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Editorial

Commemorating World Tuberculosis Day 2015

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World Tuberculosis (TB) Day falls on March 24th each year, the day in 1882 when Professor Robert Koch announced his discovery of the microbial aetiology of TB, *Mycobacterium tuberculosis* (*M. tb*). One hundred and thirty three years later, despite an effective cure available for the past half century, TB continues to plague humankind and remains one of the most common causes of death from an infectious disease worldwide.

The latest WHO annual Global TB report estimates that in 2013, there were 9 million people who developed TB of which an estimated 1.2 million (14%) were people living with HIV.[1] An ominous increase is being seen globally in the number of new cases of Multi-Drug Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB) with an estimated 480,000 new cases of MDR-TB globally in 2013.[2] World TB Day 2015 gives us an opportunity to reflect on the trials and tribulations of global TB control efforts, and to raise public and political awareness that TB today remains a 'global emergency', is responsible for 1.5 million deaths each year globally, and that MDR-TB and XDR-TB in Europe, Asia and southern Africa are now major threats to global health security. To commemorate World TB Day on March 24th 2015, we have compiled this special issue of the International Journal of Infectious Diseases, which comprises 32 articles (commentaries, viewpoints, and reviews) on a range of TB subject areas written by a global authorship.

Despite efficacy in reducing the incidence of disseminated and more severe forms of TB in children, the age old Bacille-Calmette-Guérin (BCG) vaccine has shown limited effectiveness in prevention of active disease in older children, adolescents and adults.[3] Progress is being made in the search for more effective, universally applicable TB vaccines.[4] *Chris DaCosta et al.*[5] review vaccines which are currently under evaluation in phase II clinical trials and other candidates in the pre-clinical development pipeline. These include novel recombinant mycobacterial-based priming vaccines, various booster vaccines (adjuvanted subunit, viral-vectored, whole cell), immunotherapeutic vaccines and *Mycobacterium vaccae*. *Axelsson-Robertson et al.*[6] show that a broad CD8+ T-cell response towards individual *M. tuberculosis* epitopes is required, in contrast to what has been described for viral (e.g. EBV, CMV or HIV) infections.[7] *Zumla et al.*[8] suggest the potential use of host-directed immune-modulatory interventions, like repurposed drugs and cellular therapy using the patient's own bone-marrow derived Mesenchymal Stromal Cells (MSCs) as adjunct host-directed therapies, together with anti-TB drugs, for TB pericarditis and TB meningitis. *Parida et al.*[9] review adjunct T-cell based immune-interventions in infectious diseases and particularly cellular host-directed therapy,[10] using MSCs, to balance damaging inflammation, limit bacterial proliferation and restore anti-*M.tb* directed immune responses for improving treatment outcomes in patients with MDR-/XDR-TB. *Bell and colleagues*[11] review paradoxical reactions and TB associated immune reconstitution inflammatory syndrome (TB-IRIS).

Zumla and colleagues[12] highlight the unique opportunities presented by the launch of the second programme (2015-2024) of the European & Developing countries Clinical Trials Partnership (EDCTP), a 1.4 billion Euros initiative established jointly between EU and African countries, for research and capacity building to tackle diseases of poverty including TB. *Maitra et al.*[13] provide their insights into the use of moxifloxacin, linezolid and clofazimine, tebipenem with clavulanic acid, or repurposed drugs such as thioridazine and chlorpromazine for treatment of MDR-/XDR TB. *Lessem et al.*[14] provide patient, provider and community perspectives on access to new TB drugs bedaquiline and delamanid, and the existing drug linezolid for treatment of MDR-TB. They remind us that access to these medicines even in industrialized countries remains a significant challenge because of restrictions on licensing and high cost, suggesting that improved access through drug donation programs are urgently needed. *Madansein and colleagues*[15] inform us that surgery is increasingly being explored as a treatment option particularly in MDR-TB and XDR-TB with associated lung destruction and poor results despite adequate drug treatment. Open thoracotomy is gradually being replaced with Video Assisted Thoracic Surgery (VATS), which is performed using smaller incisions. Whilst *Brown et al.* highlight the paucity of available data on health status and quality of life in both treated and untreated TB.[16]

M.tb bacilli employ various strategies to overcome antibiotic pressure such as differentiating into various physiological states ranging from drug sensitive actively dividing states to slow or non-replicating drug tolerant ones.[17,18] Slowly growing bacteria are less susceptible to drugs because of the reduced metabolic activity, and it is important to investigate the way that different *M.tb* subpopulations are formed during infection, and the *in vitro* and *in vivo* models used for understanding is reviewed by *Evangelopoulos et al.*[19] A recent meta-analysis of 9,153 patients with MDR-TB showed that the proportion of MDR-TB cases treated successfully remains sub-optimal, with 62% treatment success, 7% treatment failure or relapse, 9% death and 17% default reported.[20] In the

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XDR-TB subgroup treatment outcomes were even worse: 40% achieved treatment success, 22% failed treatment or relapsed, whereas 15% died and 16% defaulted.[21]

Early diagnosis of MDR-TB and XDR-TB is the key to treatment success and control of epidemic spread. *McNerney et al.*[22] review the rapid TB diagnostics portfolio and indicate that whilst the use of rapid, molecular diagnosis was seen as the key to earlier diagnosis, evaluation studies indicate limited impact on detection rates and patient survival, re-emphasizing the need for a rapid point of care TB test. *Skoura et al.*[23] review the usefulness of imaging for diagnosis, locating pathology and monitoring response to treatment. Chest radiography remains the mainstay and cheapest imaging option for screening of parenchymal disease in pulmonary TB. Computed tomography (CT), Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) scans are more sensitive in locating extra-pulmonary lesions, but are not widely available in resource restricted settings.

The development of drug resistance was previously thought to result mainly from poor treatment adherence, but as illustrated by *Marais et al.*, [24] in their review of the epidemic spread of MDR-TB in Johannesburg, primary transmission now drives the epidemic spread of drug resistant TB in some high incidence settings.[24] *Fonseca et al.'s*[25] review informs us that the selection of drug resistant strains involve complicated resistance determinants such as *M.tb* strain genetic background, compensatory mutations that restore "fitness", low-level changes in drug susceptibility that may not be appreciated and variability in individual pharmacokinetics. One strategy for optimizing treatment efficacy is therapeutic drug monitoring, which both ensure adequate doses and monitor compliance and this is reviewed by *Sotgui et al.*[26] *Craig and Zumla*[27] in their study of TB treatment in urban risk groups in the United Kingdom highlight that compliance to treatment in marginalized group pose particular challenges. The growing problem of TB in prisoners and *M.tb* transmission in prisons worldwide is reviewed by *Dara et al.*[28] highlighting specific difficulties in operational aspects of TB testing, management and surveillance. Weak health systems contribute to the growing burden of drug resistant TB. *Jabeen et al.*[29] highlight the contribution of poor regulatory policies and irresponsible drug use.

The specific management problems posed by TB in pregnancy, especially in high TB/HIV endemic areas, are reviewed by *Bates et al.*[30] TB in pregnancy and also congenital TB is more common than previously assumed. *Wejse et al.*[31] highlight that the risk of TB is higher in HIV-1 infected individuals compared to HIV-2 infected, and co-infection with both HIV-1 and HIV-2 did not increase the risk of TB as compared to HIV-1 only. *Negin et al.*[32] remind us that we need to take more notice of TB in older people, since they contribute a large and growing burden of disease and are more likely to have extra-pulmonary and atypical forms of TB, both of which are often more difficult to diagnose than sputum smear-positive pulmonary TB. *Byrne et al.*[33] explore the association between TB and chronic respiratory disease in a systematic review, indicating that previous TB is a risk factor for chronic obstructive lung disease (COPD), particularly in non-smokers, and contributes a large fraction of population attributable COPD risk in TB endemic areas.

The majority of TB transmission in the community and in healthcare settings occurs well before the diagnosis of TB is made. Healthcare workers (HCWs) worldwide have an increased risk of developing TB. *Von Delft and colleagues*[34] present an illuminating account from personal experiences of health care workers who contracted TB. Their viewpoint illustrates why it is important to ensure that TB infection control measures are applied in all high-risk settings so that healthcare facilities become known as places of healing and are safe, and not places associated with death and sites of contagion. The risk of TB transmission to health care workers and clients using health care services should not be underestimated. However, fear of TB infection should not influence the quality of patient care provided. This can only be adequately addressed by education and proper containment facilities.

Wejse[35] in his viewpoint on achieving TB elimination reminds us that whilst extensively promoted, the efficacy of directly observed therapy (DOT) has not been shown to be superior to self-administration. The DOT strategy also focus exclusively on symptomatic TB patients, without attempting to reduce the pool of latently infected people.[36] Large scale population-based preventive therapy to eliminate the huge reservoir of people with latent TB infection is a possible path being explored, but rapid re-infection remains a challenge in settings with uncontrolled transmission. It will require carefully designed, randomized controlled studies to establish its "real-life" impact. These studies are difficult to conduct, since they should exclude people with sub-clinical or undiagnosed TB, and it is impossible to rule out individuals harboring drug-resistant strains of *M. tb*.

In response to the alarming rates of drug resistant TB in countries of the former Soviet Union, 53 Member States of WHO European Region endorsed the five- year (2011-2016) Consolidated Action Plan to Prevent and Combat MDR-/XDR-TB in Europe.[37] *D'Ambroio and colleagues*[38] review the ERS-WHO Consortium, which recommends that management of MDR-TB and XDR-TB cases is supported by specialized teams. They highlight the need for increased resources and the fact that current programs cover only a fraction of patients in each country. *Islam et al.*[39] review the establishment of WHO regional Green Light Committees (rGLCs) to provide decentralized and better contextualized guidance to national PMDT (Programmatic Management of Drug resistant TB) efforts, and relate the successes and challenges of the Western Pacific rGLC. In March 2014, the Western Pacific Region also established a taskforce to focus on TB in children and adolescents.[40] *Graham et al.*[41] relate perspectives from the Asia-Pacific region and the experience of individual countries developing national child TB action plans. *Trinh et al.*[42] provide an overview of the TB and HIV situation in the Asia-Pacific region where HIV co-infection is not regarded as a major driver of the TB epidemic. They point out that 6.3% of TB cases tested were HIV-positive in 2013 which requires closer scrutiny, since HIV tests are only selectively performed in TB patients.

Over the past 3 decades, HIV/AIDS has attracted enormous investment in developing new drugs and decentralized models of care to turn the tide. Malaria has also mobilized huge financial resources with the distribution of cheap and effective impregnated bed nets, but investments into TB have sadly lagged behind!

The long incubation period, diagnostic difficulties and the long treatment period all create obstacles for effective control. Vertical programs are unlikely to be sufficient to achieve ultimate TB elimination without better integration into other health care services, together with enhanced and sustained efforts. *Wallstead and Maeurer*[43] remind us that TB was highly endemic 150 years ago in what are now low endemic countries in Western Europe, and give the example of TB control efforts in the pre-chemotherapy area in Sweden. *Floe and colleagues*[44] show that even in low incidence countries like Denmark, TB patients are characterized by lower income and pose an economic burden on health services. Since TB is primarily a disease of poor and disadvantaged populations, and less likely to attract investment from funders and donor countries, it requires sustained and high profile advocacy to remain on the political agenda, as exemplified by a review of the questions posted on TB in the United Kingdom parliament by *Matt Oliver and colleagues*.[45]

WHO estimates that there are 3 million men, women and children globally with active TB who are currently being missed by