

Recent tuberculosis advances in Latin America

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Purpose of review

Tuberculosis kills more people than any other infection. Despite advances in diagnostic methods and greater understanding of the reasons for treatment failure, tuberculosis remains common throughout Latin America.

Recent findings

The impact of HIV and multidrug resistance on tuberculosis control has been enormous. HIV-positive patients may be at 10 times greater risk of multidrug resistant tuberculosis than HIV-negative patients. Hopefully, improved diagnostic techniques will allow more rapid diagnosis of tuberculosis and new colorimetric systems are being developed that will enable expedited drug-sensitivity testing. However, in alarming reports, only 58% of patients were treated with the recommended treatment regime in a Brazilian study, and dropout from treatment in parts of Bolivia was common. Many failings could be combated by rigorous education of patients and physicians. In an encouraging advance, multidrug resistant tuberculosis was successfully treated in a community-based programme, saving an estimated 90% of the cost of hospital-based treatment. An opportunity to identify treatment failure earlier is demonstrated by the finding that 2 months after the initiation of therapy, positive smears were found in only 3% of those whose treatment was successful, but 74% of those whose treatment failed.

Summary

The importance of inexpensive and widely available drugs to treat HIV and multidrug resistant tuberculosis in Latin America is clear. The need for rapid, affordable tests for tuberculosis diagnosis, and for easy drug sensitivity testing is also evident. Finally, improving treatment success is achievable even in the resource poor setting.

Keywords

tuberculosis, Latin America, Central America, South America, HIV, MDR, review

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Abbreviations

BCG Bacillus Calmette-Guérin
DOTS direct observed treatment, short-course
MDR multidrug resistant
WHO World Health Organization

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Introduction

Globally, tuberculosis is responsible for more than two million deaths each year [1]. It remains endemic throughout Latin America (Table 1) despite renewed efforts in many national control programmes [2,3**] and recent advances in disease detection [4–9] and drug sensitivity testing [10,11**,12] in the resource-poor setting. Over the last 20 years, tuberculosis notification rates appear to be on a slow decline; this effect, however, is not dramatic (Fig. 1) [1]. Moreover, many young people still die from tuberculosis [3**,13] and this has major economic and social implications [14] for endemic areas. Advancing our understanding of tuberculosis and the barriers to its successful treatment is vital. This review sets out several key areas of recent research from Latin America.

HIV

The emergence of HIV, a disease just decades old, has dramatically altered the epidemiology of tuberculosis, a disease millennia old [15,16,17*]. Whilst patients with HIV are at increased risk of developing all types of mycobacterial infections, a study from Brazil has shown that of all laboratory cultures for mycobacteria, *Mycobacterium tuberculosis* was identified in 80%, but only 1.5% revealed atypical mycobacterial species, all in HIV patients [18]. In studies of HIV and tuberculosis co-infection, antiretroviral treatment significantly reduced overall mortality [19], and rates of positive tuberculosis culture fell by two thirds after increased distribution of HIV treatment in Brazil [20*]. This reaffirms the need to provide cheap antiretroviral drugs to the developing world, and to aggressively treat both diseases in co-infected patients.

Multidrug resistance

Throughout the world, multidrug resistant tuberculosis is a growing problem. Many recent studies of tuberculosis in Latin America have focused on this important area.

Multidrug resistance and HIV

As well as the threat to global tuberculosis control caused by HIV, there are increasing problems due to the well known association between HIV and multidrug resistant (MDR) tuberculosis [21*]. This was confirmed in a Peruvian study that showed 10 times greater rates of MDR tuberculosis in those with HIV than in those without [22*]. One Brazilian study, however, found antibiotic resistance was not dependant on HIV status [23].

Rise in multidrug resistance

Recent surveys under the guidance of the World Health Organization (WHO) have looked at rates of primary multidrug resistance (MDR tuberculosis found in previously untreated patients with tuberculosis). Latin American rates varied from a declining rate in Cuba, to

Table 1. Reported and estimated cases and notification rates in South and Central America

	Detected cases	Estimated cases	Estimated rate per 100 000
South America			
Argentina	11 456	17 835	48
Bolivia	10 531	18 407	216
Brazil	74 466	110 511	64
Chile	3006	3106	20
Colombia	11 480	19 970	47
Ecuador	6015	18 140	141
Guyana	422	787	103
Paraguay	2073	3491	62
Peru	37 197	51 231	196
Uruguay	689	973	29
Venezuela	6251	10 337	42
Total	163 586	254 788	88
Central America			
Belize	136	96	41
Costa Rica	630	635	15
Cuba	929	1468	13
Dominican Republic	4766	11 325	133
El Salvador	1458	3895	61
Guatemala	2419	9578	82
Haiti	10 224	27 159	328
Honduras	4435	5787	88
Mexico	18,879	34,192	34
Nicaragua	2447	3582	69
Panama	1711	1415	49
Other Caribbean islands combined	565	1252	17
Total	48 599	100 384	78

Adapted from latest World Health Organization figures [1]. These figures can be compared with an estimated rate in the USA of five per 100 000 and a global rate of 141 per 100 000.

4% or higher in the Dominican Republic and Argentina [24,25]. Ecuador had the highest rate of primary MDR at 6.6%, possibly due to their late-uptake into the direct observed treatment, short-course (DOTS) programme [25]. In Peru, despite a good national programme that has resulted in the country moving out of the WHO list of highest burden countries in recent years [1], rates of multidrug resistance in patients previously treated with tuberculosis drugs (secondary multidrug resistance) have increased to 57% in the last 7 years (Fig. 2), although overall rates of resistance (including patients who have not previously received treatment) are much lower [21*]. Other studies [26,27] also showed that drug resistance is related to prior treatment, but this finding is not universal [22*]. This rise in multidrug resistance is worrying and does not follow the decline in drug resistance seen in China or the USA after the implementation of aggressive control programmes [21*]. Furthermore, HIV rates are low in Peru (<0.5% [28]) and this confirms the potential for increases in rates of multidrug resistance even in areas of low HIV prevalence.

Community-based multidrug resistance treatment

In an exciting study [29**], the use of community-based, directly-observed, individualized therapy of MDR tuberculosis in the resource-poor setting was found to be effective, achieving 83% cure at around 10% of the cost of hospital based treatment. Risk factors for treatment failure were low body mass index and anaemia. If the strain was sensitive, use of ethambutol and pyrazinamide were associated with a favourable outcome. Although the costs of resistance treatment may be out of reach for many developing nations, the recent price reduction of many second-line anti-tuberculosis drugs should help in this regard. Furthermore, the benefits of early treatment in terms of reduction of

Figure 1. Tuberculosis notification rates in Latin America compared with a baseline rate (100) in 1990

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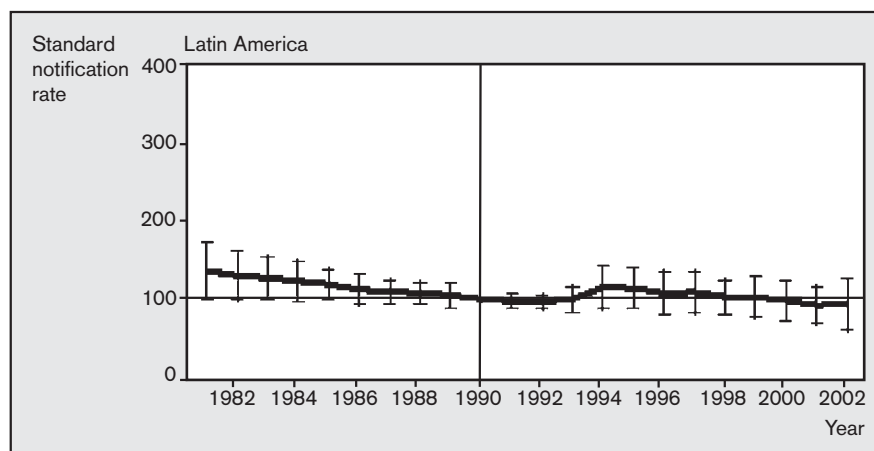
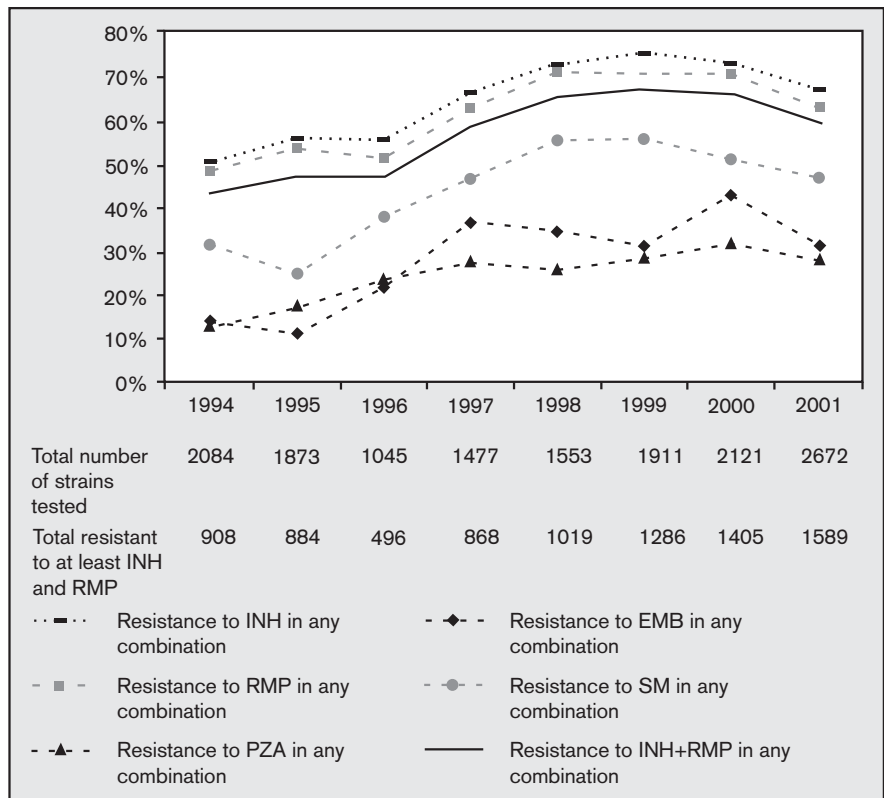


Figure 2. Percentage antibiotic resistance to the five first-line anti-tuberculosis drugs between 1994 and 2001 in previously treated patients in Peru

INH, isoniazid; RMP, rifampin; PZA, pyrazinamide; EMB, ethambutol; SM, streptomycin. Reproduced with permission [21].



multidrug resistance transmission are likely to be worth much more than the immediate financial outlay.

In a follow-up paper, the varied role of the community nurse allowed for the success of outpatient-based treatment of MDR tuberculosis [30]. The importance of psychosocial support in successful treatment was emphasized.

Psychiatric issues

As well as the psychological aspects of treatment, psychiatric issues are also important and probably undervalued in the assessment of tuberculosis patients. Of the MDR patients enrolled in this study, baseline depression and anxiety were found in 52% and 9% respectively [31]. Depression improved markedly during treatment, with a prevalence of 29%, despite a further 13% of patients developing depression after treatment initiation. Psychosis had a disturbing incidence of 12% during treatment.

Diagnostics

In the resource-poor setting, the development of cheap, rapid and accurate methods for tuberculosis diagnosis and drug sensitivity testing is vital, as many areas still rely on poorly sensitive sputum smear microscopy as the only

diagnostic test. In these areas, drug sensitivity testing, if available, usually takes many months to provide a result.

Simple drug sensitivity testing

In an encouraging study from Argentina [11], an inexpensive colorimetric assay has been shown to provide minimum inhibitory concentrations of nine second-line drugs for a cost of less than US\$5 in an average of 8 days. This will aid the development of a fast, widely available sensitivity test for patients with MDR tuberculosis.

Diagnosis in children

Accurately diagnosing tuberculosis in children can be difficult, partly due to underdeveloped immunity [32]. A useful scoring system based on clinical, radiological and epidemiological factors has been adopted by the Brazilian Ministry of Health to aid in the diagnosis of paediatric tuberculosis. Radiographic evidence was the most predictive variable of the score, followed by known exposure and tuberculosis skin test positivity [33].

According to a Peruvian study, a visible *Bacillus Calmette-Guérin* (BCG) scar is a highly sensitive indicator of past vaccination in children up to 3 years old. Indeed, 99% of newborns vaccinated 6 months

previously had a scar diameter greater than 2 mm [34•]. Furthermore, whilst many children responded to a tuberculosis skin test after vaccination, positive reactions (>10 mm diameter) did not occur in the absence of tuberculosis infection. This result is supported by one recent Brazilian study [35]; a separate study, however, recommends a cut-off of 15 mm in children in order to prevent false-positive results as it demonstrated that BCG-induced skin test results of over 10 mm were possible [36].

Advanced technologies

Several studies of more advanced technologies for diagnosis and drug sensitivity testing have been performed recently in Latin America, despite the fact that many of these technologies are often unusable by national tuberculosis control programmes due to cost. In an Argentinean study of commercially available enzyme-linked immunosorbent assay kits for tuberculosis diagnosis, sensitivities ranged from just 29 to 82% for diagnosis of smear positive tuberculosis patients [37]. Also somewhat disappointing was a recent study [38] analysing a commercial serological test kit for tuberculosis: whilst identifying 47% of smear negative patients and being unaffected by prior BCG vaccination, it only detected 64% of smear positive patients. Furthermore, much lower sensitivity rates were found in HIV-positive patients. Studies have also looked at polymerase chain reaction-based systems for improved diagnosis [5–9] and evaluation of drug resistance [12]. In epidemiological studies, DNA fingerprinting has been used to demonstrate the intercontinental patterns of strains [39,40] and clusters of strains in HIV-positive and negative individuals [41–43].

Treatment and treatment failure

Tuberculosis is generally a curable disease. Understanding the reasons behind successful treatment is clearly an important step towards improving global tuberculosis cure rates.

Treatment dropout

The WHO-promoted DOTS strategy has had recent success in South America, for instance in Peru, where improved detection and control has been associated with considerable reduction in infection rates [2]. However, although patients with single-drug resistant or MDR tuberculosis were cured with the same level of success as drug-sensitive tuberculosis in Bolivia, high rates of treatment dropout led to overall poor cure rates [44•]. This presumably contributes to Bolivia's high tuberculosis prevalence compared with other South American countries (Table 1). In Brazil, low adherence to treatment has been found in those in the lowest social class and tuberculosis/HIV co-morbidity was more common [45,46], and more often fatal [17•] in those

with the lowest level of schooling. A study from Havana, Cuba, however, showed that family dysfunction and overcrowding, but not schooling, were associated with tuberculosis incidence [14], although overall levels of tuberculosis are generally low in Cuba (Table 1) [47,48].

Strengthening of national tuberculosis control programmes

Whilst many of the recent advances in the understanding of Latin American tuberculosis have been encouraging, there is still much to be done to adequately implement successful policy and health programmes. For instance, in a paper from Rio de Janeiro that assessed 302 records from patients who had died from tuberculosis, only 69% had had acid-fast bacillary smears, and of smear-negative patients, only one had culture. Recommended treatment was implemented in just 58%. The median age of death was just 47 years old [3••]. Importantly, new strategies and procedures have been implemented in order to counter some of these statistics.

Prison tuberculosis treatment in Brazil has also been studied and found to have high rates of dropout and low rates of cure [49]. In a separate study from Brazil [50•], reasons for defaulting from treatment were assessed. Default rates were greater than 20%. Not having an appointment card, not feeling comfortable with the doctor and non-recording of blood pressure were the strongest predictors of defaulting. The conclusions focus on the need for a more structured local tuberculosis control programme.

Predicting treatment failure

Predicting failure of conventional treatment is the focus of a paper from a team working in Peru [51••]. They looked at several factors and noted that only 3% of patients who were cured at 6 months had positive sputum smears after 2 months of treatment. Conversely, 74% of failure patients had positive smears at 2, 3 or 4 months. A high level of MDR tuberculosis was found in these patients. Naturally, in order to reduce the length of time that patients remain infective whilst being treated with only partially effective drugs, individualized therapy based on early culture is the gold standard. This study, however, was case-controlled and also only used smear negativity, rather than culture negativity, as an indication of cure. This important issue will still need further clarification.

Causes of death

In a study of causes of death in tuberculosis patients in Brazil, respiratory failure was the leading cause of death, occurring in nearly 50% of patients. If figures were combined for tuberculosis being the underlying or an associated cause (mainly if HIV was the underlying

cause) of death, then mortality reached nine per 100 000, almost twice the classical rate [15].

Drug adverse affects

In a study of adverse affects of MDR tuberculosis treatment, peripheral neuropathy was identified commonly, affecting 13% of patients who did not receive pyridoxine prophylaxis [52*]. No other factors associated with neuropathy were identified, although the study size was small. Hypokalaemia is also a noteworthy adverse affect of treatment for MDR tuberculosis [53]. It was concluded in both studies that effective management of these side effects was possible without compromising treatment. Also noteworthy is a review of recreational drug use in Brazil, which demonstrates that pulmonary infections, including tuberculosis, are more common in regular cocaine users [54].

Education

DOTS is the globally preferred treatment strategy to deal with the tuberculosis pandemic. However numerous articles here have shown that education is a further vital strategy to improve patient compliance and guideline adherence by health professionals and institutions. This education must take place at a patient [29**,30*,31**,55–57], physician [55,58,59,60*] and indeed national level [58,60*,61,62], and should be carefully aimed to overcome cultural barriers [56,63].

Other work

Naturally, a wide range of ideas have been investigated in Latin American tuberculosis studies over the last year. Some of the more interesting are focused on here.

Mexico–US border

The frequent northward passage of immigrants from Mexico has increased the rates of tuberculosis (including MDR tuberculosis) in the southwestern United States [64]. For instance, rates of latent tuberculosis were found to be 21.8% in Latino versus 5.6% for non-Latino individuals in one study from San Diego [65]. Moreover, young Latinos living near the border are at higher risk for undiagnosed infection and undertreatment of latent tuberculosis [65]. Studies investigating tuberculosis prophylaxis of Latino immigrants in the USA have found that cultural barriers hinder treatment and that completion rates were poor [66]. Furthermore, 70% of Latino adolescents reported at least one side-effect of isoniazid prophylactic therapy and that side-effect reporting was negatively related to adherence [67], but this could be improved with coaching [57].

Contact tracing

Protocols for the assessment and follow-up of contacts of patients with MDR tuberculosis have yet to be

developed in high burden areas although the importance of contact tracing in tuberculosis control was demonstrated over 20 years ago. In a study from Peru [68**], 7% of close contacts of 192 index MDR tuberculosis patients developed new tuberculosis within a 2-year period. Somewhat surprisingly, only 15% of new cases had the same pattern of resistance as their index case, much lower than previous studies in this area, some of which have shown up to 83% concordance in resistance patterns. Early drug-sensitivity cultures of new cases, which allowed individualized therapy, resulted in cure more frequently than treatment with standard regimens.

Helicobacter pylori

In an underpowered yet interesting study, infection with *Helicobacter pylori* was not associated with tuberculosis skin test positivity, despite hypochlorhydria being a recognized risk factor for tuberculosis [69].

Altitude

The historical evidence that tuberculosis is less common in mountain populations was confirmed in a study from Peru that performed tuberculosis skin tests in groups living at low and high altitude. After controlling for confounding factors, average positivity rates were over four times lower at high altitude, possibly due to relative hypoxia, lower humidity or increased ultraviolet light in the mountains. Furthermore, there was greater household clustering of positive individuals in high altitude groups [70*].

Conclusion

Tuberculosis is a curable disease when rapid accurate diagnosis is combined with high levels of appropriate treatment completion. In the resource-poor setting, this is achievable, but not yet fully implemented. Recent tuberculosis research in Latin America highlights the importance of coherent national and international strategies for tuberculosis control, including education, improved tuberculosis diagnosis, early culture for drug-sensitivity, integrated tuberculosis and HIV treatment programmes and the use of the multidisciplinary team to encourage health education and treatment compliance.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- ** of outstanding interest

- 1 WHO Report: Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization; 2003. WHO/CDS/TB/2003.316.
- 2 Suarez PG, Watt CJ, Alarcon E, et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J Infect Dis* 2001; 184:473–478.

- 3 Selig L, Belo MT, Teixeira EG, *et al.* The study of tuberculosis-attributed deaths as a tool for disease control planning in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2003; 7:855–859.
- A retrospective study of 302 records of tuberculosis deaths that is critical of the current tuberculosis control programme in Rio de Janeiro, Brazil. Encouragingly, strategies to overcome the problematic issues are recommended and are currently being implemented.
- 4 Caviedes L, Lee TS, Gilman RH, *et al.* Rapid, efficient detection and drug susceptibility testing of *Mycobacterium tuberculosis* in sputum by microscopic observation of broth cultures. The Tuberculosis Working Group in Peru. *J Clin Microbiol* 2000; 38:1203–1208.
- 5 Lima DM, Colares JK, da Fonseca BA. Combined use of the polymerase chain reaction and detection of adenosine deaminase activity on pleural fluid improves the rate of diagnosis of pleural tuberculosis. *Chest* 2003; 124:909–914.
- 6 Alfonso R, Romero RE, Patarroyo ME, Murillo LA. Mtp-40 and alpha antigen gene fragment amplification for the detection of *Mycobacterium tuberculosis* in Colombian clinical specimens. *Mem Inst Oswaldo Cruz* 2002; 97:1157–1163.
- 7 Montenegro SH, Gilman RH, Sheen P, *et al.* Improved detection of *Mycobacterium tuberculosis* in Peruvian children by use of a heminested IS6110 polymerase chain reaction assay. *Clin Infect Dis* 2003; 36:16–23.
- 8 Sperhake RD, Mello FC, Zaha A, *et al.* Detection of *Mycobacterium tuberculosis* by a polymerase chain reaction colorimetric dot-blot assay. *Int J Tuberc Lung Dis* 2004; 8:312–317.
- 9 Escobedo-Jaimes L, Cicero-Sabido R, Criaes-Cortez JL, *et al.* Evaluation of the polymerase chain reaction in the diagnosis of miliary tuberculosis in bone marrow smear. *Int J Tuberc Lung Dis* 2003; 7:580–586.
- 10 Caviedes L, Delgado J, Gilman RH. Tetrazolium microplate assay as a rapid and inexpensive colorimetric method for determination of antibiotic susceptibility of *Mycobacterium tuberculosis*. *J Clin Microbiol* 2002; 40:1873–1874.
- 11 Morcillo N, Di Giulio B, Testani B, *et al.* A microplate indicator-based method for determining the susceptibility of multidrug-resistant *Mycobacterium tuberculosis* to antimicrobial agents. *Int J Tuberc Lung Dis* 2004; 8:253–259.
- This paper studies the results of a rapid, inexpensive method for identifying resistance patterns in MDR tuberculosis. It recommends clinical trials for this test, which could prove a very useful adjunct to the DOTS-plus strategy.
- 12 Mayta H, Gilman RH, Arenas F, *et al.* Evaluation of a PCR-based universal heteroduplex generator assay as a tool for rapid detection of multidrug-resistant *Mycobacterium tuberculosis* in Peru. *J Clin Microbiol* 2003; 41:5774–5777.
- 13 Tindo H, Cesar Cavalcante S, Werneck-Barroso E. Gender differences in tuberculosis in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2004; 8:388–390.
- 14 Molina Serpa I, Lopez Pardo C, Alonso Hernandez R. An ecologic study on tuberculosis in a Cuban municipality [in Spanish]. *Cad Saude Publica* 2003; 19:1305–1312.
- 15 Santo AH, Pinheiro CE, Jordani MS. Multiple-causes-of-death related to tuberculosis in the State of Sao Paulo, Brazil, 1998 [in Portuguese]. *Rev Saude Publica* 2003; 37:714–721.
- 16 Gomez i Prat J, de Souza SM. Prehistoric tuberculosis in America: adding comments to a literature review. *Mem Inst Oswaldo Cruz* 2003; 98 (Suppl 1):151–159.
- 17 Aerts D, Jobim R. The epidemiological profile of tuberculosis in southern Brazil in times of AIDS. *Int J Tuberc Lung Dis* 2004; 8:785–791.
- This presents an interesting discussion about HIV and tuberculosis co-infection in Brazil.
- 18 Pasqualotto AC, Rosa DD, Fontoura Pereira Mdo C, *et al.* Retrospective study of 668 cultures for mycobacteria in a reference hospital for AIDS in southern Brazil. *Braz J Infect Dis* 2003; 7:126–128.
- 19 Carvalho AC, Nunes ZB, Martins M, *et al.* Clinical presentation and survival of smear-positive pulmonary tuberculosis patients of a university general hospital in a developing country. *Mem Inst Oswaldo Cruz* 2002; 97:1225–1230.
- 20 Hadad DJ, Palaci M, Pignatari AC, *et al.* Mycobacteremia among HIV-1-infected patients in Sao Paulo, Brazil: 1995 to 1998. *Epidemiol Infect* 2004; 132:151–155.
- This study showed that publicly funded antiretrovirals reduced the incidence of tuberculosis in a 3-year period.
- 21 Vasquez-Campos L, Asencios-Solis L, Leo-Hurtado E, *et al.* Drug resistance trends among previously treated tuberculosis patients in a national registry in Peru, 1994–2001. *Int J Tuberc Lung Dis* 2004; 8:465–472.
- This article provides reference laboratory data on increased multidrug resistance in previously treated patients, and discusses the use of such information in improving national control programmes.
- 22 Campos PE, Suarez PG, Sanchez J, *et al.* Multidrug-resistant *Mycobacterium tuberculosis* in HIV-infected persons, Peru. *Emerg Infect Dis* 2003; 9:1571–1578.
- This paper shows that co-infection with HIV results in 10 times greater MDR tuberculosis. Prior treatment or prophylaxis did not increase rates of multidrug resistance.
- 23 Liberato IR, de Albuquerque Mde F, Campelo AR, de Melo HR. Characteristics of pulmonary tuberculosis in HIV seropositive and seronegative patients in a Northeastern region of Brazil. *Rev Soc Bras Med Trop* 2004; 37:46–50.
- 24 de Kantor I N, Latini O, Barrera L. Resistance and multiresistance to antitubercular drugs in Argentina and in other Latin American countries [in Spanish]. *Medicina (B Aires)* 1998; 58:202–208.
- 25 WHO. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance 1999–2002. Geneva: World Health Organization; 2003.
- 26 Natal S, Valente JG, Sanchez AR, Penna ML. Isoniazid and rifampicin resistance and prior treatment for tuberculosis [in Portuguese]. *Cad Saude Publica* 2003; 19:1277–1281.
- 27 Ferdinand S, Sola C, Verdol B, *et al.* Molecular characterization and drug resistance patterns of strains of *Mycobacterium tuberculosis* isolated from patients in an AIDS counseling center in Port-au-Prince, Haiti: a 1-year study. *J Clin Microbiol* 2003; 41:694–702.
- 28 WHO. Epidemiological Fact Sheets on HIV/AIDS and Sexually Transmitted Infections. Geneva: World Health Organization. <http://www.who.int/hiv/pub/epidemiology/pubfacts/en/>. [Accessed 25th July 2004].
- 29 Mitnick C, Bayona J, Palacios E, *et al.* Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348:119–128.
- This exciting paper investigates community-based treatment for MDR tuberculosis and finds very encouraging results, even in a resource poor setting. Early initiation of appropriate therapy was key.
- 30 Palacios E, Guerra D, Llaro K, *et al.* The role of the nurse in the community-based treatment of multidrug-resistant tuberculosis (MDR-TB). *Int J Tuberc Lung Dis* 2003; 7:343–346.
- This encouraging paper describes greater use of nurses as part of the community treatment of MDR tuberculosis.
- 31 Vega P, Sweetland A, Acha J, *et al.* Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2004; 8:749–759.
- This important case series identifies high rates of mental illness in patients with MDR tuberculosis. The development of new psychiatric illness on treatment is also discussed. Therapy options are discussed, and it is concluded that treatment of the mental illness need not compromise anti-tuberculosis therapy.
- 32 Mukherjee JS, Joseph JK, Rich ML, *et al.* Clinical and programmatic considerations in the treatment of MDR-TB in children: a series of 16 patients from Lima, Peru. *Int J Tuberc Lung Dis* 2003; 7:637–644.
- 33 Sant'Anna CC, Orfalais CT, March MF. A retrospective evaluation of a score system adopted by the Ministry of Health, Brazil in the diagnosis of pulmonary tuberculosis in childhood: a case control study. *Rev Inst Med Trop Sao Paulo* 2003; 45:103–105.
- This brief paper describes a scoring system for diagnosing childhood tuberculosis. A full evaluation is now needed.
- 34 Santiago EM, Lawson E, Gillenwater K, *et al.* A prospective study of bacillus Calmette-Guerin scar formation and tuberculin skin test reactivity in infants in Lima, Peru. *Pediatrics* 2003; 112:e298.
- This prospective study of BCG scar as a clinical indicator of prior vaccination added positive evidence in a controversial area.
- 35 Militao de Albuquerque MF, Ximenes RA, Campelo AR, *et al.* Neonatal BCG vaccine and response to the tuberculin test in BCG vaccinated children in contact with tuberculosis patients in Recife, Brazil. *J Trop Pediatr* 2004; 50:32–36.
- 36 Bierrenbach AL, Cunha SS, Barreto ML, *et al.* Tuberculin reactivity in a population of schoolchildren with high BCG vaccination coverage. *Rev Panam Salud Publica* 2003; 13:285–293.
- 37 Imaz MS, Comini MA, Zerbini E, *et al.* Evaluation of commercial enzyme-linked immunosorbent assay kits for detection of tuberculosis in Argentinean population. *J Clin Microbiol* 2004; 42:884–887.
- 38 Perkins M, Conde MB, Martins M, Kritski AL. Serologic diagnosis of tuberculosis using a simple commercial multiantigen assay. *Chest* 2003; 123:107–112.
- 39 Calusni AL, Roscani GN, Villares MC, *et al.* IS6110 restriction fragment length polymorphism of *Mycobacterium tuberculosis* isolated from patients with pulmonary tuberculosis in Campinas, Brazil: evidence of intercontinental distribution of strains. *Mem Inst Oswaldo Cruz* 2003; 98:655–658.

- 40 Fllioli I, Driscoll JR, van Soolingen D, et al. Snapshot of moving and expanding clones of *Mycobacterium tuberculosis* and their global distribution assessed by spoligotyping in an international study. *J Clin Microbiol* 2003; 41:1963–1970.
- 41 Palmero D, Ritacco V, Ambroggi M, et al. Multidrug-resistant tuberculosis in HIV-negative patients, Buenos Aires, Argentina. *Emerg Infect Dis* 2003; 9:965–969.
- 42 Ahmed N, Caviedes L, Alam M, et al. Distinctiveness of *Mycobacterium tuberculosis* genotypes from human immunodeficiency virus type 1-seropositive and -seronegative patients in Lima, Peru. *J Clin Microbiol* 2003; 41:1712–1716.
- 43 Baptista IM, Oelemann MC, Opromolla DV, Suffys PN. Drug resistance and genotypes of strains of *Mycobacterium tuberculosis* isolated from human immunodeficiency virus-infected and non-infected tuberculosis patients in Bauru, Sao Paulo, Brazil. *Mem Inst Oswaldo Cruz* 2002; 97:1147–1152.
- 44 Olle Goig JE, Sandy R. Prognosis of mono- and polydrug resistant pulmonary tuberculosis in the city of Santa Cruz, Bolivia [in Spanish]. *Arch Bronconeumol* 2003; 39:382–386.
- This retrospective review of treatment identifies similar cure rates in single and poly-drug resistance compared with drug-sensitive patients. However, high rates of treatment abandonment are noted.
- 45 Laguardia J, Merchan-Hamann E. Risk factors for tuberculous disease in AIDS cases reported in Brazil, from 1980 to 2000 [in Spanish]. *Rev Esp Salud Publica* 2003; 77:553–565.
- 46 Song AT, Schout D, Novaes HM, Goldbaum M. Clinical and epidemiological features of AIDS/tuberculosis comorbidity. *Rev Hosp Clin Fac Med Sao Paulo* 2003; 58:207–214.
- 47 Borroto Gutierrez SM, Gonzalez Ochoa E, Armas Perez L, et al. Tuberculin reactivity among ninth-grade schoolchildren in the city of Havana, Cuba [in Spanish]. *Rev Panam Salud Publica* 2003; 14:209–214.
- 48 Sevy Court JI, Pelaez Sanchez O, Arteaga Yero AL, et al. Tuberculosis in Havana City, 1995–1999 [in Spanish]. *Rev Saude Publica* 2003; 37:326–332.
- 49 de Oliveira HB, Cardoso JC. Tuberculosis among city jail inmates in Campinas, Sao Paulo, Brazil [in Spanish]. *Rev Panam Salud Publica* 2004; 15:194–199.
- 50 Salles CL, Conde MB, Hofer C, et al. Defaulting from anti-tuberculosis treatment in a teaching hospital in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2004; 8:318–322.
- This important study investigated the reasons that people default from tuberculosis treatment.
- 51 Chavez Pachas AM, Blank R, Smith Fawzi MC, et al. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. *Int J Tuberc Lung Dis* 2004; 8:52–58.
- This paper highlights the importance of identifying treatment failure at the earliest stage and gives encouraging results. It recommends culture and drug-sensitivity testing in all patients who remain sputum smear positive at 2 months.
- 52 Shin SS, Hyson AM, Castaneda C, et al. Peripheral neuropathy associated with treatment for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2003; 7:347–353.
- This interesting case series highlights the dangers of neglecting pyridoxine prophylaxis during treatment for MDR tuberculosis. Treatment strategies for neuropathy in these cases are outlined.
- 53 Shin S, Furin J, Alcantara F, et al. Hypokalemia among patients receiving treatment for multidrug-resistant tuberculosis. *Chest* 2004; 125:974–980.
- 54 Terra Filho M, Yen CC, Santos Ude P, Munoz DR. Pulmonary alterations in cocaine users. *Sao Paulo Med J* 2004; 122:26–31.
- 55 Alvarez Gordillo GC, Alvarez Gordillo JF, Dorantes Jimenez JE. Educational strategy for improving patient compliance with the tuberculosis treatment regimen in Chiapas, Mexico [in Spanish]. *Rev Panam Salud Publica* 2003; 14:402–408.
- 56 Shrestha-Kuwahara R, Wilce M, DeLuca N, Taylor Z. Factors associated with identifying tuberculosis contacts. *Int J Tuberc Lung Dis* 2003; 7 (Suppl 3):S510–S516.
- 57 Hovell M, Blumberg E, Gil-Trejo L, et al. Predictors of adherence to treatment for latent tuberculosis infection in high-risk Latino adolescents: a behavioral epidemiological analysis. *Soc Sci Med* 2003; 56:1789–1796.
- 58 Aguilar R, Garay J, Villatoro M, et al. Impact of a model training course for private and public specialist physicians in El Salvador. *Int J Tuberc Lung Dis* 2004; 8:473–479.
- 59 Caminero JA, Billo NE. Involving private practitioners and chest physicians in the control of tuberculosis. *Tuberculosis (Edinb)* 2003; 83(1–3):148–155.
- 60 Caminero JA. Is the DOTS strategy sufficient to achieve tuberculosis control in low- and middle-income countries? 1. Need for interventions in universities and medical schools. *Int J Tuberc Lung Dis* 2003; 7:509–515.
- This is a comprehensive overview of the specific limitations of DOTS in middle income countries with strategies designed to overcome them.
- 61 Martinez-Guarneros A, Balandrano-Campos S, Solano-Ceh MA, et al. Implementation of proficiency testing in conjunction with a rechecking system for external quality assurance in tuberculosis laboratories in Mexico. *Int J Tuberc Lung Dis* 2003; 7:516–521.
- 62 Coreil J, Lauzardo M, Heurtelou M. Cultural feasibility assessment of tuberculosis prevention among persons of Haitian origin in South Florida. *J Immigr Health* 2004; 6:63–69.
- 63 Morisky D, Ebin V, Mallote C, et al. Assessment of tuberculosis treatment completion in an ethnically diverse population using two data sources. Implications for treatment interventions. *Eval Health Prof* 2003; 26:43–58.
- 64 Granich RM, Moore M, Binkin NJ, McRay E. Drug-resistant tuberculosis in foreign-born persons from Mexico, the Philippines, and Vietnam-United States, 1993–1997. *Int J Tuberc Lung Dis* 2001; 5:53–58.
- 65 Sipan C, Blumberg E, Hovell M, et al. Screening Latino adolescents for latent tuberculosis infection (LTBI). *Public Health Rep* 2003; 118:425–433.
- 66 Kandula NR, Dworkin MS, Carroll MR, Lauderdale DS. Tuberculosis prevention in Mexican immigrants: limitations of short-course therapy. *Am J Prev Med* 2004; 26:163–166.
- 67 Berg J, Blumberg EJ, Sipan CL, et al. Somatic complaints and isoniazid (INH) side effects in Latino adolescents with latent tuberculosis infection (LTBI). *Patient Educ Couns* 2004; 52:31–39.
- 68 Bayona J, Chavez-Pachas AM, Palacios E, et al. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2003; 7 (Suppl 3):S501–S509.
- This study showed that contact tracing of patients with MDR tuberculosis resulted in identification of 8% multidrug resistance in close contacts. Improved outcome was associated with individualized therapy, and knowledge of patterns of resistance. The results are elegantly discussed.
- 69 Torres MA, Passaro DJ, Watanabe J, et al. No association between *Helicobacter pylori* and *Mycobacterium tuberculosis* infections among gastrointestinal clinic attendees in Lima, Peru. *Epidemiol Infect* 2003; 130:87–91.
- 70 Olender S, Saito M, Apgar J, et al. Low prevalence and increased household clustering of *Mycobacterium tuberculosis* infection in high altitude villages in Peru. *Am J Trop Med Hyg* 2003; 68:721–727.
- This elegant prospective study showed reduced tuberculosis skin test positivity at greater altitude despite increased household clustering. Potential mechanisms are succinctly discussed.