International Journal of Infectious Diseases 56 (2017) 10–13

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

# Tuberculosis eradication versus control

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ARTICLE INFO

*Article history:*
Received 5 October 2016
Received in revised form 7 November 2016
Accepted 10 November 2016

**Corresponding Editor:** Eskild Petersen, Aarhus, Denmark

*Keywords:*
Drug susceptibility testing
Diagnostics
Vaccination
Chemotherapy

SUMMARY

According to the World Health Organization (WHO), 10.4 million people died of tuberculosis (TB) in 2015, and the disease is now the number one cause of death from a preventable infectious disease worldwide. A bold vision is needed from global leaders to end the TB epidemic and plans to this end have been proposed. However enthusiasm must be matched by tangible and achievable goals based on the science and available funding. In order to reach the target and goals set by the WHO End TB Strategy, the challenges for TB eradication need to be addressed. In order to achieve the targets, several areas need to be bolstered, including the requirement to better identify and treat existing drug-susceptible cases and diagnose all the drug-resistant forms of the disease. Although treatment is available for most TB patients, stock-outs and other delays are problematic in some settings, resulting in ongoing transmission, especially for the drug-resistant forms of the disease. Despite the fact that a majority of multidrug-resistant cases are linked to treatment, the cure rate is only 50%, which highlights the need for safer, shorter, and more efficacious drug regimens that are more tolerable to patients. Prospects for a more efficacious vaccine are limited, with no correlates of protection identified; thus the availability of a vaccine by 2025 is highly improbable. Support for instituting infection control methods should be prioritized to subvert transmission while patients seek treatment and care. Finally, more adequate financial mechanisms should be instituted to reduce patient expenditures and support national TB programs. Moreover, funding to support basic science, drug development, clinical trials, vaccine development, diagnostics, and implementation research needs to be secured in order to reduce global TB incidence in the future.



## 1. Introduction

On May 19, 2014, the 67th World Health Assembly adopted the World Health Organization (WHO) Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015.[1] The post-2015 global tuberculosis (TB) plan, known as the End TB Strategy,[2] was formed and developed through consultation with a wide range of stakeholders. The strategy sets ambitious goals for the post-2015 agenda. A 90% reduction in TB-related mortality, an 80% decline in TB incidence, and the abolition of catastrophic expenditures for TB-affected people by 2030 are targeted by this strategy. Strong government commitment and adequate financing from all countries, together with community engagement and appropriate investments in research, are necessary in order to reach these targets.[3] The strategy has a vision of making the world free of TB, with zero deaths, disease, and suffering due to the disease. An admirable strategy but how realistic is it?

*Mycobacterium tuberculosis* can cause a spectrum of clinical manifestations, from latent asymptomatic infection and asymptomatic sub-clinical disease to the full spectrum of symptomatic clinical disease affecting any organ of the body. Thus the true burden of TB remains difficult to quantify. Although there are several commercially approved culture and molecular-based diagnostic tests to identify active TB, the tools used programmatically in high burden countries still rely on the century-old method of smear microscopy and in-house culture, which is known to miss many cases due to poor accuracy and the need for specialized culture facilities.

For latent *M. tuberculosis* infection (LTBI), the accuracy of these assays at predicting TB disease during the lifetime of the individual or identifying previous exposure remains to be seen.[4,5] Exposure would include those who are colonized, as well as those individuals who have been able to inhibit the establishment of infection. The diagnosis and treatment of LTBI is a tool for global TB

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http://dx.doi.org/10.1016/j.ijid.2016.11.007

control, especially in close contacts. However, accurate data on the diagnosis and treatment of LTBI under operational field conditions are scarce from high TB burden countries, and the benefits of LTBI management remain to be determined. Primary healthcare clinics in Sao Paulo reported high proportions of contacts without evaluation, incomplete assessments, and incorrect records of contraindication to LTBI treatment, and a lack of notes regarding the identification and evaluation of contacts.[6] This highlights the need for on the ground improvements in infrastructure and organization for routine contact investigation. The need is global in scope and includes improved coordination of TB screening in Europe as well, in order to implement the goals outlined by the End TB Strategy.[7]

In 1998, Dowdle proposed a definition of 'control' as a reduction in the incidence, prevalence, morbidity, or mortality of an infectious disease to a locally acceptable level; 'elimination' as a reduction to zero of the incidence of disease or infection in a defined geographical area; and 'eradication' as a permanent reduction to zero of the worldwide incidence of infection.[8] Inherent in these definitions of control and elimination is the requirement of continued interventions to prevent the re-emergence and re-establishment of transmission. It is this need for continued surveillance and intervention after reaching control or elimination targets that is essential to sustain disease control. However, most countries typically cut budgets in response to declining disease incidence and prevalence rates. Neglect or complete cessation of intervention activities can lead to the re-emergence of the disease in vulnerable populations.

## 2. Eradication

In theory, if adequate funding, appropriate tools, and political commitment were available, all infectious diseases including TB would be eradicable. The important indicators of eradicability include the availability of effective interventions, including practical, affordable, and implementable diagnostics, prevention tools, treatment, and adequate funding.[8] To date, only smallpox[9] and rinderpest[10] have been successfully eradicated. Both diseases had these tools available, coupled with serious political commitment to effectively interrupt transmission and reduce prevalence to zero. Currently, six ongoing programs are in progress: poliomyelitis, yaws, dracunculiasis, malaria, hookworm, and yellow fever. In addition, the International Task Force for Disease Eradication at the Carter Center has identified neonatal tetanus, leprosy, onchocerciasis, trachoma, and lymphatic filariasis as additional potential candidates for elimination.

There are three major pre-conditions that make it scientifically more feasible to eradicate a disease: (1) epidemiological vulnerability, (2) effective interventions, and (3) feasibility of elimination. For TB, the disease is not vulnerable to eradication for the following reasons: it is easily transmitted; transmission occurs throughout the year and is not linked to a cyclical disease cycle (e.g., like influenza); there is no natural immunity to prevent re-infection; it is not easily diagnosed (current estimates from the WHO suggest that nearly one third of all TB cases are not detected); disease relapse is documented in a proportion of patients who complete treatment; and there is an LTBI reservoir that can re-activate at any time in an individual's lifetime. In addition, TB elimination has never been documented from any country in the world, indicating that the likelihood of achieving global TB eradication is low.

## 3. Prevention tools

In regards to effective preventive interventions, a safe and effective *M. tuberculosis* vaccine is not available despite intense research efforts over the past two decades. The current bacille Calmette–Guérin (BCG) vaccine in use today does not prevent infection but may reduce mortality in young recipients. BCG has been implemented for nearly a century, and despite its widespread use, TB continues to be a major global problem. A vaccine to prevent *M. tuberculosis* infection or disease remains an important tool for elimination, but the development of such a vaccine is considerably hindered by the complex biology of *M. tuberculosis* and the lack of basic information on protective immune responses.[11] There is currently no correlate of protection identified for a vaccine and no prospects of what protective host responses the vaccine should mount, or what response magnitudes are needed. Furthermore, immune responses may need to be elicited at mucosal surfaces to control or prevent *M. tuberculosis* infection, since the site of infection is the lung. Surprisingly little attention has been given to the understanding of *M. tuberculosis* mucosal immune responses in the lung. In the absence of this critical information there is no easy path forward and thus one cannot generate a timeline for the development of an effective preventative TB vaccine. Even if a correlate of protection is identified and a promising vaccine construct is identified, it will take an additional 10 years to complete the required clinical trials. Therefore, as of 2017, it is impossible to expect a vaccine by 2025 (Figure 1).

## 4. Chemotherapy

A single tool (such as a vaccine) can impact incidence and prevalence over time but cannot eliminate TB. Disease elimination will require a well-coordinated and long-term funded effort. Drugs can help and these represent another tool in the global health toolkit. Nevertheless, as has been observed over the past half century since effective TB drugs and treatment regimens have been available, it requires a massive coordination effort and resources to scale up and reach a critical level of penetration, with backup for tackling the development of resistance. A new diagnostic, such as the GeneXpert MTB/RIF assay is important for early detection and reducing the duration of infectiousness, but by itself it has not been shown to affect treatment outcomes.[12] The lack of adequate funding to develop new tools and for scaling up and implementing the existing tools, coupled with the lack of any prospect of a preventative vaccine within the next decade, makes it likely that the End TB Strategy regarding global elimination will not materialize.

Current standard TB drug therapy can be effective and affordable, but is not well tolerated, is toxic, and the treatment duration is too long. Moreover, the issue of drug resistance has been increasing steadily, requiring longer, more toxic and painful treatments that are more expensive, steeped in stigma, and require additional clinical monitoring, and which are not affordable or available to most multidrug-resistant (MDR) TB patients. Recent reports of new TB patients with diabetes mellitus at increased risk of drug-resistant TB disease suggest that new synergies between infectious and non-infectious diseases may be important to monitor.[13,14]

After many years of financially constrained research, bedaquiline and delamanid were recently approved by stringent regulatory authorities to treat MDR-TB in 2012 and 2014, respectively. As of 2016, no official drug susceptibility test (DST) method has been approved to monitor the eventual development of resistance to these new drugs, despite their availability and use over the past several years to treat patients at a programmatic level. Bedaquiline and delamanid may save lives for difficult to treat infections, but it remains to be determined whether they will have any impact on the global epidemiology of TB for which shorter and more effective regimens for both drug-susceptible disease and LTBI are necessary.[3] The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs,

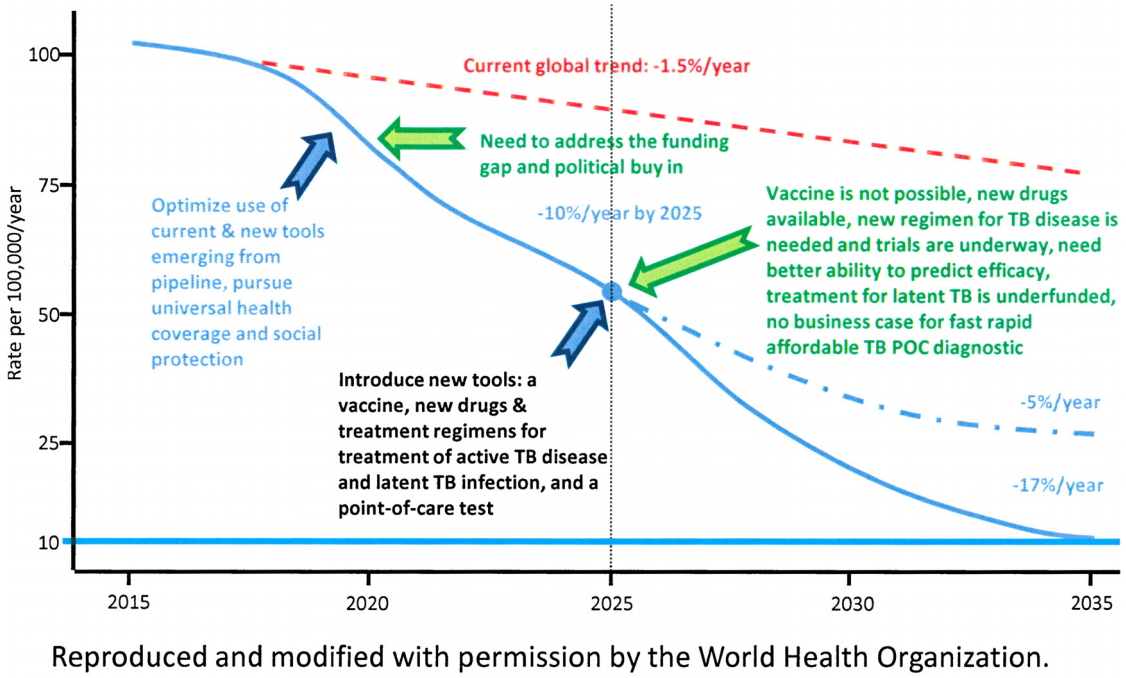


**Figure 1.** Projected decline in global TB incidence based on the deployment and optimization of new emerging tools and the challenges associated with their successful introduction. Reproduced and modified with the permission of the World Health Organization.

optimal management of TB in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research and are being addressed by the Critical Path to TB Drug Regimens (http://www.cptrinititive.org) along with stakeholder partners. Nanotechnology drug delivery systems have considerable potential for the treatment of TB. The novel properties of nanotechnology enable improvements in the bioavailability of drugs, can reduce the dosage and frequency of administration, and may solve the problem of non-adherence to prescribed therapy, which is a major obstacle to the control of TB.[15]

## 5. Diagnostics and drug resistance

Many patients do not have access to laboratory facilities that can determine TB-DST beyond first-line drugs. New diagnostic tools are particularly needed in order to improve the diagnosis of disease and latent infection, the rapid detection of drug resistance, and for use across special (HIV and pediatric) populations. Several new diagnostic devices or methods have been endorsed by the WHO since 2007 and many others are under investigation. Despite the WHO endorsement of diagnostic tools, the reality in the field is that many have not been rolled-out or sufficiently scaled-up. As a result many TB patients are assessed by sputum smear microscopy and started on treatment empirically. Targeted sequencing is being optimized directly from sputum (in the absence of culture) to identify mutations within days,[16] and a global data-sharing platform (https://platform.reseqtb.org) was recently launched to address the bioinformatics need for predicting drug resistance using sequencing technologies.[17] This approach may be potentially useful together with routine diagnostic tests in order to quickly build up individualized therapeutic regimens in severe cases of MDR-TB and extensively drug-resistant TB (XDR-TB),[3] as well as inform surveillance programs. Although sequencing is not immediately implementable in all healthcare settings, resources must be developed to support the bioinformatic sequencing needs as the technology, cost, turnaround times, and clinical outcomes improve.

The current and future control of MDR-TB relies significantly on the correct and optimal use of new diagnostics and new drugs, together with the consistent application of the following five core interventions at the programmatic level. First is the need to prevent the development of MDR-TB through high quality treatment of drug-susceptible TB. However, recent modeling suggests that the vast majority of MDR-TB is spread through transmission rather than by programmatic mismanagement,[18] highlighting the need to bolster infection control efforts. Second is the need to expand rapid testing and detection of drug-resistant TB. This requires significant funding, infrastructure, and support. Third is the need to provide immediate access to effective treatment and proper care. From the 2015 Global WHO TB report, a major success is the fact that >90% of MDR-TB patients who are identified are linked to care and put on treatment. However, more work is needed to address the need to have shorter, safer, and more effective regimens. Fourth is the requirement to prevent transmission through infection control, which is an ongoing need in most settings.[19–21] Fifth is the need for an increase in political commitment and financing (programmatic and research). Reportedly in excess of four billion dollars is desperately needed to address the now number one global infectious disease killer.[22] Despite more than 1.8 million people dying of TB in 2015, funding for TB programs through the US Global Health Program account totaled US$191 million for 2017, a US$45 million decrease (19%) below the FY16 level.[23]

## 6. Conclusions

Whilst some countries may be able to shift resources to achieve the goal of control (defined as <10 TB cases per 100 000), many confounding issues including but not limited to increased migration, war, refugee crises, poverty, comorbidities, non-tuberculous mycobacteria, animal TB, and malnutrition, together with the identified funding gap, thwart the goal of reducing TB prevalence. This will become apparent as new disease estimates using molecular methods begin to trickle in and the size of the MDR-TB population is better characterized on a global scale,

revealing a larger problem than current estimates provide. It is essential to increase resources to bolster the support to address the issues that have been neglected. For too long the response of the Global Fund and other donor agencies for TB investments has been unbalanced, resulting in TB languishing second rate to HIV and malaria.

Until many of these scientific and funding challenges are addressed, the likelihood of achieving goals beyond controlling TB is bleak. Even if it was scientifically feasible to eradicate TB, there are operational and health systems issues that must be considered, such as the perceived burden of the disease, expected cost of eradication, synergy of eradication efforts with other interventions, and the necessity for eradication rather than control.[8] In addition, since the poorest and socially excluded groups carry the largest burden of disease, it is essential to properly address the social determinants of health through poverty reduction measures and to target interventions at high-risk populations,[24] including the millions who are displaced. The spread of MDR-TB requires special attention and highlights the need to bolster research on new TB drugs, vaccines, and diagnostics. There is a need to differentiate the development of new technologies, including the endorsement, adoption, and scale-up, from the training, implementation, and health systems challenges on a global scale. Although significant progress has being made in the fight against TB over the last 25 years, significant challenges remain and much greater political and funder investment is still needed to achieve global elimination.

*Funding:* This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Conflict of interest:* No competing interest declared.

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