid with HIV. The clinicians diagnosed 20 and 29 deaths respectively as TB-related and upon harmonization they settled on 21 deaths. This yielded a combined over-diagnosis of 91%. Among the 11 TB deaths; clinicians VA correctly detected 3 (Sensitivity: 27% [95%CI 10-57]) and InterVA4 algorithm detected 2 (Sensitivity: 18% [95%CI 5-48]). Among the 66 patients with non-TB as cause of death, InterVA4 over-diagnosed TB in 14 (specificity: 78%, [95%CI 66-86]) and clinicians over-diagnosed TB in 18 (specificity: 72% [95%CI 65-86]). Agreement between the clinicians and InterVA4 was at (0.51 [95%CI 0.29-0.73]).

Conclusions and key recommendations: Current VA methods overestimate TB mortality burden in a setting with high HIV prevalence. Low sensitivity and specificity

imply they cannot function as interim proxy measures of TB mortality. Vital registration systems and minimally invasive autopsy are options for policy makers to consider.

SOA-626-06 A TB-HIV integration intervention and morbidity, mortality and retention in care among individuals with TB and HIV: MERGE cluster randomised trial

T Chakezha (née Kufa),^{1,2} K Fielding,³ P Hippner,¹ K Kielmann,⁴ A Vassall,³ G Churchyard,^{1,2} A Grant,^{2,3} S Charalambous^{1,2} ¹RESEARCH, The Aurum Institute, Johannesburg, ²University of the Witwatersrand, Johannesburg, South Africa; ³London School of Hygiene & Tropical Medicine, London, ⁴Queen Margaret University, Edinburgh, UK. e-mail: tendesayik@yahoo.com

Background: There are limited data on effectiveness of interventions to improve TB and HIV integration and their effect on patient relevant outcomes. We describe results from a cluster-randomised trial to evaluate the effect of a TB and HIV integration intervention on morbidity and/ or mortality and retention in care, in South Africa.

Design/Methods: Eighteen primary care clinics were randomised to intervention or control. The intervention was clinic-specific activities supported by intervention staff (TB-HIV integration and TB screening officers) that helped address gaps in integration and improve TB screening for HIV-positive people. The control arm was current standard of care. The composite outcome of death or hospitalisation during 12 months of follow up was measured in two cohorts of newly diagnosed (i) TB and (ii) HIV patients. Retention in care was measured as the proportion of HIV-positive TB patients who remained in HIV care 12 months after enrolment.

Results: Of 4003 individuals screened, 3024 and 731 individuals newly diagnosed with HIV and TB, respectively, were enrolled. In the HIV and TB cohorts 62.3% and 45.5% were female, median ages 34 and 36 years. In the TB cohort 79.6% (582) were HIV-positive. The incidence of death/hospitalisation was similar between the arms: i) HIV cohort: adjusted rate ratio (aRR) 1.09 (95% confidence interval [CI] 0.85- 1.40) and ii) TB cohort: aRR 1.16 (95%CI 0.65- 2.07). The proportion of HIV-positive individuals newly diagnosed with TB and retained in care at 12 months was also similar between the arms: aRR 1.08 (95%CI 0.91- 1.28)(see Table). Although there was evidence that the intervention was understood and well received by participating clinic staff, intervention staff spent most of their time providing direct patient care as opposed to the more strategic roles that were intended. At the end of the intervention period, there was no evidence of increased co-location of services or higher coverage of integrated TB-HIV services at intervention vs. control clinics.

Conclusion: The intervention as implemented did not have an effect on morbidity, mortality or retention in care among individuals newly diagnosed with TB and with HIV, likely because the intervention did not improve

integration. Other interventions to improve integration need to be evaluated.

Table: Rates, adjusted and unadjusted risk ratios for the outcome comparing intervention with control arms

Outcome	Intervention Rate / 100 pyrs (# cases / pyrs)	Control Rate / 100 pyrs (# cases / pyrs)	Unadjusted Rate Ratio ¹ (95% CI)	Adjusted Rate Ratio ^{1,2} (95% CI)
Morbidity and/ mortality within 12 months among individuals :				
Newly diagnosed with HIV	13 (182/1395)	10.8 (146/1352)	1.18 (0.93- 1.50)	1.09 (0.85- 1.40)
Newly diagnosed with TB	17.9 (67/375)	11.4 (32/280)	1.37 (0.77- 2.43)	1.16 (0.65- 2.07)
Retention in care among HIV positive individuals newly diagnosed with TB	% (n/N) 63.4% 231/336	% (n/N) 56.0% 141/252	unadjusted Risk Ratio ¹ (95% CI) 1.11 (0.89 - 1.37)	adjusted Risk Ratio ^{1,2} (95% CI) 1.08 (0.91- 1.28)

¹Comparing intervention vs control; ²adjusting for age, sex and baseline imbalances

SOA-627-06 An integrated community based TB-HIV adherence support model provides an alternative to DOT for TB patients in Cape Town, South Africa

R Kaplan,¹ J Caldwell,² S Adriaanse,² S Hermans,^{1,3} L Mtshwa,¹ L-G Bekker,¹ K Jennings,² R Wood¹

¹University of Cape Town, Cape Town, ²City Health, Cape Town, South Africa; ³University of Amsterdam, Amsterdam, Netherlands. e-mail: Richard.Kaplan@hiv-research.org.za

Background: Directly observed therapy (DOT) is advocated by the WHO to support adherence to TB treatment. In Cape Town, with TB-HIV co-infection rates of 50% and patients on antiretroviral treatment (ART) self-supervising treatment with the support of community care workers (CCWs), the need was perceived for a single adherence support programme for TB and HIV-positive patients. In 2011, the City of Cape Town introduced an integrated adherence support model as an alternative to DOT at primary care TB and HIV clinics. The model consisted of educational sessions on TB and HIV treatment by facility based counselors; home assessments by CCWs and a multidisciplinary meeting after 2 weeks of in-clinic DOT to decide whether patients were eligible for community support with weekly home visits by CCWs or whether they should continue with daily supervised treatment as either in-clinic, field-based

or workplace DOT. We evaluated the impact of this model on TB default and death rates.

Methods: We retrospectively analysed the electronic TB register data of patients treated during a 6 month period before and after the introduction of the new adherence model. Multivariable random effects Cox regression analyses were used to compare the hazard of default and death before and after the intervention adjusting for age, gender, HIV status, calendar year, type of TB and for clustering by clinic.

Results: The pre-intervention population consisted of 8761 TB patients and the post-intervention population of 7433 treated in 46 primary care TB clinics. Baseline characteristics were similar; 50% were HIV positive, median age was 32 years (IQR 24-41) and 55% were male. More HIV-positive patients were on ART at the start of TB treatment after the intervention (31% vs. 24%) and more patients who were not on ART, started antiretroviral treatment after the intervention (76% vs. 60%). After the intervention, 79% of patients were placed out for community adherence support compared to 51% who received field-based DOT before the intervention. The adjusted hazard ratio (aHR) for death associated with the intervention was 1.03 (95%CI 0.78-1.36) and the aHR for default was 1.01 (95%CI 0.82-1.25).

Conclusion: The integrated adherence support model did not result in higher default or death rates when compared to DOT and was associated with an increase in ART uptake. It could provide a viable alternative adherence support system for an integrated TB and HIV treatment programme.

SOA-628-06 CD4 count distribution, ART uptake and TB treatment outcomes among HIV-positive TB patients in Cape Town, 2009-2013

R Kaplan,¹ S Hermans,^{1,2} J Caldwell,³ K Jennings,³ L-G Bekker,¹ R Wood¹ ¹University of Cape Town, Cape Town, South Africa; ²University of Amsterdam, Amsterdam, Netherlands; ³City Health, Cape Town, South Africa. e-mail: Richard.Kaplan@hiv-research.org.za

Background: In Cape Town, the roll-out of antiretroviral treatment (ART) in primary health care clinics has increased steadily over the last decade with an estimated coverage of 63% of HIV positive patients in 2013. How this has influenced the characteristics of the population of patients presenting to the primary care TB programme is unknown. This study aimed to examine the HIV prevalence and ART usage among TB patients in the primary care TB programme in Cape Town from 2009 to 2013 and to evaluate the degree of immunosuppression through an analysis of the CD4 count distribution.

Methods: Data from the electronic TB register (2009-2013) on all newly registered TB patients ≥ 15 years were analyzed retrospectively. Descriptive statistics were used to quantify the annual changes in CD4 counts, ART usage at start of TB treatment, ART uptake during TB treatment and TB treatment outcomes (available for years 2009-2012). Differences in HIV prevalence and

median CD4 counts were tested using the Chi² test for trend and the Cuzick nonparametric test for trend respectively.

Results: 122 762 patients were treated in 101 primary care TB clinics over the 5 year period. The absolute number of notified HIV-positive TB cases decreased by 11% over the time period, from 12 567 in 2009 to 11 162 in 2013. The HIV prevalence among TB patients decreased from 50% in 2009 to 48% in 2013 ($P < 0.001$). The median CD4 count at the start of TB treatment increased from 152 cells/mm³ [interquartile range (IQR) 69-278] in 2009 to 176 cells/mm³ [IQR 74-324] in 2013 ($P < 0.001$). The CD4 count distribution showed a shift to CD4 categories >200 cells/mm³ in 2013 with the greatest decrease occurring in the categories between 100 – 200 cells/mm³ (Figure). More patients entered the TB programme on ART in 2013 compared to 2009 (34% vs. 10%) and ART uptake among those not on ART increased substantially from 37% to 76%. TB treatment outcomes showed an 82% cure or completion in 2012 compared to a 79% cure or completion rate in 2009.

Conclusion: The increase in median CD4 counts, the high treatment cure or completion rate and the increase in ART uptake indicate well-functioning TB and ART treatment programmes. However the absolute decrease in HIV-positive TB cases, while promising, was modest and the proportion of highly immune compromised patients was still high, indicating that the increased ART coverage has not lead to a substantial decline in TB cases.

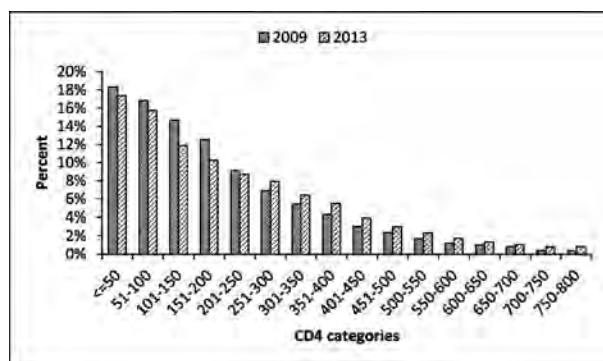


Figure 1. A comparison of CD4 count distribution in 2009 and 2013.

SOA-629-06 TB as a cause of hospitalization and death among people living with HIV worldwide: a systematic review and meta-analysis

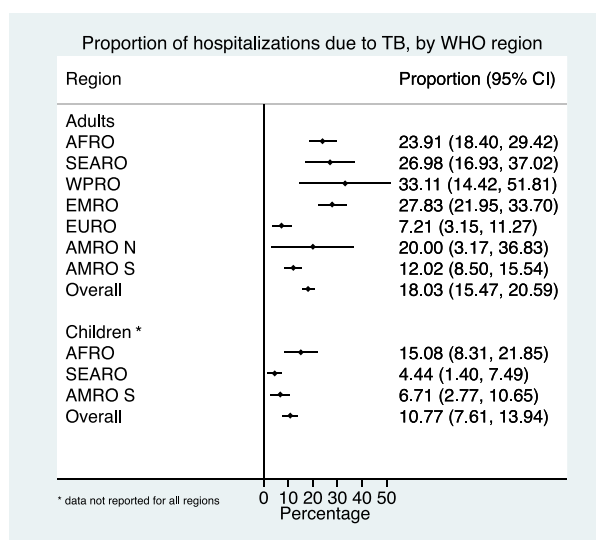
N Ford,¹ Z Shubber,² A Matteelli,¹ G A Meintjes,³ K Kranzer,⁴ B Grinsztejn,⁵ M Doherty,¹ H Getahun¹

¹World Health Organization, Geneva, Switzerland; ²Imperial College, London, UK; ³University of Cape Town, Cape Town, South Africa; ⁴London School of Hygiene & Tropical Medicine, London, UK; ⁵Ministry of Health, Brazil, Rio de Janeiro, Brazil. e-mail: ford@who.int

Background: Despite significant progress in improving access to antiretroviral therapy (ART) over the last

decade, substantial numbers of people living with HIV/AIDS (PLHIV) in all regions continue to experience severe illness and require hospitalization. We undertook a global review of the proportion of hospitalizations and deaths due to tuberculosis (TB) in PLHIV.

Design/Methods: Seven databases were searched using a pre-defined protocol for studies reporting causes of hospitalizations among PLHIV since 01 January 2007 irrespective of age or geographical region and without language restriction (earlier cohorts were included provided they also reported data from 2007 onwards). The proportion of hospitalizations and in-hospital mortality attributed to TB and other illnesses was estimated using random effects meta-analysis and the influence of antiretroviral therapy and calendar year (study midpoint) was assessed by meta-regression.



Results: From an initial screen of 9049 records, 68 cohorts were identified, providing data on 30 981 adults (32 832 hospitalizations) and 2526 children (2792 hospitalizations) across 39 countries. 70.7% (95%CI 49.0-92.4%) of patients were already known to be HIV positive at the time of admission but only 47.7% (31.2-64.1%) were on antiretroviral therapy. Overall, 18.0% (15.5-21.6%) of all adult hospitalizations were due to TB, making it the leading cause of hospitalization overall; the proportion of adult hospitalizations due to TB exceeded 10% in all regions except the European region (Figure). 10.8% (7.6-13.9%) of all paediatric hospitalizations were due to TB and TB was the 4th leading cause of hospitalization (after bacterial pneumonia, diarrhoea, and severe anaemia). Among patients who died following hospitalization, TB accounted for 26.1% (19.4-32.8%) of all adult deaths and 30.1% (11.2-48.9%) of all paediatric deaths. In meta-regression, an increase in the proportion of patients on ART at admission was associated with a decrease in the proportion of hospitalizations attributable to TB ($P < 0.01$). There was no change in TB as a cause of hospitalization over time.

Conclusion: TB continues to be a leading cause of hospitalization and death among adults and children living with HIV worldwide. Increased coverage of antiretroviral therapy reduces the risk of hospitalization; however, the relative importance of TB as a cause of severe illness has not decreased in recent years. The contribution of TB to hospitalization and death may be underestimated due to limited availability and sensitivity of diagnostics in resource-limited settings. This study underscores the continued need to scale up TB prevention and expedite TB diagnosis among PLHIV.

SOA-630-06 HIV and alcohol intake are important determinants of non-adherence to tuberculosis treatment in pragmatic settings in urban Uganda

H Babikako,¹ A Okwera,² C C Whalen,³ E Mupere¹

¹College of Health Sciences, Makerere University, Kampala,

²Mulago National Referral Teaching Hospital, Kampala, Uganda; ³College of Public Health, University, Athens, GA, USA. e-mail: babikako@yahoo.com

Background: Control of tuberculosis (TB) epidemic in most sub-Saharan Africa countries is challenged by human immunodeficiency virus (HIV) infection, and yet the systematic understanding of the impact of HIV and its treatment on adherence to TB treatment is not well characterized. We established non-adherence to TB treatment among HIV positive and negative adult patients attending programme clinics in Kampala, the capital of Uganda in Africa.

Design/Methods: Using a cross-sectional study design, 469 smear positive TB patients attending five programme clinics in Kampala were studied. Adherence was measured using a Morisky scale among patients completing 2, 5 and 8 months of treatment.

Results: The study found 29% (135/469) of the study participants to be non-adherent. Of the 135 participants that were non-adherent, 33% were HIV positive. Non-adherence increased with the duration of TB treatment. The proportion for non-adherence was 21% (40/190) at 2 months, 30% (41/135) at 5 months, and 38% (54/144) at 8 months. HIV positive patients who had completed medication at 5 and 8 months had an increased likelihood for non-adherence, respectively. For example, HIV positive patients who had completed medication at 5 months were three times more likely to be non-adherent (OR 3.21 (95%CI: 1.354, 7.647)) compared to patients that had completed treatment at month two, adjusting for age, sex, patient being new or transfer in, alcohol intake status, duration of treatment. Among 314 HIV negative participants, patients with history of alcohol intake were two times (OR 2.211 (95%CI: 1.229, 3.980)) more likely to be non-adherence, adjusting for age, sex, patient being new or transfer in, duration of treatment.

Conclusion: The study found a high burden of non-adherence among patients receiving care in national programme TB clinics in urban Uganda; HIV positive patients and HIV negative with history of alcohol intake

were more likely to be non-adherent. Tuberculosis programmes should enhance pre- and in-treatment adherence counseling and education throughout the duration of therapy, and HIV positive and patients with history of alcohol intake should be targeted.

SOA-631-06 Point-of-care C-reactive protein based TB screening may improve the efficiency of ICF and increase uptake of IPT among patients new to HIV/AIDS care

C Yoon,¹ F Semitala,^{2,3,4} J Katende,² P Byanyima,⁴

A Andama,^{3,4} I Ayakaka,⁴ M Kanya,^{2,3,4} A Cattamanchi¹

¹University of California, San Francisco, San Francisco, CA,

USA; ²Makerere University Joint AIDS Program, Kampala,

³Makerere University College of Health Sciences, Kampala,

⁴Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda. Fax: (+1)415 695 1551. e-mail: christina.yoon@ucsf.edu

Background: Tuberculosis (TB) is the leading killer of PLHIV. Early initiation of antiretroviral therapy (ART), early diagnosis of TB, and early provision of isoniazid preventive therapy (IPT) can substantially reduce the number of HIV-TB deaths. However, many patients with HIV present late to care leading to delayed ART initiation and increased risk of TB. We compared the efficiency of intensified case finding (ICF) and opportunities to provide IPT when patients new to HIV/AIDS care were screened for TB using point-of-care (POC-CRP) levels vs. symptom-based assessment.

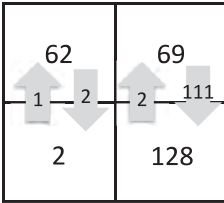
Methods: We performed symptom-screen assessment, POC-CRP testing (normal ≤ 10 mg/l), and sputum-based TB testing (Xpert x1, culture x2) on consecutive ART-naïve adults with CD4 ≤ 350 cells/ μ l entering care at an HIV/AIDS clinic in Uganda from July 2014 to April 2015. We compared the proportion of TB cases detected by Xpert and culture among patients who screened-positive, and the proportion of patients eligible for immediate IPT (specificity), by either screening strategy.

Results: Of 261 patients new to care (median CD4 144 cells/ μ l), 64 (25%) had culture-positive pulmonary TB. Nearly all patients (92%, 241/261) screened-positive for TB by symptoms including 63/64 patients with TB (sensitivity 98%, 95%CI: 92-100). Xpert testing of the 241 symptomatic patients identified 35 (57%) culture-positive TB cases. Of the 197 patients without TB, only 19 patients screened-negative by symptoms (specificity 10%, 95%CI: 6-15) and would have been immediately eligible for IPT. In contrast, 50% (131/261) of all patients screened-positive for TB by POC-CRP, including 62/64 patients with TB (sensitivity 97%, 95%CI: 89-100). Xpert testing of the 131 patients with elevated POC-CRP also identified 35 (57%) culture-positive TB cases but required only half as many Xpert assays. Of the 197 patients without TB, 128 patients screened-negative by POC-CRP levels (specificity 65%, 95%CI: 58-72), a greater than 6-fold increase in the proportion of patients immediately eligible for IPT without the need for confirmatory testing, compared to the symptom screen.

Conclusion: 1 in 4 patients new to HIV/AIDS care have culture-positive TB; this population is an extremely high-

risk group for whom TB screening should be prioritized. Targeting POC-CRP based- rather than symptom-based screening to patients new to care can improve the efficiency of ICF and increase uptake of IPT while maintaining a similar TB case detection yield.

Figure 1. Performance characteristics of TB screening tests

	WHO SYMPTOM SCREEN			POC CRP		
	TB	No TB		TB	No TB	
Screen + (Refer for Xpert)	63	178		62	69	
Screen - (Refer for IPT)	1	19		2	111	
	Sensitivity 98% (92-100)			Sensitivity 97% (89-100)		
	Specificity 10% (6-15)			Specificity 65% (58-72)		
	NPV 95% (75-100)			NPV 99% (95-100)		
	PPV 26% (21-32)			PPV 47% (39-56)		

SOA-632-06 Chronic respiratory disease in older children and adolescents with vertically acquired HIV infection

G Mchugh,¹ J Rylance,^{2,3} E Majonga,^{1,4} J Metcalfe,⁵ T Bandason,¹ H Mujuru,⁶ K Kranzer,⁴ R Ferrand^{1,4}
¹Biomedical Research and Training Institute, Harare, Zimbabwe; ²University of Liverpool, Liverpool, ³Liverpool School of Tropical Medicine, Liverpool, ⁴London School of Hygiene & Tropical Medicine, London, UK; ⁵University of California San Francisco, San Francisco, CA, USA; ⁶University of Zimbabwe, Harare, Zimbabwe. e-mail: graceandandre@gmail.com

Background: Chronic lung disease is a major cause of morbidity in vertically HIV-infected children and adolescents. While we have previously shown that the burden in these children is extremely high, the association between chronic lung disease and HIV has not been established due to the lack of a comparison group. We compared symptoms of lung disease and spirometry in HIV-infected and HIV-uninfected older children and adolescents.

Design/Methods: HIV infected older children and adolescents (age 6-16 years) with vertically-acquired HIV on antiretroviral therapy for at least 6 months attending an HIV clinic in Harare, Zimbabwe were consecutively recruited. Assessment included a symptom questionnaire, MRC dyspnoea scale, clinical examination, spirometry and shuttle walk testing. Frequency age-matched HIV-negative children were recruited from 7 primary health care clinics in Harare.

Results: 200 HIV-infected and 69 HIV-uninfected children were recruited. Age (median 11 years) and sex of the two groups was comparable (see table). In the HIV infected group, median CD4 count was 729 cells/ μ l (iqr 479-935), mean age at diagnosis was 5 years old and 157 (84%) had an undetectable HIV viral load (<1000cp/ml). One third of the HIV-infected children ($n=76$, 38%)

had been treated for tuberculosis compared to only one child among the HIV-uninfected children (1%). The proportion of children previously diagnosed with asthma was similar in both groups (3% vs. 3.5%). A quarter of the HIV-infected children ($n=41$, 25%) who had spirometry performed showed either obstruction or reduced FVC with poor reversibility, compared to only 4% of HIV-uninfected participants with spirometry data HIV+ $N=200$ HIV- $N=69$ P Age, y, median (iqr) 11(9-12) 11(9-13) 0.72 Sex-Male, % 52 39 0.06 MRC Dyspnoea scale >1, % 14 0 <0.01 Height for age, z score <-2, % 34 10 <0.01 Weight for age, z score <-2, % 28 9 <0.01 Oxygen saturation <88% at rest, % 1 0 0.39 Desaturation $\geq 5\%$ on exercise, % 12 9 0.39 Duration of shuttle walk, mins, mean 10m 23s 11m28s 0.03 FEV zscore, mean(sd) -0.73(1.20) 0.29(0.82) <0.01 FVC zscore, mean(sd) -0.79(1.24) 0.25(0.90) <0.01 FEF 25%-75% zscore mean(sd) -0.082(1.21) 0.08(1.02) 0.49

Conclusion: There is a substantial burden of chronic lung disease among HIV-infected older children despite treatment with antiretroviral therapy, in comparison to HIV negative counterparts. The aetiology of such chronic lung disease needs investigation and interventions to treat lung disease are urgently required.

04. TB epidemiology: from Malawi to Taiwan

SOA-633-06 Risk stratification of adult tuberculosis contacts: a population-based study in Taiwan

J-Y Feng,¹ S Chen,¹ W Fan,¹ S Wei-Juin,¹ C Liu¹ ¹Taipei Veterans General Hospital, Taipei, Taiwan. e-mail: peterofeng@vghtpe.gov.tw

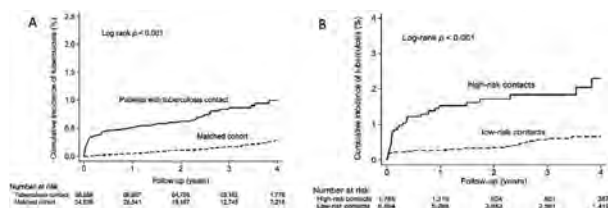
Background and challenges to implementation: Contact investigation is an important and effective active-case finding strategy for TB control programs, but also requires abundant resources in public health. The current World Health Organization (WHO) recommendation for contact investigation suggests follow-up screening in the first year after exposure. However, most of the TB contacts studies have included both adults and children, or enrolled children only. The adequacy of one-year follow-up screening for all TB contacts remains uncertain. Understanding the dynamic pattern of active TB occurrence among TB contact and identifying contacts with the highest risk are of paramount clinical importance.

Intervention or response: We retrieved the data from the National Health Insurance Research Database in Taiwan from 2000 to 2011, which covered more than 99% of the 23 million people of Taiwan. TB contacts were identified by diagnostic codes (V01.1 in the International Classification of Diseases, 9th revision, and the clinical modification ICD-9-CM) in conjunction with chest plain film and/or sputum acid-fast smear examination and/or tuberculin skin test (TST). We matched each TB contact

with four non-exposed subjects by age and sex, and presence of comorbidities on the same index date of diagnosis. The occurrence of TB, the major outcome of the present study, was determined based on the compatible ICD-9-CM code (010-018 in ICD-9-CM). The diagnosis of TB was validated by the prescription of at least two anti-TB medications for more than 28 days. We compared the difference in the occurrence of active TB between TB contact and matched cohort. The clinical risk factors associated with TB occurrence were also investigated.

Results and lessons learnt: A total of 8659 adult TB contacts and 35 636 matched cohorts were included for analysis. Overall, 72 TB contacts and 67 matched cohorts were documented with active TB during the follow-up period, and the mean annual incidence of TB were 312.8 and 72.2 cases per 100 000 person-years, respectively (adjusted HR 4.39, 95%CI 3.15–6.12, $P < 0.001$). The incidence rate of active TB in the first, second, and third years were 567.1 cases, 106.4 cases, and 229.3 cases per 100 000 person-years, respectively, for TB contacts. The adjusted hazard ratio of the first, second, and third years were 12.30 (95%CI 6.73–22.48), 1.64 (95%CI 0.64–4.23) and 4.10 (95%CI 1.63–10.33), respectively. In the multivariate analysis, the independent risk factors associated with active TB development among adult TB contacts were being ≥ 65 years old (HR 2.15, 95%CI 1.22–3.81), male (HR 1.74, 95%CI 1.07–2.81), having autoimmune diseases (HR 2.60, 95%CI 1.40–4.81), COPD (HR 1.95, 95%CI 1.16–3.27), and liver cirrhosis (HR 2.61, 95%CI 1.03–6.65). When categorize the TB contacts into high-risk population (two or more risk factors) and low-risk population (less than two risk factors), Kaplan-Meier analysis demonstrated that high-risk TB contacts had a significantly higher cumulative incidence of active TB and the curves separated immediately after exposure.

Conclusions and key recommendations: This nationwide, population-based cohort study from a TB endemic area indicated that although the annual incidence of TB is highest during the first year, the annual incidence remains significantly higher in TB contacts during the third year. The extension of the follow-up period to three years should be considered for adult TB contacts, especially those with more risk factors.



SOA-634-06 Deciphering tuberculosis dynamics in East Greenland: genome based molecular epidemiology of *Mycobacterium tuberculosis* in a high-incidence area

K Bjorn-Mortensen,¹ A Bengaard Andersen,² B Soborg,¹ T Lillebaek,¹ A Koch,¹ K Ladefoged,³ T Kohl,⁴ S Niemann^{4,5} ¹Statens Serum Institut, Copenhagen, ²University Hospital of Copenhagen, Copenhagen, Denmark; ³Queen Ingrid Hospital, Nuuk, Greenland; ⁴Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften, Borstel, ⁵German Center for Infection Research (DZIF), Borstel, Germany. e-mail: kabm@ssi.dk

Background: Tuberculosis (TB) is again a major health problem in Greenland. TB outbreaks often occur in isolated settings with complex social networks revealed by contact tracing. This complexity makes it difficult to identify cases of active *Mycobacterium tuberculosis* transmission in order to confine the outbreaks. TB incidence in the isolated East Greenland has increased dramatically in recent years to approximately 1000 notified TB cases per 100 000 inhabitants and approximately 40% of the East Greenlandic population is infected with *M. tuberculosis*. Since 2004, all culture-positive TB samples from East Greenland have been genotyped with mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR). Available data showed that almost all strains were from two major clusters with very similar MIRU-VNTR genotypes, making it difficult to distinguish new from old cases.

Objective: The study aimed to characterize transmission patterns in a population-wide whole genome sequencing (WGS) study including all culture-positive cases within a 21-year period. The main objective was to determine to what extent WGS contributes to the understanding of an outbreak in a high TB incidence, low diversity setting.

Methods: Using Illumina Nextera XT library preparation kits and the NextSeq500 next generation sequencing platform, we performed WGS of 182 isolates (98% of culture-positive cases). After reference mapping to the H37Rv genome, detected variants were combined to yield a set of phylogenetically informative single nucleotide polymorphism (SNP) positions.

Results: A maximum parsimony tree based on these positions revealed the same pattern as seen with MIRU-VNTR, but with a much higher resolution. Employing a maximum distance of 12 SNPs between isolates, four groups were created, which overall correlated well with the MIRU-VNTR clustering. Both time and place of notification correlated well with WGS data, and transmission links suggested by WGS fit well with expansion over time. Also, epidemiological data and WGS data together suggest a very clear geographical distinction of clones.

Conclusion: WGS based genotyping describes in detail the longitudinal transmission pattern of tuberculosis in an isolated, high incidence, low variance setting. Therefore, even among isolates with the same, or almost identical, MIRU-VNTR type in a high incidence setting,

WGS performs well and offers a much higher resolution than previously used genotyping methods.

SOA-635-06 Increasing burden of tuberculosis among foreign-born populations in Japan: trend and issues

L Kawatsu,¹ A Ohkado,^{1,2} K Uchimura,¹ S Yoshimatsu,¹ K Izumi,^{1,2} K Ito¹ ¹Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, ²Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. e-mail: kawatsu@jata.or.jp

Background: Compared to other industrialized countries, the burden of tuberculosis (TB) among the foreign-born populations has been relatively low in Japan - however, with social and economic factors, including the shortage of workers in several industries such as construction and care for the elderly, pushing Japan for a more open immigration policy, more foreigners are expected to enter Japan. TB control among foreign-born persons has thus become an urgent issue.

Objective: To identify the trend of TB among foreign-born populations in Japan and issues for TB control.

Method: We analyzed the publicly available data from the Tuberculosis Surveillance Center to identify the trend of TB by age-groups, nationality and time of entry to Japan for the period 2003-2013. We also compared the treatment results of foreign-born to Japanese patients, and in terms of occupational category. χ^2 test was performed to compare proportions and calculate odds ratios.

Results: The number of foreign-borns among newly notified TB patients had increased from 906 in 2003 to 1064 in 2013. The proportion of foreign-borns among the newly notified TB patients was largest among those aged 20 to 29 years - in 2013, 42.7% of patients aged 20-29 were born outside Japan. Of the 1064 foreign-born patients, 432, of whom 34% were from China, had entered Japan within the last five years. Of the 184 foreign-born patients who had been staying in Japan for more than five years, 29.1% were from the Philippines. Compared to the Japanese patients, lost to follow-up and transferred-out was significantly higher among the foreign-borns both in the age groups 20-59 (odds ratio (OR) = 3.54, 95% Confidence Interval (CI) 2.47-5.05, $P = 0.000$) and aged above 60 (OR=5.44, 95%CI 2.11-12.50, $P = 0.000$). However, death was significantly higher among the Japanese patients than foreign-borns in the age group 20-59 (OR=7.16, 95%CI 1.22-290.00, $P = 0.016$). Multi-drug resistance was significantly higher among foreign-born patients ($\chi^2=52.27$, $P = 0.000$). Treatment results did not differ significantly in terms of occupational category among the foreign-born patients.

Conclusion: Lost to follow-up and transferred-out was significantly higher in foreign-born patients than the Japanese counterparts in both age groups 20-29 and 60 and above. Public health effort must be strengthened to deliver effective patient education and adherence support, as we continue to expect increasing number of foreigners arriving to Japan.

SOA-636-06 Diversity of MIRU-VNTR among *Mycobacterium tuberculosis* Central Asian family isolates from Nepalese patients

Y Shah,¹ A Poudel,¹ H Mahmoud Diab,¹ J Thapa,¹ C Menda,¹ B Maharjan,^{1,2} C Nakajima,¹ Y Suzuki¹ ¹Hokkaido University, Sapporo, Japan; ²German Nepal TB project (GENETUP), Kathmandu, Nepal. e-mail: yogendra.90@gmail.com

Background: Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and poses major challenges and public health problems in Nepal. Central Asian Strain (CAS) family has been reported as one of the most predominant genotypes of *M. tuberculosis* in South Asian countries including Nepal. Mycobacterial interspersed repetitive units-variable number of tandem repeats (MIRU-VNTR) is a reliable and reproducible genotyping method for the differentiation of *M. tuberculosis* isolates. The main aim of this study was to elucidate the epidemiological link among *M. tuberculosis* CAS family strains within Nepal and those in surrounding countries, as well as providing insight into the transmission of TB for better monitoring of disease and strengthening of control measures.

Design/Methods : A total of 145 *M. tuberculosis* CAS isolates from Nepalese patients were analyzed by spoligotyping and 24 loci MIRU-VNTR. The individual and cumulative Hunter Gaston Discriminatory index (HGDI) were calculated and result categorized as poor, moderate and highly discriminatory. Clustering analysis was analyzed using www.miru-vntrplus.org.

Results: Based on spoligotyping results, SIT26 was the most prevalent (47%, $n = 63$) shared type followed by SIT599 (10.34%, $n = 15$). The cumulative HGDI of 24-locus VNTR were equal to the 15-loci MIRU-VNTR (HGDI, 0.9942; clustering rate, 26.2%). Combining both MIRU-VNTR and spoligotyping identified 47 isolates exhibiting 19 clusters (RTI-20%), which suggested that those isolates were from patients with ongoing transmission between them. On other hand, the majority of (80%) isolates did not show clustering but had unique patterns suggesting a long history of *M. tuberculosis* CAS strain in Nepal.

Conclusion: The proposed 15 loci MIRU-VNTR typing scheme are well suited to assess the *M. tuberculosis* population structure and diversity, trace back the transmission dynamic and epidemiological link among *M. tuberculosis* CAS family strain within Nepal and surrounding countries; this will enhance the TB national epidemiological surveillance and management program for control of TB transmission in Nepal.

SOA-637-06 High mortality and prevalence of undiagnosed HIV and tuberculosis in adults with chronic cough in Malawi: a prospective cohort study

M Nliwasa,¹ P Macpherson,² M Mukaka,³ A Choko,³ A Mdolo,³ G Chipungu,¹ H Mwandumba,³ L Corbett^{1,3,4}

¹Helse Nord Tuberculosis Initiative, Blantyre, Malawi;

²University of Liverpool, Liverpool, UK; ³College of Medicine, University of Malawi, Blantyre, Malawi; ⁴London School of Hygiene & Tropical Medicine, London, UK. e-mail: mniwasa@gmail.com

Background: Chronic cough is associated with high mortality in health facility attenders and hospitalized adults in Africa. However, the fate of adults with chronic cough at community level has not previously been investigated.

Methods: Adults reporting chronic cough (≥ 2 weeks) during a household census of 19 936 adults in urban poor setting in Blantyre, Malawi were randomly sampled and age-frequency matched with adults without chronic cough (controls). At 12 months, participants were traced to establish vital status, offered HIV testing and counselling and investigated for tuberculosis (sputum for Xpert® MTB/RIF, smear microscopy and culture, followed by hospital clinician review) if symptomatic. Verbal autopsies to establish cause of death were performed.

Results: Seventy one per cent (245/345) of participants with baseline cough and 70.4% (243/345) of controls were traced. A significantly higher proportion of participants with baseline cough (16/178, 8.9%) compared to controls (7/187, 3.7%; $P = 0.039$) were diagnosed with tuberculosis. Over one-third (56/162, 34.6%) of participants with baseline cough were HIV-positive, substantially higher than among controls (32/170, 18.8%; $P = 0.005$), with 26.8% and 18.8% respectively being previously undiagnosed. The 12-month risk of death was high in both participants with baseline cough (10/245, 4.1%) and controls (6/243, 2.5%, $P = 0.317$).

Conclusion: In high HIV and tuberculosis burden settings, undiagnosed HIV and tuberculosis are worryingly common among adult community members with chronic cough, and the subsequent risk of death is high. Upscaling of community active case finding and interventions to promote timely seeking of HIV and TB care are urgently needed.

SOA-638-06 Will the European Union reach the United Nations Millennium Declaration target of a 50% reduction of tuberculosis mortality between 1990 and 2015?

M Van Der Werf,¹ F Hrubá,¹ S Bonfigli¹ ¹European Centre for Disease Prevention and Control, Stockholm, Sweden. Fax: (+46) 8 5860 1296. e-mail: marieke.vanderwerf@ecdc.europa.eu

Background: At the end of 2015, the world will assess achievements on the Millennium Development Goals (MDG), including MDG 6 targets to reduce tuberculosis

(TB) death rate by 50% compared with 1990. In the European Union (EU), high quality vital registration data with detailed information on cause of death allows assessing whether the target set for TB mortality has been reached or is within reach by 2015.

Design/Methods: We obtained information from the statistical office of the European Union (Eurostat) database on population number, total number of deaths, and causes of death for 28 EU countries for years 1994–2011. Using the number of TB deaths reported in the causes of death data registration and the population data on the 1st of January in the same year, we calculated the TB death rate and estimated its reduction. We also calculated the adjusted TB death rate by taking into account incomplete coverage (deaths with no cause documented) and ill-defined causes of death (International Classification of Diseases – 10th Revision codes R00–R99) as described in the technical appendix of the Global Tuberculosis Report 2014. Finally, we interpolated missing data between existing data points and predicted the death rate for the years up to 2015 using exponential smoothing state space models for time series. Due to data completeness, data from years 1999–2011 were used for EU estimates.

Results: The TB death rates in EU countries ranged from 0.27 to 11.3 per 100 000 in 1994 and from 0.22 to 7.04 per 100 000 in 2011. Between 1999 and 2011 the TB death rate decreased from 1.81 to 1.04 per 100 000, i.e., by 42% for the 28 EU countries. Adjusting the TB death rate for incomplete coverage and ill-defined causes of death provided a 49% reduction, from 2.09 in 1999 to 1.08 per 100 000 in 2011 in the EU. The projected reduction in adjusted TB death rate for 2015 was 64%.

Conclusion: We predict that the EU Member States will reach the MDG target for reduction of TB death rate by 50% by 2015. The new ‘End TB Strategy’ requires a further reduction of the number of TB deaths of 35% by 2020 compared to 2015, which will challenge TB prevention and care in the EU.

SOA-639-06 A historic view on understanding causes of the tuberculosis epidemic: mortality and living conditions in Bern, Switzerland, between 1890 and 1950

K Zürcher,¹ M Ballif,¹ M Zwahlen,¹ M Egger,¹ L Fenner^{1,2}

¹Institute of Social and Preventive Medicine, Bern, ²Swiss Tropical and Public Health Institute, Basel, Switzerland. e-mail:

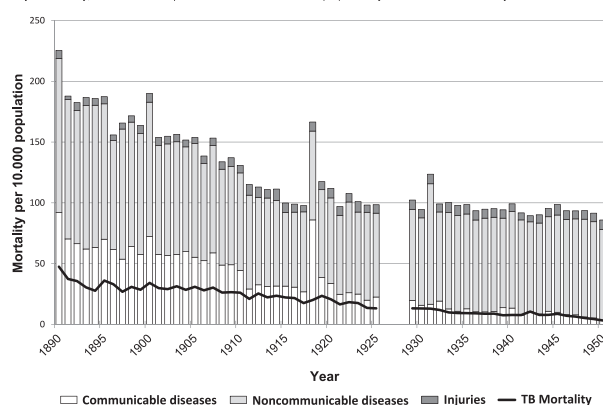
Background: Poor living conditions are the breeding ground for poverty-related diseases such as tuberculosis (TB). In low-income countries with a high TB incidence, such living conditions are common, but not in high-income settings. We studied TB mortality and living conditions in the capital city of Bern, Switzerland, a hundred years ago.

Methods: We screened mortality registries (certified by official autopsies) and public health reports from 1890 to 1950 which were available at the city council of Bern.

Causes of death were grouped in three categories: injuries, communicable and non-communicable diseases. **Results:** Overall mortality steadily decreased from 225 to 86 deaths per 10 000 population between 1890 and 1950 (Figure), but peaked in 1918 due to the influenza epidemic. During the same time period, the population increased from 46 000 to 146 700. The absolute number of deaths due to communicable diseases declined from 467 in 1890 to 48 in 1950, while deaths due to noncommunicable diseases increased from 644 to 1099. During this period, TB mortality decreased 14-fold, from 47.4 to 3.3/10 000 (Figure). Construction of new residential areas offered better living conditions in the city outskirts from 1898 onwards, but improvements in the city centre started only later in 1911. TB mortality differed substantially within the city, with higher mortality in areas of higher population density (correlation coefficient $r = 0.98$, $P = 0.003$), areas with a lower number of rooms per apartment ($r = -0.79$, $P = 0.007$), and areas with a lower number of windows per apartment ($r = -0.72$, $P = 0.02$, based on data from 1911). The densely populated city centre showed a 2-fold higher TB mortality compared to the outskirts: 36.6 versus 15.1/10 000 in 1911-1915, and 20.3 versus 13.7/10 000 in 1921-1925. According to a survey from 1896, the city centre had a higher dwelling density compared to the outskirts (2.2 versus 1.4 persons per room), and considerably lower indoor airspace (18 versus 60 m³ / person).

Conclusion: Poor living conditions characterized by overcrowding and poor indoor ventilation fuelled the TB epidemic in the Swiss capital city Bern in the last century. Similar conditions can be found today in large cities of low-income countries. Improved living conditions and public control measures likely led to the decline in TB mortality in Bern before effective treatment options became widely available.

Figure. Changes in the mortality due to injuries (including homicide), communicable (infectious diseases and infant death), and non-communicable diseases (including cancer) in the capital city of Bern, Switzerland, between 1890 and 1950. Bars represent average 5-year mortality; the black curve represents the overall tuberculosis (TB) mortality. Data not available for the years 1926 to 1928.

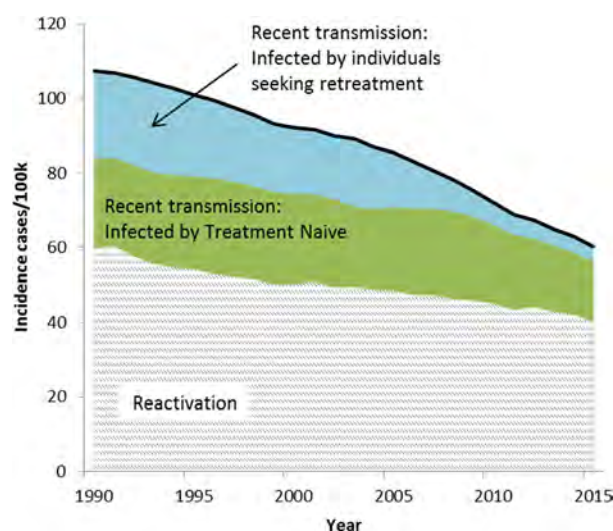


SOA-640-06 Tuberculosis control strategies to reach the 2035 global targets in China: the role of changing demographics and reactivation disease

G Huynh,¹ D Klein,¹ D Chin,² B Wagner,¹ P Eckhoff,¹ R Li,³ L-X Wang³ ¹Institute for Disease Modeling, Bellevue, Washington, ²The Bill & Melinda Gates Foundation, Seattle, Washington, USA; ³Chinese Center for Disease Control and Prevention, Beijing, China. e-mail: ghuynh@intven.com

Background: In the last 20 years, China ramped up a DOTS (directly observed treatment, short-course)-based tuberculosis (TB) control program with 80% population coverage, achieving the 2015 Millennium Development Goal of a 50% reduction in TB prevalence and mortality. Recently, the World Health Organization developed the End TB Strategy, with an overall goal of a 90% reduction in TB incidence and a 95% reduction in TB deaths from 2015-2035. As the TB burden shifts to older individuals and China's overall population ages, it is unclear if maintaining the current DOTS strategy will be sufficient for China to reach the global targets.

Design/Methods: We developed an individual-based computational model of TB transmission, implementing realistic age demographics and fitting to country-level data of age-dependent prevalence over time. We explored the trajectory of TB burden if the DOTS strategy is maintained or if new interventions are introduced using currently available and soon-to-be-available tools. These interventions include increasing population coverage of DOTS, reducing time to treatment, increasing treatment success, and active case finding among elders > 65 years old. We also considered preventative therapy in latently infected elders, a strategy limited by resource constraints and the risk of adverse events.



Results: Maintenance of the DOTS strategy reduces TB incidence and mortality by 42% (95% credible interval, 27-59%) and 41% (5-64%), respectively, between 2015 and 2035. A combination of all feasible interventions nears the 2035 mortality target, reducing TB incidence and mortality by 59% (50-76%) and 83% (73-94%).

Addition of preventative therapy for elders would enable China to nearly reach both the incidence and mortality targets, reducing incidence and mortality by 84% (78-93%) and 92% (86-98%).

Conclusion: The current decline in incidence is driven by two factors: maintaining a low level of new infections in young individuals and the aging out of older latently infected individuals who contribute incidence due to reactivation disease. While further reducing the level of new infections has a modest effect on burden, interventions that limit reactivation have a greater impact on TB burden. Tools that make preventative therapy more feasible on a large scale and in elders will help China achieve the global targets.

SOA-641-06 The burden of tuberculosis among acute emergency-affected displaced populations

A Tate,¹ S McNabb,¹ S Cookson² ¹Rollins School of Public Health, Atlanta, GA, ²U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA. e-mail: sgc0@cdc.gov

Background: A substantial proportion of the world's population is affected by conflict-generated (humanitarian) or natural emergencies. By the end of 2013, 51.2 million people had been forcibly displaced, many acutely. Unfortunately, little is known about the tuberculosis (TB) burden among displaced populations. Yet TB is prevalent, and these settings both increase the risk of new infection and decrease the chances of completing TB therapy. So quantifying the TB burden in these settings will help guide the need for prevention and control efforts.

Design/Methods: Countries in 2009, 2011, and 2013 affected by acute emergencies with 350 000 new internally displaced persons (IDPs) were identified from several datasets. Estimated TB burden (number and proportion) among newly displaced IDPs, and newly returning IDPs and refugees was determined using WHO national TB prevalence rates. Weighted estimates were aggregated by WHO Regions, emergency type, and World Bank country economic classification.

Results: Forty-five countries were identified; the newly displaced population ranged from 17 814 666 in 2009 to 29 906 491 in 2013. Most countries experienced both humanitarian (conflict-generated) and natural emergencies; the WHO African Region had the most countries with both ($n = 18$). Natural disasters produced the greatest number of IDPs (>35 million) and the highest estimate of displaced populations with TB (55 846). Although countries experiencing only conflict did not have the highest number of IDPs (>19 million), the weighted TB burden was highest in these countries, with IDPs accounting for 1.83% of the estimated TB burden compared with 0.44% for natural disasters and 1.61% for both types (Table). According to the World Bank's economic classification, the TB burden among IDPs ranged from 0.03% for high-income to 1.32% for low-income countries.

Conclusion: We found a high TB burden among acute emergency-displaced populations and countries affected by conflicts had the highest estimated TB burden based on national TB prevalence compared with countries affected by other types of emergencies. This raises concern about disrupted treatments, including for TB control. Implementing TB prevention and control programs as soon as possible in the acute phase of a humanitarian emergency will minimize the risk of transmission and maximize chances of completing therapy.

SOA-642-06 Use of nucleic acid amplification tests for determining risk of tuberculosis transmission

Y Xie,¹ W Cronin,² R Oatis,² S Cohn,³ L Paulos,² J Razeq,² R Chen,¹ S Dorman³ ¹Tuberculosis Research Section, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, ²Maryland Department of Health and Mental Hygiene, Baltimore, MD, ³Johns Hopkins University School of Medicine, Baltimore, MD, USA. Fax: (+1) 301 480 5705. e-mail: yingda.xie@nih.gov

Background: Sputum smear microscopy-negative pulmonary tuberculosis (PTB) patients typically are less infectious than smear (SM)-positive PTB patients. Nevertheless, molecular epidemiology studies have shown that SM-negative PTB patients contribute significantly to transmission. Compared to smear microscopy, nucleic acid amplification tests (NAAT) have a lower (diagnostically more favorable) limit of bacillary detection. We hypothesized that the risk of transmission from sputum NAAT-negative PTB patients is exceedingly low. **Objective:** To estimate the risk of *M. tuberculosis* transmission from sputum NAAT-negative vs. sputum NAAT-positive PTB patients.

Design/Methods: Retrospective study was performed using existing TB program data in MD, USA, from 2004 to 2009, during which *M. tuberculosis* fingerprinting and contact investigations were performed routinely for all culture-positive PTB patients and NAAT (Amplified *Mycobacterium tuberculosis* Direct Test [Gen-Probe, San Diego, CA]) was performed routinely for PTB suspects. Patients with *M. tuberculosis* isolates having the same fingerprint were assigned to clusters; transmission events were approximated by collection order of individuals' first culture-positive specimens. Transmission risk was assessed in 2 ways. First, we assessed the risk of being identified as a genotypic cluster index case. Second, we assessed the number of consecutive transmission events among secondary cases who immediately followed and had the same sputum NAAT result as the index case. As a point-of-reference, we also estimated risk of transmission from sputum SM-positive vs. sputum SM-negative PTB patients.

Results: Among 822 culture-positive PTB individuals, 697 (85%) had complete laboratory and genotyping data and were analyzed. Compared with NAAT-positive PTB patients, NAAT-negative PTB patients were 81% less likely to be classified as index cases (RR=0.19, 95%CI

0.01-1.17) and 91% less likely to transmit TB (RR=0.09, 95%CI 0.01 to 0.52). Compared with SM-positive PTB patients, SM-negative PTB patients were 34% less likely to be classified as index cases (RR=0.66, 95%CI 0.36-1.18) and 61% less likely to transmit TB (RR=0.39, 95%CI 0.23-0.64).

Conclusion: Risk of transmission from NAAT-negative PTB patients is substantially less than that from NAAT-positive PTB patients. NAATs may have a role in infection control and decisions about respiratory isolation and contact investigations, and therefore may be important public health tools.

05. Training for the fight against TB

SOA-643-06 Onsite coaching: an effective way to improve laboratory performance in external quality assurance, Ghana

F Dzata,¹ E Mensah,² F Sorvor,³ F Bonsu¹ ¹National TB Control Program, Accra, ²Public Health Laboratory, Effia Nkwanta, ³Konongo Hospital, Konongo, Ghana. e-mail: francaus@gmail.com

Background and challenges to implementation: The Laboratory plays a critical role in TB diagnosis because early detection will lead to early treatment and reducing the risk of spread of the infection. External Quality Assurance (EQA) for TB microscopy is an integral part of the TB program and it is done to ensure laboratories produce accurate and reliable results for patient management. A review of Laboratories performance in EQA showed the Ashanti region which has the second highest number of diagnostic centers (laboratories) had only 57.6% of these facilities attaining the national performance target of 85%.

Intervention or response: The national TB laboratory team organized onsite coaching on TB microscopy at the different diagnostic centers in the region in the first quarter of 2014. The objective was to train laboratory staff on TB microscopy and all components of EQA. The onsite coaching was to ensure that all staff receive the training in their work setting using their own equipment and not only selected staff being trained at a central point. This was also to enable the national team assess the functionality of the microscopes and other equipment and reagents on site. The team visited the laboratories in the region and at each site staff were given hands on training on documentation, logistics management, smear preparation, biosafety measures, microscope use/maintenance and Internal Quality Control (IQC). Training was in form of power point presentations and practical sessions in the laboratory.

Results and lessons learnt: After one week onsite coaching of laboratories in the region, EQA assessment for all quarters in 2014 showed 92.5% of laboratories in the region attained the national performance target of 85%, an improvement of 35.4% over the 2013 performance. Monitoring and support visits paid to laboratories in the region after the onsite coaching also

showed 92% of laboratories improved their biosafety measures, 80% improved in documentation in the TB laboratory register, all facilities had the required level of reagents and consumables and almost all (70%) facilities performed IQC

Conclusions and key recommendations: Onsite coaching is an effective and innovative method to improve laboratories performance in EQA by ensuring every staff is trained in their own work environment. We recommend onsite coaching for all laboratories performing below the national EQA performance target of 85%.

SOA-644-06 How medical colleges in India are contributing to ensuring universal access to TB care in India: a case study from Himachal Pradesh State

A Bhardwaj¹ ¹Dr. Rajendra Prasad Government Medical College, Tanda, Kangra, India. e-mail: ashoknonu@gmail.com

Background Revised National Tuberculosis Program (RNTCP) in India in 1997 recognized the role of Medical College in providing comprehensive TB care services and now is the largest national health program globally to have documented contribution of Medical Colleges in program implementation. Himachal Pradesh (pop; 7 million) is a hilly state in India with difficult geographical terrains and sparse population. There are two medical colleges (IGMC Shimla and RPGMC Tanda) in the state. During initial years of RNTCP launch in Himachal between 1997 and 2002, the program faced several challenges in service delivery, lack of infrastructure and skilled human resource. Medical College's involvement provided solutions to many of the problems; as a result, program has been achieving its objective of case detection and cure rate for last several years. This study documents the functioning of medical colleges for implementing RNTCP and contributions made by the medical colleges in state of Himachal Pradesh.

Intervention or response: A State Task Force (STF) at state level and core committees in both Medical Colleges were formed to implement and review the program. DMC cum DOTS centers were opened in both colleges with an objective to provide the quality assured diagnosis and standard treatment. Series of trainings were conducted both at national and state level. Diagnostic and treatment services were established at both medical colleges for MDR-TB cases.

Results and lesson learnt: Medical colleges in Himachal Pradesh contributed in a major way in finding more TB cases. In 2013 and 2014, medical colleges contributed 15 percent of total cases, 10% of smear negative and 40% of extra-pulmonary TB cases in the state. However, there is some gap in service delivery. All referred for treatment cases are not being followed up in the districts; as a result, there is a high initial default rate. Medical College's faculties are earnestly following RNTCP guidelines. State Task Force in 2014 supported two PG dissertations, 14 major operational research projects and

ten Short Term operational research projects under RNTCP.

Conclusion: There is a systematic involvement of medical colleges in RNTCP implementation in Himachal Pradesh. However, in view of providing Universal access to quality TB care and meeting new targets under National Strategic Plan 2012-17, medical colleges has to play a bigger role in capacity building, service delivery by improving coordination and operational research.

SOA-645-06 Health service provider's availability and knowledge about TB in 45 districts from India: implications for TB prevention and care

K Sagili,¹ A Das,¹ B Entoor Ramachandran,¹ B Thapa,¹ P Banuru Muralidhara,¹ S Pandurangan,¹ S Mohanty,¹ S Chadha¹ ¹International Union Against Tuberculosis and Lung Disease, South East Asia Office, New Delhi, India. Fax: (+91) 11 4605 4430. e-mail: ksagili@theunion.org

Background: Availability of trained Health Service Provider (HSP) and their correct knowledge about health conditions like Tuberculosis (TB) is essential for early identification and appropriate disease management. This reduces the delay in diagnosis and treatment initiation and duration of transmission which is essential in reducing the burden of TB.

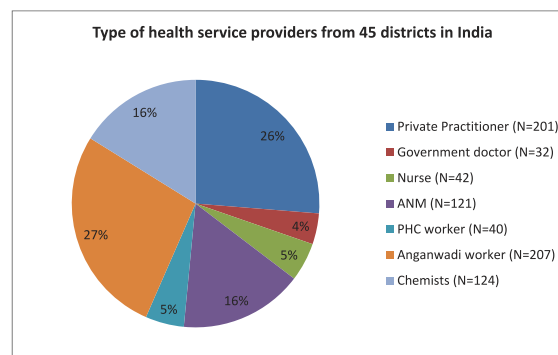
Design/Methods: A KAP survey was conducted to capture the knowledge, attitude and practice about TB among HSPs in 45 districts from 17 states in 2013. Stratified cluster sampling was carried for districts selection. From each district, 10 primary sampling units (PSU) were selected by population proportionate to size method, with each unit having an approximate 200 households. Hence a total of 450 PSUs covering about 90 000 households were surveyed. The HSPs were identified with the reference from general population and interviewed using a semi-structured questionnaire. For the study purpose, the HSPs were defined as those to whom general population would approach for their day-to-day medical needs at village or ward level. These included qualified government doctors, nurses, auxiliary nurse midwives (ANM), anganwadi workers (AWW) and primary health centre (PHC) staff from public health system and chemists and qualified/non-qualified practitioners from private sector.

Results: A total of 767 health service providers were line-listed and interviewed during the survey. Of these majority identified based on their availability were AWW's (27%) followed by private practitioners (26%), ANM's (16%) and chemists (16%) (Figure). The availability of qualified government doctors was minimal (4%). Among the providers from public health system, 69% doctors, 38% nurses, 50% ANMs and 35% PHC workers and AWWs had correct knowledge about TB (symptom+diagnosis+treatment). And among private sector 24% practitioners and 15% chemists had correct knowledge. Important issue to be noted is the non-availability of government doctors at village or ward

level, only 32 were found from 450 villages/wards covering about 90,000 households.

Conclusion: The knowledge about TB among health service providers in India whether government or private providers is inadequate. Non-availability of qualified government doctors at village/ward level is an issue requiring intervention at the earliest. This situation if not intervened immediately will have serious implications in TB prevention and care, posing a threat to the End TB strategy.

Figure 1: Type of health service providers available at village or ward level at the time of KAP survey in 2013 conducted in 45 districts from 17 states in India



SOA-646-06 Effectiveness of a training course on quality assurance of chest radiography in Laos

A Ohkado,¹ P Vangvichit,² T Sorsavanh,² O Rasphone,³ M Mercader,⁴ K Osuga,⁵ T Date⁶ ¹Research Institute of Tuberculosis / Japan Anti-Tuberculosis Association, Kiyose, Japan; ²National Tuberculosis Control Programme, Ministry of Health, Vientiane, ³X-ray Unit of Health Science University of Lao PDR, Vientiane, Laos; ⁴Radiology Department, Gat Andres Bonifacio Memorial Hospital, Manila, Philippines; ⁵Stop TB, Office of the World Health Organization Representative in Viet Nam, Western Pacific Regional Office, Hanoi, Viet Nam; ⁶College of Healthcare Management, Miyama, Japan. Fax: (+81) 424 93 5529. e-mail: ohkadoa@jata.or.jp

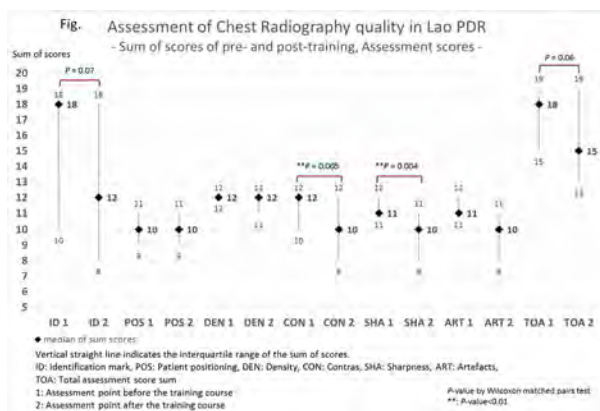
Background: Chest radiography (CXR) plays a major part of X-ray facility functions in the world. It is of critical importance to improve and maintain the quality of CXR to avoid faulty diagnosis of smear-negative/CXR suggestive pulmonary tuberculosis (PTB) patients. The present study aims to determine the effectiveness of training in improving the quality of CXR among radiological technologists (RTs) in Laos.

Design/Methods: This was a cross-sectional study through on-site investigation of X-ray facilities, interviewing RTs, and reviewing CXR films before and after the training in 2013 in Laos. In all, 19 government X-ray facilities with RTs selected by Laos National Tuberculosis Control Program were eligible for inclusion. The profiles of the X-ray facilities were collected using a semi-structured questionnaire form. Three recently taken CXR films of men and another three of women aged over 15 years were collected both before and after the

training course from all of the RTs. The quality of the CXR films was assessed using "Assessment sheet for Imaging Quality of Chest Radiography" developed by the Tuberculosis Coalition for Technical Assistance. The scores per every six assessment factor were summed. Wilcoxon matched pairs test was applied to compare the scores on CXR films taken before and after the RTs attended the training course.

Results: In all, 19 RTs from 19 facilities at 16 provinces across Laos participated in the training course. Among them, 17 RTs submitted the required set of CXR films, i.e. 204 in total. A wide range of X-ray machine settings became apparent, e.g. tube voltage ranged from 40 to 120 kV and tube current from 50 to 500 mA. The assessment of CXR films indicated that the training was effective in improving the CXR quality with respect to contrast ($P = 0.005$), sharpness ($P = 0.004$) (Figure), and total sum score of the six assessment factors ($P = 0.009$). While the training did not seem effective in improving other assessment factors such as identification mark, patient positioning, density, artefacts, and total assessment score sum, but the sum scores of both the identification mark ($P = 0.07$) and total assessment score ($P = 0.06$) tended to show an improvement.

Conclusion: The significant improvement of the total sum score of the six assessment factors in addition to contrast and sharpness strongly suggests the positive impact of the training course to improve the quality of CXR in a sample-population of RTs in Laos.



SOA-647-06 Distance-learning pilot course for front-line staff of the Peruvian National Tuberculosis Program guidelines

J Lulli,¹ A Mendoza-Ticona,² L Otero,¹ G Córdova,¹ K Castillo,³ C Montero,² A Valentina Antonieta,² E Gotuzzo¹ ¹Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, ²Estrategia Sanitaria Nacional para la Prevención y Control de la Tuberculosis, Ministerio de Salud, Peru, ³Facultad de Medicina Alberto Hurtado, Universidad Peruana Cayetano Heredia, Lima, Peru. e-mail: jose.lulli@upch.pe

Background: The Peruvian National Tuberculosis (TB) Program (NTP) issued a new version of the TB guidelines in November 2013. A distance education program to

train front line TB workers was implemented in a joint collaboration with the NTP and the Instituto de Medicina Tropical Alexander von Humboldt and the Telemedicine Unit of the School of Medicine, at Universidad Peruana Cayetano Heredia. We report the pilot implementation.

Methods: A well organized and good performing district health division in Lima was selected for the pilot. A single face-to-face training session introduced students to the online platform. Upon completion of a baseline survey, a pretest evaluation, participants started the 12 week, 6 hours-per-week course which included: 20-minute lectures recorded by country experts, scientific and programmatic literature, videos, brief post-tests and forum interaction. On a weekly basis, two district coordinators provided standard answers for pooled questions from the forum. Personalized SMS delivered course and TB-related news to participants as well as single reminders to those about to miss a deadline. Technical support was provided by phone and mail. Participants missing at least 7 post-tests were considered dropouts.

Results: We registered 108 students (30 medical doctors (MD), 39 registered nurses (RN) and 39 nurse aids (NA). Among the 92 who completed the survey: 86% (79) were women, median age was 39 years (IQR: 32-47). Median time from graduation was 8 years (IQR: 6-17) and they had been in their post for 3 years (IQR: 1-6). Prior participation in a distance education program was reported by 20% (18), 84% (77) owned a home computer and 27% (25), a smartphone. Internet use was reported daily by 30% (28), several times per week by 27% (25) and less than once per week by 37% (34). The pretest evaluation median was 16 (IQR: 14-17) with no significant differences by staff profession. Mid-term scores were 11.8 for RN, 13.0 for MD and 10.9 for NT. Dropouts began on week 4 and increased on weeks 5 to 10 irregularly. In total, 17 (15.7%) students dropped out with no difference by staff profession. Among the dropouts, 70% cited time constraints as the main reason for dropout and 30% cited constraints in accessing a computer.

Conclusions: Overall course retention was high, most NTP staff were active in most course activities. Course support to students may increase course participation. A distance-learning course is a good alternative for NTP staff training.

SOA-648-06 Fortalecimiento de la comunicación e implementación de nuevas técnicas para la colección de muestras de esputo para incrementar la carga bacilar

K Tintaya,¹ M Mendoza,¹ J Jajaycucho,¹ C Pinedo,¹ L Lecca,¹ C C Contreras,² J Coit,² C Mitnick² ¹Socios En Salud Sucursal Perú, Lima, Peru ; ²Harvard Medical School, Boston, MA, USA. e-mail: ktintaya_ses@pih.org

Background: Se identificó la necesidad de establecer mejoras en la educación del paciente y adicionar nuevas técnicas en la colección de muestras de esputo. Esto debido a que aun cuando existen guías proporcionadas

por el Ministerio de Salud (MINSA), existe sobrecarga de trabajo y falta de tiempo en el personal de salud, para brindar educación al paciente y obtener una muestra adecuada que permitan obtener resultados y tratamientos oportunos. En un estudio previo, de 107 encuestados, el 80% obtuvo una buena calidad de sus muestras y fueron aquellos que recibieron una educación previa por parte del personal (Armas, Y. 2010).

Design/Methods: Se buscó a pacientes con baciloscopia (++) o (+++) para incluirlos a un ensayo clínico. Se buscó en 61 establecimientos de salud de Lima Metropolitana durante 13 meses (febrero 2014 a febrero 2015). Se incluyó a todos los pacientes que tuvieron un resultado de baciloscopia positiva (+) a través de un personal del estudio. Se entrevistó a cada paciente y se brindó materiales para colección de muestra que debía de usar durante la obtención de su segunda muestra (frasco de colección, cepillo dental y agua gasificada). Además se educó al paciente acerca de los criterios que se debe considerar para mejorar la calidad de la muestra. Al día siguiente, el paciente entregaba su segunda muestra al personal de salud, quienes enviaban para su procesamiento, al mismo laboratorio que brindó el primer resultado.

Results: Se identificaron 196 pacientes que tuvieron una baciloscopia (+) en su primera muestra. Luego de implementar las nuevas técnicas y brindar educación para mejora de la calidad de la muestra, se obtuvo que el 22% mejoró la carga bacilar a (++) o (+++); el 30% mantuvo su misma carga bacilar; el 13% obtuvo una segunda muestra negativa; y en 35% no se pudo obtener información de la segunda muestra. Nuestro estudio intenta demostrar que la educación que se brinda al paciente y la implementación de las técnicas incrementa la calidad de la muestra.

Conclusion: Intervenciones en educación e incorporación de nuevas técnicas que mejoren la colección de esputo, ayuda a que el paciente incremente sus posibilidades de un diagnóstico y tratamiento oportuno. Se recomienda que los programas locales de TB consideren que intervenciones sencillas, pueden contribuir a mejorar la carga bacilar y a su vez, fortalecer la relación entre los pacientes y el personal de salud.

SOA-649-06 Interactions between nurses and doctors in caring for TB patients

T Fedotkina,¹ V Sarkisova,² O Komissarova,² P Volkova,³ N Serebrennikova,² M Driever,⁴ B Mandleco⁵ ¹Tomsk Oblast TB Center, Tomsk, ²Russian Nurses Association, St Petersburg, ³Marii El TB Department, Joshkar Ola, Russian Federation; ⁴Self-Employed, Seattle, WA, ⁵Brigham Young University, Provo, UT, USA. e-mail: fedot-tanya@yandex.ru

Background: It is obvious that caring for TB patients requires constant interaction between doctors and nurses, the quality of which plays an important role in providing quality patient-centred TB care. Therefore, this study aimed to identify key issues discussed by doctors and nurses in the process of their interaction and describe the kind of interaction happening between

doctors and nurses while caring for TB patients and their families.

Design/Methods: A qualitative descriptive study was conducted to look at the interaction between doctors and nurses. Respondents completed a questionnaire consisting of demographics, five open-ended questions and an assessment tool to measure the benefits of joint doctor-nurse discussions about patient care on a scale of one to 10.

Results: Eighty-three TB doctors and nurses (43 doctors and 40 nurses) from 16 Russian regions participated. Twenty-one doctors (49%) and 20 nurses (50%) responded that joint discussions of patient care issues was of maximal benefit. However, respondents raised a number of obstacles to such productive professional dialogue. High workload and lack of time to jointly discuss patient care issues was raised as a barrier. Both doctors and nurses reported that the clear distinction between the roles of doctors and nurses presented a challenge for teamwork and joint patient care management. For example, doctors tend to regard a nurse's job as unimportant and nurses lack confidence in their own professional value for doctors and patients. Nurses reported that they sometimes doubt doctors' professional competence (appropriate treatment regimen, prescriptions not ordered on time, unwillingness to accept and use the information about the patient, etc.) and doctors may doubt nurses' qualifications which hindered useful interaction. Nurses felt doctors underestimate the nurses' influence on patients' treatment outcomes.

Conclusion: About half of the doctors and nurses included in the study were satisfied with their professional relationship and describe their interaction as mutually beneficial. To improve the quality of inter-professional cooperation joint conferences should be organized for nurses and doctors, providing a platform to discuss individualized patient-centred care, teamwork and mutual trust in colleagues' professionalism.

SOA-650-06 Evaluation of different models of training to improve health care worker knowledge of childhood TB at primary health care level in South Africa

L Du Plessis,¹ K Du Preez,¹ M Palmer,¹ V Azevedo,² E Mhlope,³ A Hesseling¹ ¹University of Stellenbosch, Cape Town, ²City Health, Cape Town, ³USAID TB Program, Johannesburg, South Africa. e-mail: lienkiduplessis@gmail.com

Background: There is limited evidence regarding appropriate childhood TB training strategies in high-burden low-resource settings. There is currently a shift in education models, moving away from didactic approaches, towards decentralised interactive self-study models. Guidance regarding feasible and effective training strategies is needed.

Design/Methods: As part of a paediatric TB health system strengthening project (Kid-care) implemented in Khayelitsha, Cape Town (2013/4), we conducted 15 four week training sessions on childhood TB at primary care

level. Groups were randomized to 1 of 3 models of support (lectures, peer-groups or self-learning). Impact of the training on knowledge was measured with a 55-question test at three time points: pre-training, post-training and 10 weeks thereafter.

Results: 131 nurses (median age 41 years (SD 10.2), 122(95%) female) were enrolled from 9 clinics; 100 (76%) completed post-test and 79 (60%) retention testing, while 27(21%) had provided TB care during the preceding 2 years. The mean baseline knowledge was 66% (SD4.6), and was not age-associated. Overall pre-post knowledge gained was 11%, with the lecture model gaining 14.8% and peer-groups 8.4% compared to self-learning (Table). No significant difference between knowledge retention was observed between training models (Table). Externally facilitated lectures were better attended than participant facilitated sessions (attending >2/4 sessions: 94% lecture learners, 26% self-learners and 30% peer-group learners). Despite higher baseline knowledge amongst TB nurses [72% (95%CI 68-75) vs. 64% (95%CI 62-67), $P = 0.001$], there was a comparable increase in knowledge [8% (95%CI 1-16) vs. 1.2% (95%CI 7-17), $P = 0.3210$].

Conclusion: Focussed training increased knowledge of childhood TB amongst all participants irrespective of work area, highlighting the need for training initiatives to target HCWs across services. This is of particular importance as children may access care at multiple health services entry points and staff turn-over is often high. Although the lecture model achieved the highest mean increase, the results may reflect dedicated time spent on course content rather than the effects of a didactic model. Training initiatives need to consider multiple setting specific factors to ensure participant engagement. Longer term retention assessment should be considered and the impact of training on clinical practice and patient outcomes evaluated.

Table 1: Cluster level analysis of overall knowledge gained and retained on childhood TB, stratified by model of training support received in primary care nurses completing a standard childhood TB training program in Cape Town South Africa (n= 15 clusters, 5 per model of support)

Comparing knowledge increase between pre and post-test						
	Mean % (SD) Pre test ¹	Mean % (SD) Post test ²	Mean % (SD) Increase	Difference in mean % from baseline ³	95% CI	p-value
Overall results						
All participants	66.0 (4.6)	77.3 (6.3)	11.3 (8.1)	n/a	6.8-15.8	0.0001
Stratified by Model of Support						
Self-learning	69.0	72.5	3.5	(Baseline)	-	-
Peer-groups	65.5	77.5	12.0	8.4	2.6-14.3	0.01
Lectures	63.5	81.9	18.3	14.8	6.1-23.5	0.004
Comparing knowledge retention between immediate post-test and retention test						
	Mean % (SD) Post test ²	Mean % (SD) Retention test ⁴	Mean % (SD) difference	Difference in mean % from baseline ⁵	95% CI	p-value
Overall results						
All participants	77.3 (6.3)	80.9 (6.2)	3.7 (5.7)	n/a	0.5-6.8	0.025
Stratified by Model of Support						
Self-learning	72.5	78.9	6.4	(Baseline)	-	-
Peer-groups	77.5	81.0	3.5	-2.9	-10.9-5.0	0.418
Lectures	81.9	83.0	1.1	-5.3	-13.4-2.8	0.169

¹15 clusters obtained from 131 individual observations

²15 clusters obtained from 100 individual observations

³Comparing other models of support with Self-learning (baseline)

⁴15 clusters obtained from 79 individual observations

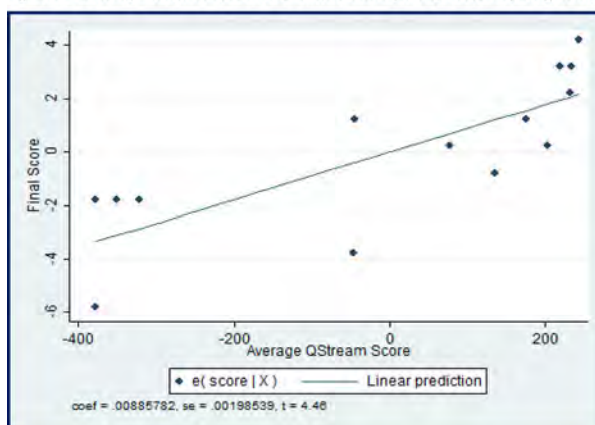
SOA-651-06 Targeted, repetitive intervention to improve MDR-TB knowledge retention in Rayong Province, Thailand

D Punpipitt,¹ S Chareonsiri,¹ J Indrasap,² C Thibbadee,³ A Innes¹ ¹FHI 360 Asia Pacific Regional Office, Bangkok, ²Rayong Provincial Health Office, Rayong, ³Rayong Provincial Hospital, Rayong, Thailand. e-mail: ainnes@fhi360.org

Background: Effective pre-service education and in-service training are critically important for the health care work force to maintain and update knowledge. Multi-drug resistant tuberculosis (MDR-TB) is a complex disease, and effective patient management requires knowledge and application of clinical and public health guidelines. Repetitive, interval reinforcement creates a “spacing effect” that has been shown to improve knowledge retention. Presenting information and reinforcing it over intervals of time is the principle behind QStream, an internet-based application that has been shown in clinical trials to improve knowledge retention, change behavior to improve adherence to guidelines, and increase learner engagement.

Intervention: In Rayong, Thailand, the USAID Control and Prevention-Tuberculosis (CAP-TB) project pilot-tested QStream to teach clinical concepts for TB, MDR-TB, and TB-HIV. Regular teaching conferences with the TB team identified key learning points that formed the basis for quiz questions (multiple choice or true/false). Following each teaching conference, these quiz questions were sent to the team in Rayong, a multi-disciplinary group of physicians, registered nurses, pharmacists, laboratory technicians, and coordinators. The QStream platform determined the frequency between each question based on the number of questions (4-5) in each quiz and the duration of the quiz (1-2 months). Each question had to be answered twice correctly before it could be retired. Questions were designed to take less than 5 minutes to complete, maximizing efficient learning while on the job.

Figure 1. TB knowledge and retention (Final Score) is associated with QStream participation (Average Score)

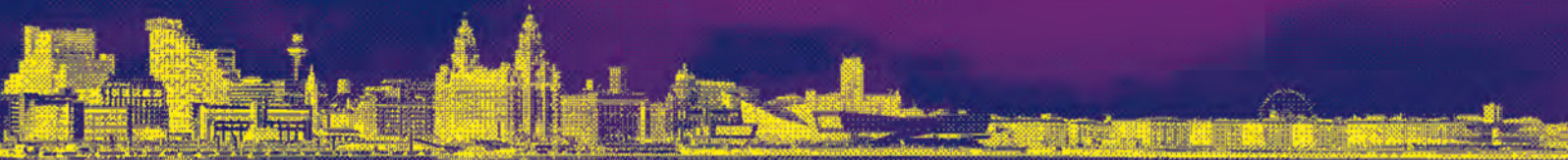


Results: Over one year, a total of 6 quizzes were sent to the Rayong TB team. At the end of the year, a final test was administered that comprised all questions from the year. We found that TB knowledge was positively correlated with participation in the teaching conferences

and QStream quizzes throughout the year ($R = 0.59$, Figure). This result shows that people who did well on the quizzes throughout the year also did well on the final test.

Conclusion: Although the sample size is small, the results suggest that a targeted, repetitive method of teaching is effective to acquire and retain TB knowledge. Given the high turnover among TB staff in Thailand, it is important to identify an effective method to certify and maintain basic TB knowledge among all staff, both new and old. Using QStream to reinforce and solidify key concepts may be one solution.

CONFRONTING RESISTANCE: FUNDAMENTALS TO INNOVATIONS



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