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# Shifting from tuberculosis control to elimination: Where are we? What are the variables and limitations? Is it achievable?

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ABSTRACT

Tuberculosis (TB) is a priority in terms of incidence and mortality, with about 10.4 million new incident cases and 1.8 million deaths in 2015. The End-TB strategy recently launched by the World Health Organization in the context of the post-2015 agenda, aimed to achieve TB elimination, represents an evolution of the previous historical strategies originally aimed to achieve TB control. Globally, the current decline in TB incidence is rather slow at approximately 1,5% per year to reach the TB pre-elimination phase by 2035 (A more aggressive approach based on diagnosis and treatment of latently infected individuals has been proposed in the context of TB elimination to ensure future generations free of TB. We describes 4 scenarios which, combined, describe the TB epidemiology in a given setting: 1) in absence of interventions, 2) with early TB diagnosis and effective treatment, 3) with irregular TB treatment, 4) with TB co-infected by HIV not undergoing anti-retroviral treatment. To achieve TB Elimination, a more concerted action by funders and governments will be required for further investments into TB prevention, detection and treatment.



The latest World Health Organization (WHO) 2016 global tuberculosis (TB) report estimates that 10.4 million new TB cases occurred worldwide in 2015, with six countries (India, Indonesia, China, Nigeria, Pakistan, and South Africa) accounting for 60% of the total burden.[1] An estimated 1.8 million people died from TB during 2015, of whom 0.4 million were co-infected with HIV. TB is now the top cause of death due to infectious disease globally, surpassing HIV and malaria.[1] Despite recent advances in TB diagnostics and investments in national TB services, the diagnosis and notification of TB remain sub-optimal in high TB burden countries in Africa, Europe, and Asia. Only 6.1 million cases were detected and reported in 2015 globally out of the 10.4 million cases estimated by the WHO. This important 4.3 million gap is attributed by the WHO to TB underreporting from countries with a rampant private sector, while under-diagnosis is mainly observed in low-income countries (where barriers to access to care still exist).[1]

The continuing spread of multidrug-resistant TB (MDR-TB) is also of growing concern. The WHO estimated 480 000 new MDR-TB cases occurring in 2015, and 100 000 were reported to be rifampicin-resistant TB following the roll-out of the GeneXpert MTB/RIF assay.[1] The countries with the highest MDR-TB burden – India, China, and the Russian Federation – notified 45% of the total number of cases (580 000) eligible for MDR-TB treatment.[1] Only 20% of the estimated 580 000 cases were enrolled for second-line treatment in 2015, highlighting that one out of five MDR-TB cases are treated at present, while the treatment success rate remains overall as low as 52%.[1] In 2015, 22% of the existing HIV-positive TB patients had no access to antiretroviral therapy (ART), as recommended by the WHO. However, over 900 000 people living with HIV started ART in the same year, including 87 000 children under 5 years of age (e.g., 7% only of those being eligible).[1]

The End TB Strategy, recently launched by the WHO, represents an evolution of the previous historical strategies originally aimed at achieving TB control,[2–7] but now focuses on achieving TB 'elimination'. Mathematical modelling has been used extensively to predict future TB trends and guide public health strategies. The recent trajectory of TB incidence proposed in the WHO framework for TB elimination is a good example of a possible (and epidemiologically plausible) evolution of the disease from 2015 to 2050 (Figure 1).[6,7] Globally, the current decline in TB incidence is rather slow at approximately 1.5% per year.[1] It is

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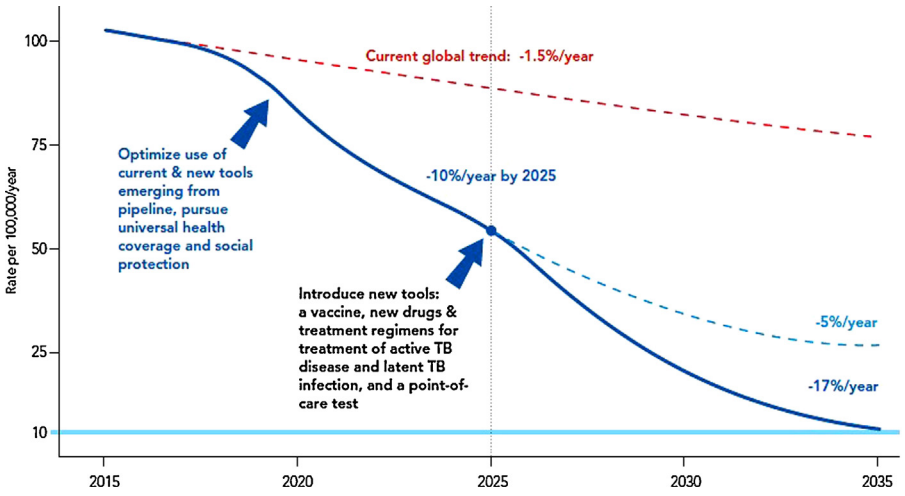


**Figure 1.** Projected acceleration in the decline of global tuberculosis incidence rates to target levels (from Ref. 4).

derived from an average of the global picture, i.e. from a very slow decline in parts of Africa and Asia, an intermediate decline in countries like China and Cambodia (around 5% per year), and a significant decline in low TB incidence countries. This rate of decline needs to accelerate to a 4–5% annual decline by 2020 to reach the first milestone of the End TB Strategy.[1]

In order to move towards the TB pre-elimination phase by 2035 (defined as less than 10 cases of TB per million population) and then progress to TB elimination by 2050 (defined as less than 1 case per million population), more rapid progress is necessary, over and above the present trends.[6,7] The WHO hypothetical modelling decline shows a different slope before and after 2015. The model suggests that all possible efforts need to be made to utilize the resources available today in terms of diagnostics, treatment regimens, and public health strategies.[8]

The End TB Strategy is based on three main pillars (Table 1).[3,4] Pillar one summarizes the main technical interventions aimed at controlling TB, which include (1) rapid diagnosis, now achievable with the GeneXpert MTB/RIF assay and new generation line probe assays,[9–12] (2) effective treatment with available treatment regimens including the recent introduction of the new shorter MDR-TB regimen,[12–14] and (3) TB prevention with the new package, which for the first time considers the potential effects of diagnosing and treating latent TB infection (LTBI) in high-risk groups (a TB elimination intervention) in addition to vaccination.[6,7,15] It is important to note that the present vaccination with bacillus Calmette–Guérin (BCG), which the WHO recommends is given at birth in high TB incidence countries, only confers incomplete and time-limited protection, preventing TB meningitis and other disseminated forms of TB.[16] Thus, BCG makes only a limited contribution to the decline in TB incidence.[6,7]

Another important clarification required is related to the management of LTBI, an important intervention strategy among eight proposed to reach TB elimination targets (Table 1).[6,7] It aims

**Table 1**
The End TB Strategy pillars and TB elimination priority action areas (adapted from Refs. 4 and7)

| End TB Strategy pillars and components | |
|---|---|
| 1. Integrated, patient-centred care and prevention | A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups<br>B. Treatment of all people with TB including drug-resistant TB, and patient support<br>C. Collaborative TB/HIV activities, and management of co-morbidities<br>D. Preventive treatment of persons at high risk, and vaccination against TB |
| 2. Bold policies and supportive systems | A. Political commitment with adequate resources for TB care and prevention<br>B. Engagement of communities, civil society organizations, and public and private care providers<br>C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control<br>D. Social protection, poverty alleviation, and actions on other determinants of TB |
| 3. Intensified research and innovation | A. Discovery, development, and rapid uptake of new tools, interventions, and strategies<br>B. Research to optimize implementation and impact, and promote innovations |

| Priority action areas to reach TB elimination | End TB Strategy pillars and components |
|---|---|
| 1. Ensure political commitment, funding, and stewardship for planning and essential services of high quality | 1. A–D<br>2. A–D |
| 2. Address the most vulnerable and hard-to-reach groups | 1. A–D<br>2. B–D |
| 3. Address special needs of migrants and cross-border issues | 1. A–D<br>2. B–D |
| 4. Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups, and provide appropriate treatment | 1. A, D |
| 5. Optimize the prevention and care of drug-resistant TB | 1. A–D<br>2. A–D<br>3. A–B |
| 6. Ensure continued surveillance, programme monitoring, and evaluation and case based-data management | 2. A–C |
| 7. Invest in research and new tools | 3. A–B |
| 8. Support global TB prevention, care, and control | 1–3 |

TB, tuberculosis; LTBI, latent tuberculosis infection.

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**Table 2**
Recommended treatment options for LTBI (adapted from Ref. 18)

| Treatment options for LTBI |
|---|
| 6 months isoniazid |
| OR 9 months isoniazid |
| OR 3-month regimen of weekly rifapentine plus isoniazid[a] |
| OR 3–4 months isoniazid plus rifampicin[a] |
| OR 3–4 months rifampicin alone[a] |

LTBI, latent tuberculosis infection.
[a] Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment, due to potential drug–drug interactions (see also http://www.cdc.gov/mmWr/preview/mmwrhtml/mm4909a4.htm).

to reduce the pool of latently infected individuals from which future TB cases may be generated. Whilst each individual undergoing a complete cycle of LTBI treatment with one of the recommended LTBI regimens (Table 2)[17,18] will benefit individually in terms of a reduced probability of progression to developing active TB disease, the possibility of achieving a public health impact will depend on the number of individuals with LTBI at risk of progression to active TB who are correctly diagnosed and treated.

The increase in TB decline shown in Figure 1 could hopefully result from a combination of factors, including a full implementation of the principles of Pillar two of the End TB Strategy (universal access and social protection among others), new regimens to treat TB and LTBI, and hopefully a more effective TB vaccine (of which 15 are in the pipeline).[1] An example of important declines almost reaching 20% per year have been observed in Canada among Inuits, where an aggressive programme of LTBI management has been successfully implemented.[19] In the absence of such an 'aggressive' approach to LTBI, and success in tackling the other priority issues summarized in Table 1 (managing immigrants, refugees, and hard-to-reach populations, MDR-TB, TB–HIV co-infection, etc.), TB elimination will not be reached in low TB incidence countries.[6,7]

The current slow decline in the global TB incidence curve needs to be viewed from a historical perspective with findings of ancient *Mycobacterium tuberculosis* DNA in mammoth bones, Egyptian mummies, and in our pre-historical ancestors.[20]

Karel Styblo (1921–1998) tried to describe the main epidemiological and control scenarios with his famous model.[21,22] A simplified description of some of the scenarios that, in different proportions, tend to determine the real epidemiology of TB in a given setting is proposed below (Figure 2). In the absence of interventions, an infectious (e.g., a sputum smear-positive) patient infects 10 persons a year for 2 years before healing spontaneously or dying (Figure 2A). Given a 10% lifetime probability of acquiring disease given the infection and the 50% probability of becoming sputum smear-positive, a case generates another case, contributing to keeping the epidemic level stable. Although, theoretically, control interventions are present globally, situations of difficult implementation (e.g., difficult access, disaster and conflict situations, war settings, etc.) still exist. In a scenario where rapid diagnosis and effective treatment can be applied (Figure 2B), only five individuals are infected and, as a result, only 0.25 cases are generated by the original infectious case. That is similar to saying that we need four sputum smear-positive cases to generate a new infectious one. This shows that an adequate implementation of the directly observed treatment short course (DOTS) strategy (as it was known at the time it was launched) could have a substantial impact on the epidemic in the absence of factors working in an opposite direction, like HIV or any other factor increasing the probability of acquiring TB disease given infection (e.g., diabetes, stress as observed in war areas or in migrants/refugees, etc.).

If irregularities or interruptions occur during treatment (as is the case in several settings with a high prevalence of MDR-TB), it is sufficient to prevent death and prolong the infectious period, so

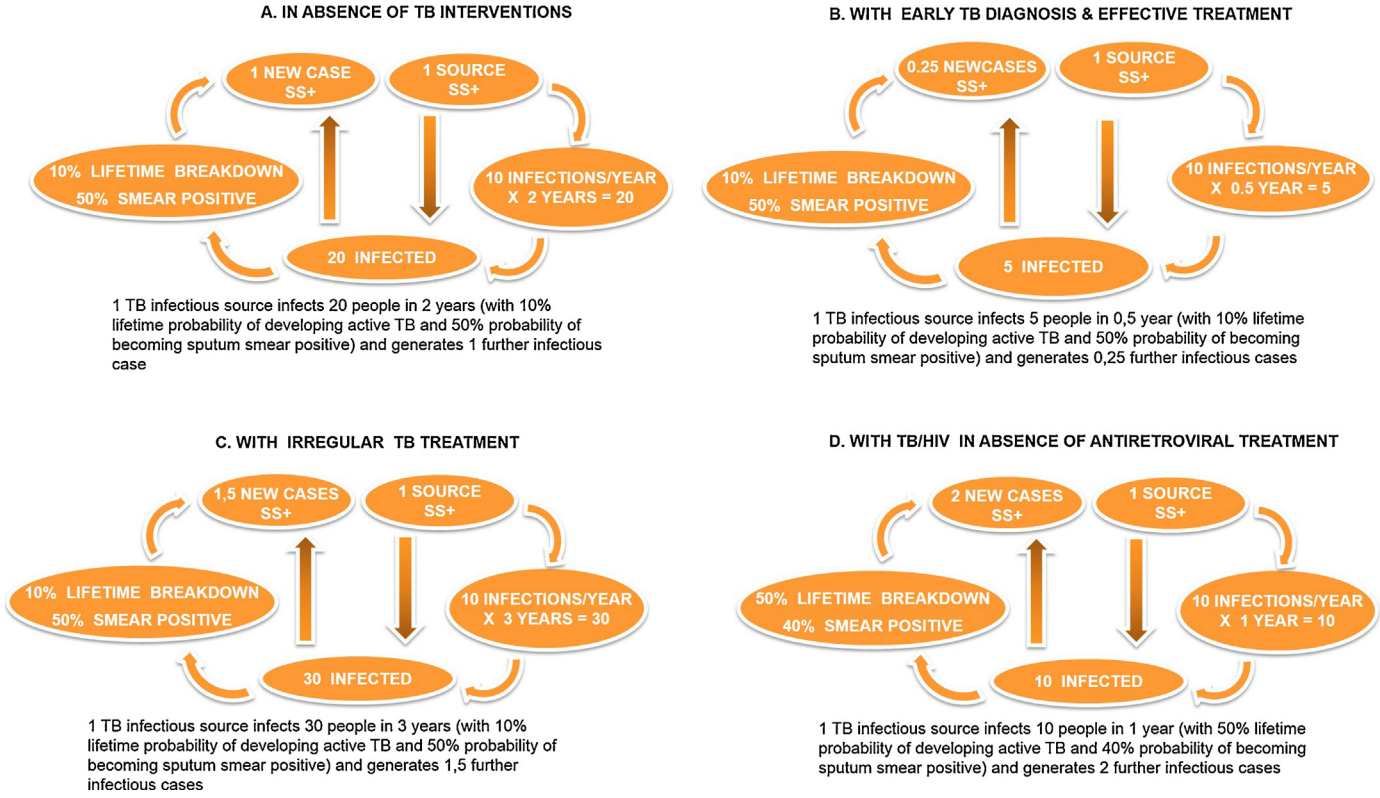


**Figure 2.** Tuberculosis transmission model: (A) in the absence of TB interventions; (B) with early TB diagnosis and effective treatment; (C) with irregular TB treatment; (D) in the absence of antiretroviral treatment with TB/HIV co-infection.

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that one case can produce up to 1.5 new infectious cases, which in turn will gradually result in a more severe drug resistance pattern (Figure 2C). This explains why in some countries, particularly in the Former Soviet Union, over 18–20% of new cases and 50% of retreatment cases harbour MDR strains of *M. tuberculosis*.[23–26]

Under the hypothetical scenario of a population with TB co-infected by HIV not undergoing ART (Figure 2D), with a different mechanism than in Figure 1A (e.g., on the left part of the ring, due to the higher breakdown rate infection–diseases), one infectious case generates another two cases, again contributing to reducing the speed of decline. Although no country has a 100% TB/HIV co-infection rate, there are settings with an HIV prevalence in the general population of between 20% and 70% in specific risk groups. Whilst a large proportion of countries are rolling out antiretrovirals, there are always settings where difficult access or logistical problems make it difficult to cover all individuals needing them.

In summary, if the End TB Strategy is to be successful in achieving TB elimination, a more concerted action by funders and governments will be required for further investment in TB prevention, detection, and treatment.

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