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Innovative strategies for TB control – Dr Carlton Evans

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For 4 years, a **Wellcome Trust Career Development Fellowship** has funded the above employees and trainees, supported by *collaborators*, in identifying and evaluating 'short-cuts to development' for controlling TB in resource-poor regions, realised through training/capacity-building in Peru.

TB-Susceptibility. We demonstrated that micronutrient deficiency is frequent and associated with antimycobacterial immunosuppression, cutaneous anergy and impaired TB-treatment response. Using TB skin-tests and an *in vitro* whole-blood assay that we adapted for developing country use, we found that antimycobacterial immunity is augmented by micronutrient supplementation administered *in vitro*, topically and orally. 1800 participants have been recruited to a randomised, placebo-controlled trial of micronutrient supplementation, testing whether this nutritional augmentation of antimycobacterial immunity is sufficient to prevent TB disease.

TB-Diagnosis. TB is usually diagnosed by microscopy in developing countries and we have evaluated and refined low-cost strategies for concentrating TB from samples to increase diagnostic sensitivity. Our research has demonstrated the benefit of rapid-culture over microscopy, doubling diagnostic sensitivity and facilitating MDRTB diagnosis by combining isoniazid and rifampicin in a single 'MDRTB-detection' culture. We have also overcome the technical difficulties that have prevented routine pyrazinamide susceptibility-testing and have demonstrated the clinical significance of these tests. For patients who cannot produce sputum, we have shown that TB survives the intestinal tract, allowing reliable stool-based TB diagnosis.

TB-Treatment. Patients in developing countries are usually only tested for MDRTB if they fail first-line TB-therapy. We demonstrated that this delay in MDRTB-testing is unnecessary because early treatment-associated symptom-persistence and weight-loss identify patients likely to have MDRTB, allowing focused early MDRTB-testing. First-line TB-therapy often appears to cure MDRTB, but we have shown this to be associated with delayed treatment response, prolonged infectiousness and early relapse, emphasizing the need for earlier MDRTB-testing.

TB-Transmission. TB treatment clusters susceptible patients being cured of antibiotic-susceptible TB in the same airspace with unrecognised MDRTB-patients who remain infectious whilst they fail to respond to first-line therapy. We identified frequent resultant MDRTB acquisition during TB therapy, associated with changes in TB-DNA fingerprint and mortality. We also found that poor ventilation is a risk-factor for TB infection, identifying a potential strategy for preventing transmission.

Conclusion. This Wellcome Trust-funded research program has identified novel strategies for TB control and is evaluating their translation into practice in resource-poor settings.