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International Journal of Infectious Diseases xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Editorial

Engaging high and low burden countries in the "TB end game"

Keywords:
World TB Day
Tuberculosis
Advocacy

Tuberculosis (TB) is now the single biggest infectious disease killer in the world, surpassing malaria and HIV/AIDS. In 2014, there were an estimated 9.6 million incident TB cases and 1.5 million deaths.[1] It is not widely appreciated that TB is also a major cause of disease and death in young children.[2,3] New estimates from the World Health Organization (WHO) are that 1 million children developed TB during 2014.[1] This is disconcerting because children have poor access to TB services in most resource-limited settings and paediatric cases provide an accurate reflection of uncontrolled TB transmission within communities. Although the cost-effective DOTS strategy helped to bring the global tuberculosis (TB) epidemic under control in many parts of the world, progress has been limited in areas affected by poverty, war and rising rates of drug resistant TB.[4,5]

The emergence and spread of multi-drug resistant (MDR)-TB pose a major threat to recent gains.[4,5] It is estimated that nearly half a million (480 000) MDR-TB cases occurred in 2014; accounting for 3.3% of new and 20% of re-treatment TB cases.[1] The highest MDR-TB case-loads exist in the Indian subcontinent, China, the Russian Federation and Southern Africa.[1] For many years the epidemic potential of transmitted MDR-TB was ignored and the dogma that most MDR-TB cases acquire drug-resistance because of poor treatment adherence became firmly entrenched. The perception that drug resistant strains have reduced "fitness" and are unlikely to be transmitted had a major influence on TB control policy. It motivated a renewed focus on basic DOTS to stop the generation of MDR-TB cases; "turning off the tap" was considered an adequate public health response.

The relative over-representation of MDR-TB among re-treatment cases is often used to support this dogma; although the majority of MDR–TB cases are now diagnosed among new cases.[1] Recent modelling data suggest that even among MDR-TB cases diagnosed at re-treatment, the majority represent transmitted (not acquired) MDR-TB disease.[6] The description of multiple well-defined clonal MDR-TB outbreaks provides genotypic evidence of epidemic spread,[7,8] as does the fact that ~60% of Mongolian TB patients in whom first-line treatment failed were resistant to streptomycin; a drug to which they have never been exposed before.[9] The high number of children with MDR-TB and the fact that child MDR-TB cases are consistently co-located with adult cases provide epidemiological proof of MDR-TB transmission within households and communities.[2,10] A recent analysis of 100 paediatric specimens held in the strain library of the Chinese Centre for Disease Control and Prevention demonstrated high rates of drug-resistance; any drug resistance in 55% and MDR in 22%.[11]

It is important to ensure optimal basic TB program performance and to limit the generation of newly acquired drug resistance. However, if TB treatment and prevention programs focus exclusively on drug susceptible disease, uncontrolled MDR-TB transmission could lead to future epidemic replacement, where MDR-TB strains become more prevalent than drug-susceptible strains. The possibility of epidemic replacement is illustrated by parts of the Russian Federation where over 30% of newly diagnosed cases have MDR-TB.[3] Sub-Saharan Africa represents the epicentre of human immunodeficiency virus (HIV) and TB co-infection. Swaziland report TB/HIV co-infection rates exceeding 80%, with high rates of MDR-TB among co-infected patients.[12] Since delayed MDR-TB diagnosis might facilitate transmission among immune compromised patients, the occurrence of an *rpoB*1419F mutation that is not detected by the Xpert MTB/RIF® assay is particularly problematic.[12]

High and rising rates of MDR-TB have relevance beyond the worst affected areas, since TB does not respect national borders. People are highly mobile and their mobility underpins global economic activity. Large scale population movements are also triggered by war and famine, with appeals for safe refuge. Interventions to screen for active TB and latent *M. tuberculosis* infection are compromised if prophylactic treatment options are ineffective in those harbouring MDR-TB strains. Current diagnostic tests are unable to identify latent infection with an MDR strain, or to detect a re-infection event after previous preventive therapy or TB treatment. There is an urgent need for improved epidemiological understanding of MDR-TB spread, guided by a better description of the evolution and transmission dynamics of drug-resistant *M. tuberculosis* strains.

1. The new "End TB strategy"

The World Health Assembly approved the new End TB Strategy in May 2014.[13] The End TB Strategy includes ambitious targets to reduce TB deaths by 95% and cut new cases by 90% from 2015 to 2035, and to ensure that no family is burdened with catastrophic expenses due to TB. It calls on all governments to demonstrate high-level political commitment by prioritizing efforts to end TB, backed by adequate resource allocation and inclusion of the most

http://dx.doi.org/10.1016/j.ijid.2016.03.015

vulnerable sections of society. The main focus of the "End TB strategy" is to reduce global disease burdens, with the greatest gains to be made in high burden countries. The strategy does not include specific targets for low burden countries apart from encouragement to aim for TB elimination, defined as an annual TB incidence of less than 1 case/1 million population. The reality in most low burden countries is that TB is essentially an imported disease with minimal local transmission. Given its limited health impact, compared to things like obesity, diabetes and cardiovascular disease or cancer, it is difficult to maintain high-level engagement and justify continued domestic investment in TB control efforts. A new paradigm is required to engage low TB burden countries and add momentum to global TB control efforts.

2. Engaging low burden countries

A potential mechanism to encourage continued TB investment in low-burden countries is to create a pathway for formal recognition as being "TB transmission free". Achieving and maintaining a "TB transmission free" status could provide strong impetus for regional action in low burden areas, similar to the focus provided by the "Roll back Polio" campaign.[14] Challenging low burden countries to aspire to this goal may galvanize national action and encourage the incorporation of cutting-edge molecular tools into routine TB control activities, together with the development of active response systems. Benefits of rapid advances in pathogen genomics and whole genome sequencing include simultaneous detection of drug-resistance mutations (allowing for earlier initiation of effective medications, thereby cutting transmission) and accurate identification of transmission clusters to guide outbreak investigation. It will allow TB control efforts to be at the forefront of the "genomic revolution", linking sophisticated strain and drug-resistance mutation analysis to enhanced patient care and better targeted public health responses.[15,16]

A policy of TB elimination that focuses exclusively on absolute case numbers, as defined in the WHO "Framework for TB elimination in low-incidence countries",[17] raises practical and ethical challenges. Increasing the intensity and scope of screening programs for latent TB infection (LTBI) is clearly important as part of an overall TB elimination strategy, given the long latency periods experienced by some TB patients.[18] However, careful consideration should be given to the strategies required to ensure safe and efficient implementation.[18,19] Managing LTBI in vulnerable and disadvantaged groups will require new ways of working with local communities, social welfare organisations, and government departments. No comprehensive analysis has been undertaken to explore the ethical, economic and social impacts of a policy shift towards TB elimination, intending to eliminate the "pool of latent infection" from which future cases may arise. Given high population mobility and significant re-infection risk, eradicating the "pool of latent infection" is not a feasible aim. Careful consideration should be given to the risk:benefit ratio of preventive therapy in individual patients, with clear benefit in young children and immune compromised patients.[20] However, there is a difficult ethical tension between the interests of low risk individuals with LTBI, who stand to benefit very little from preventive therapy, and potential societal benefits if the "pool of latent infection" is reduced. In "TB transmission free" settings, where local transmission is limited to an absolute minimum (<1 case of locally transmitted TB/1millon population), the societal benefit derived from the LTBI treatment is minimal and the patient's best interest becomes the sole determining factor. This provides additional motivation for countries to strive towards "TB transmission free" status.

3. Engaging high burden settings

The stigma associated with TB, at the individual and community levels, is well characterized and presents a major hurdle to TB control activities in many high burden settings.[20] However, an issue that is less often discussed or studied is the political stigma associated with TB.[21] Politicians in countries with rapidly growing economies aspire to be seen as progressive and making a contribution to rid their country of the "shackles of poverty". Given TB's intimate association with poverty and deprivation there is reluctance to acknowledge the full extent of the TB disease burden, especially in settings where this remains stubbornly high. This may explain some of the discrepancies observed between notified cases, disease burden estimates and actual prevalence surveys. Re-assessment of Indonesia's estimated TB incidence, after a recent prevalence survey detected double the number of case expected, now places Indonesia ahead of China as the country with the second highest number of TB cases, surpassed only by India.[1] Issues related to political stigma issues are compounded by rising rates of MDR-TB in many Asian countries, with pressure on TB control programmes to "solve the problem", despite inadequate resource allocation.

Due to rapid economic growth many countries that were previously supported by the Global Fund no longer qualify. It is imperative that the Global Fund establishes a clear transition pathway to secure domestic funding streams (or other support mechanisms) that can sustain MDR-TB treatment programmes and prevent a recurrence of the setbacks suffered by MDR-TB treatment programmes in China when Global Fund support ended in 2015. Increased domestic resources could be secured through innovative health financing mechanisms, such as universal health insurance and social protection schemes. However, low income countries will continue to require external donor support. Major funding shortfalls demonstrate the need for greatly increased advocacy and strong regional political commitment. Innovative regional funding mechanisms should be explored that are dynamic and responsive to local circumstances, especially in the Asia-Pacific where economic growth has been strong and contributions to traditional funding mechanisms limited.[21]

Dr. Margaret Chan, Director General of the WHO, made the following call when announcing the ambitious End TB strategy [13]: "Everyone with TB should have access to the innovative tools and services they need for rapid diagnosis, treatment and care. This is a matter of social justice, fundamental to our goal of universal health coverage. Given the prevalence of drug-resistant tuberculosis, ensuring high quality and complete care will also benefit global health security. I call for intensified global solidarity and action to ensure the success of this transformative End TB Strategy." The real challenge is identifying the international "levers" that can translate these worthy ambitions into concerted action with strong contributions from high and low burden countries.

Conflicts of interests: Authors declare no conflicts of interest.

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Please cite this article in press as: Marais BJ, et al. Engaging high and low burden countries in the "TB end game". Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.03.015

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Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

15 March 2016
Accepted 15 March 2016