International Journal of Infectious Diseases 32 (2015) 152–155

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

# Tuberculosis elimination in the post Millennium Development Goals era

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ARTICLE INFO

*Article history:*
Received 12 November 2014
Received in revised form 20 November 2014
Accepted 22 November 2014

*Keywords:*
Tuberculosis
Elimination
Case-finding
Preventive therapy

SUMMARY

The Millennium Development Goal for tuberculosis (TB) is to stop the increase in incidence and halve the mortality of TB between 1990 and 2015. This goal has now been reached on a global scale, although not in the most affected region of Africa. The new target is TB elimination, defined as one case of active TB per one million population per year, which is to be reached before 2050. This review will discuss the main tools in play, namely case-finding and new diagnostics, increased access and effectiveness of anti-TB therapy (directly observed therapy, short course (DOTS)), preventive therapy for latent infection, and vaccination. Each approach is discussed and a way forward in research and management is suggested.


## 1. Introduction

Achieving the control of tuberculosis (TB) is very difficult in resource-poor countries with a high burden of TB. Few and at times poorly skilled health workers try to control the epidemic by treating overt cases using the directly observed therapy supervised approach (directly observed therapy, short course (DOTS)). This will only treat the top of the TB iceberg;[1] the transmission of TB will continue due to delayed treatment, transmission from undiagnosed patients, and from an increasing pool of latently infected individuals who may progress to active disease. The current agenda is to reach the Millennium Development Goal (MDG) of stopping the increase in incidence and halving the mortality of TB between 1990 and 2015, and this goal is likely to be reached on a global scale but not in Africa.[2,3]

The next goal set by the World Health Organization (WHO) Stop TB Program is the elimination of TB by 2050. Elimination is defined as zero disease in a defined geographic area as a result of deliberate efforts, with control measures needed to prevent reestablishment of transmission; this is different from eradication, which is zero disease globally as a result of deliberate efforts where control measures are no longer needed.[4] In terms of TB, elimination has been defined as less than one case of active smear-positive TB per one million population per year.[5] This will require a reduction in TB incidence of 16% per year, however the current rate is 1%.[6] This is therefore not likely to happen using current approaches,[6] hence focus has been directed towards possible new technological advances such as new diagnostics and a new TB vaccine.[2,6,7] Nevertheless, for the global community to achieve the elimination of TB, it will likely be necessary to utilize low-cost intervention programs feasible in areas where TB reigns, and to target the hidden part of the TB iceberg by addressing the latently infected.[8] The path towards elimination of TB in high-burden areas may be found using a number of approaches; these approaches are reviewed below.

## 2. New diagnostics

One of the obstacles in targeting TB disease is the difficulty associated with diagnosing active disease. Smear microscopy is the most widely used method, but this has a sensitivity of only 50–60%,[9] leaving a large portion to be treated from clinical judgment and radiography evaluation. Culture is the gold standard, but requires a high degree of laboratory capacity, which is often not available in high-burden areas. A major advance in diagnostics has been automated PCR using the GeneXpert MTB/RIF platform, which is more sensitive than smear microscopy and can also detect drug resistance.[9] Rolling-out this new diagnostic as a point-of-care tool in peripheral health facilities has just been attempted in several African countries, in a landmark trial testing Xpert MTB/RIF

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http://dx.doi.org/10.1016/j.ijid.2014.11.020

against standard methods using smear microscopy and chest X-ray. The results of the trial were somewhat disappointing, in that the Xpert MTB/RIF arm did not place more patients on treatment than the microscopy arm: 43% of people with suspected TB were given treatment by day 56 in the Xpert MTB/RIF group compared to 42% in the microscopy group, although a slightly higher proportion of those treated were culture-positive.[10] Xpert MTB/RIF improved same-day treatment initiation (23% in the Xpert group vs. 15% in the microscopy group), and fewer culture-positive patients in the Xpert MTB/RIF group who had a positive MTB/RIF test result did not receive treatment (8% vs. 15%), halving drop-out. Nevertheless there was no effect on the primary outcome, which was a difference in morbidity according to the TBscore.[11] Also, mortality was 8% in both arms, but the study was not powered to detect differences in mortality.

This promising diagnostic tool is definitely an advance, but in terms of adding to the difficult task of case-finding and reducing the number of missed cases, it has brought little extra to the table, and simpler less costly methods such as follow-up of the assumed TB-negative (ATBneg; i.e., former TB suspects),[12] or simple clinical scores for TB suspects,[13] may be more useful. Indeed for eliminating TB, Xpert MTB/RIF will not be the magic bullet many had hoped for and the associated costs are also prohibitive for large-scale roll-out.[14]

## 3. Directly observed therapy, short-course (DOTS)

The treatment of active disease is a cornerstone in the fight against TB, and apart from saving the lives of those treated, it also invariably reduces the transmission of TB. In light of this, scaling up access to treatment has been a major focus in recent years, and is still the primary focus in the WHO Global Report on TB.[2] DOTS was developed in the early 1990s as a response to the reemergence of TB that was seen following the HIV epidemic. It consists of five key programmatic elements: (1) A government commitment to mobilize sufficient resources for TB control. (2) Case detection through passive case-finding using sputum smear microscopy in patients with respiratory symptoms. (3) Treatment using standard short-course chemotherapy regimens containing rifampin, administered under direct observation for at least the first 2 months of treatment. (4) Securing a regular supply of essential anti-TB drugs. (5) Establishing a reliable monitoring, recording, and reporting system for program supervision and evaluation.[15]

Yet, the central element for the patient is the direct observation of treatment, which has been questioned because of the imposition on patient autonomy,[16] and this approach has not been found to be more effective than self-supervision of treatment.[17,18]

Further, in terms of effectively combating TB and leading the path towards elimination, DOTS alone will likely be a very insufficient measure;[19,20] a number of approaches will be needed. Mathematical modeling shows that even in the best of scenarios, with a high case detection rate and optimal cure rates, DOTS will be insufficient to eliminate TB. At best it may more than halve the incidence, but it will not reduce it by the factor of 1000 needed in many high-burden areas.[1,6]

## 4. Preventive therapy of latent tuberculosis

Preventive treatment for latent TB infection (LTBI) was shown to be effective 50 years ago in Alaska. Comstock et al. undertook large-scale trials in the Inuit population and showed a long-lasting effect on the TB burden in the population.[21–23] This approach is standard in most developed countries as part of contact investigation, but has not so far been attempted in high-burden areas except among the HIV-infected.[17] Although recommended by the WHO, it is not implemented in most high-burden areas due to the fear of adverse events, poor adherence, and the facilitation of drug resistance.[24] Leading WHO officers in the Stop TB department recently concluded that further research is needed to establish its cost-effectiveness and feasibility, especially in low-income and middle-income countries.[25] Yet, there is now growing evidence that mass, community-wide screening for TB may be of benefit in some situations for enhanced case-finding.[26,27] There is also growing evidence that isoniazid preventive treatment (IPT) for the latently infected is indeed feasible and effective, even in very low resource settings with poor infrastructure.

We have shown in Guinea Bissau that adherence to IPT can be quite high[28] and that IPT in children in households with a recent case of TB lowers mortality.[29] However, a recent cluster randomized trial among 78 744 miners of three gold-mining companies in South Africa showed that IPT had only a short-lasting effect on overall TB incidence in this high-risk population with a high HIV prevalence.[30] Nevertheless, if looking only at the first 9 months when miners were actually taking isoniazid, the TB incidence in the IPT cohort was significantly lower (1.1 cases per 100 person-years) compared to the control cohort (2.9 cases per 100 person-years). So mass IPT did not reduce TB incidence at the community-level; however, among those who were documented to receive IPT, the TB incidence was reduced during the 9-month treatment period, but the protective effect was lost immediately after treatment was discontinued. An explanation for this may be the variable participation of miners in the intervention clusters and a suboptimal proportion of miners taking IPT. Also, the loss of protection immediately after discontinuation of isoniazid may be due to the reactivation of inadequately treated latent infections or re-infection caused by high rates of ongoing transmission and it is therefore less clear what the effect of IPT will be in populations other than the extremely high-risk group of gold-miners.

## 5. New vaccines

Bacille Calmette–Guérin (BCG) is the most widely used vaccine in the world, and in fact there is a high coverage rate in most high-burden areas. It is known to be effective against TB meningitis and miliary TB among children, but the effect wanes and there is virtually no effect on adult TB. Disappointingly, large-scale mass BCG vaccination has not had a long-lasting effect on TB epidemiology.[31] There are now several new vaccine candidates, but so far no major breakthroughs have occurred.[32] The only vaccine candidate that has been tested so far in a phase 2B trial for effectiveness is MVA85A, a BCG booster vaccine. The trial enrolled 2797 infants but showed no effect on the primary outcome, which was TB incidence.[33] Thirty-two children in the intervention arm developed TB versus 39 in the placebo arm, hence a vaccine efficacy of 17% was seen, which was not significant. There was also no effect on TB infection determined by developing a positive Quantiferon test. Two other vaccine candidates are now in phase 2B: AERAS-402/Crucell Ad35 in infants and GlaxoSmithKline's GSK M72 in adults. Both are post-exposure subunit booster vaccines (http://www.aeras.org/candidates/). In addition, two candidates from Statens Serum Institute are in phase 2; they both use combined antigens with characteristics of early infection and latency and have been found to protect mice against TB disease before and after exposure to infection.[34] The hopes for these vaccines are high, but the results so far from the only one reaching clinical efficacy trials have been disappointing.

## 6. Discussion and conclusions

We are approaching 2015, the target year for the completion of the MDGs. Although the overall target related to the MDGs of halting and beginning to reverse the TB epidemic had already been