Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models

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Summary

Background The post-2015 End TB Strategy proposes targets of 50% reduction in tuberculosis incidence and 75% reduction in mortality from tuberculosis by 2025. We aimed to assess whether these targets are feasible in three high-burden countries with contrasting epidemiology and previous programmatic achievements.

Methods 11 independently developed mathematical models of tuberculosis transmission projected the epidemiological impact of currently available tuberculosis interventions for prevention, diagnosis, and treatment in India, China, and South Africa. Models were calibrated with data on tuberculosis incidence and mortality in 2012. Representatives from national tuberculosis programmes and the advocacy community provided distinct country-specific intervention scenarios, which included screening for symptoms, active case finding, and preventive therapy.

Findings Aggressive scale-up of any single intervention scenario could not achieve the post-2015 End TB Strategy targets in any country. However, the models projected that, in the South Africa national tuberculosis programme scenario, a combination of continuous isoniazid preventive therapy for individuals on antiretroviral therapy, expanded facility-based screening for symptoms of tuberculosis at health centres, and improved tuberculosis care could achieve a 55% reduction in incidence (range 31–62%) and a 72% reduction in mortality (range 64–82%) compared with 2015 levels. For India, and particularly for China, full scale-up of all interventions in tuberculosis-programme performance fell short of the 2025 targets, despite preventing a cumulative 3·4 million cases. The advocacy scenarios illustrated the high impact of detecting and treating latent tuberculosis.

Interpretation Major reductions in tuberculosis burden seem possible with current interventions. However, additional interventions, adapted to country-specific tuberculosis epidemiology and health systems, are needed to reach the post-2015 End TB Strategy targets at country level.

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Introduction In May, 2014, the World Health Assembly approved the post-2015 End TB Strategy, setting “ambitious but feasible” targets for reducing the global burden of tuberculosis by 2035.12 The strategy is aiming for a 50% reduction in global tuberculosis incidence and a 75% reduction in global tuberculosis mortality by 2025, and 90% and 95% reductions in these outcomes, respectively, by 2035.2 Policy makers must identify what interventions, and at which level of scale-up, will be needed to meet these targets at country level.

The End TB targets are deliberately ambitious, and any single intervention (defined here as a group of activities leading to an improvement in a specific area of tuberculosis control—eg, treatment outcomes) is unlikely to achieve these goals.3 Instead, national tuberculosis programmes will need improvements across the tuberculosis care pathway, together with preventive measures.

The End TB Strategy describes two phases of future efforts to control tuberculosis.1 In phase 1, the focus of this Article, progression towards the 2025 milestones will largely depend on optimising the use of existing tools, enabled by investments in universal health coverage and social protection.2 Post-2025 in phase 2, novel tools (diagnostics, drugs, and vaccines) are expected to enable further acceleration of tuberculosis decline towards the 2035 targets.1 For both phases of the End TB Strategy, policy makers require guidance about which interventions and technologies to use—questions that are unlikely to be answered by empirical studies, given
The post-2015 Global TB Strategy envisions and is aiming for a 50% reduction in tuberculosis incidence and a 75% reduction in tuberculosis mortality by 2025, using existing or near-existing tools. Given that this period starts in 2016, there is an urgent need to inform policy discussions on how these targets can be reached on a country level. Modelling can be a powerful tool to address this need by projecting the potential effect of a combination of different interventions. Additionally, by using multiple models to address the same question, it can be used to identify findings robust to between-model variation, increasing confidence in the conclusions. We reviewed existing modelling studies that assessed the individual and combined impact of a range of existing interventions, and other multimodelling exercises in the field of tuberculosis. We built on a systematic review by the TB Modelling and Analysis Consortium who gathered all tuberculosis modelling papers and extended the review to June, 2015. PubMed was searched using the following search query: (tuberculosis OR TB) AND ((mathem* AND (model OR models)) OR (mathem* modell*)) OR (mathem* modeling) OR (modeling OR modellers) OR “Population Dynamics” [MeSH Terms] OR ”Population Dynamics” OR “System Dynamics” OR “Computer Simulation” OR “Computer Simulation” [MeSH Terms]). We also did specific searches in mathematical modelling journals, and searched private libraries, and references of existing modelling reviews. We only included English language papers and we used no date restrictions. Ours is the first study to compare multiple tuberculosis models to answer a public health question. Single models have usually evaluated a single intervention, making it difficult to understand the full potential, including potential synergy, or non-synergy, of a combination of interventions implemented simultaneously. Other multimodel exercises have been published, most notably in the field of HIV, which focused on questions around antiretroviral therapy scale-up to inform UNAIDS policy.

**Added value of this study**

This study highlights the uncertainty in the natural history of tuberculosis that drives between-model differences, while still identifying relatively consistent findings of public health importance. It explores how a range of existing interventions across the tuberculosis care pathway, scaled up to country-specific levels, can take China, India, and South Africa towards the 2025 global tuberculosis targets. Our results show that expansion of existing interventions should enable South Africa to reach the 2025 targets, while for India and China additional context-specific activities are likely to be needed.

**Implications of all the available evidence**

Although major reductions in tuberculosis burden seem possible with current tools and 2025 targets might be met in South Africa, additional interventions, adapted to the country-specific tuberculosis epidemiology and health systems, are likely to be needed to reach the post-2015 Global TB Targets in other key countries such as China and India. These might include interventions such as tackling the latent tuberculosis infection reservoir in elderly people in China and undernutrition in India. This decision making can be informed by rigorous data analysis and the logical framework that mathematical models provide.
Methods

Participating models

After a global call from the TB Modelling and Analysis Consortium for expressions of interest, 11 modelling groups contributed results for at least one of the countries (China, India, or South Africa). These models varied in their frameworks, population stratifications, and approaches used to model disease and intervention mechanisms. An overview of participating models and references is in table 1.

Data and country context for baseline

To calibrate the models and provide a baseline scenario, modellers were provided calibration targets reflecting tuberculosis burden (as incidence and mortality) in 2012, and tuberculosis control activities. Because half the participating models only included adult groups (aged ≥15 years), calibration targets and results also focused on adults (appendix). For China, the calibration targets included 2000 and 2010 tuberculosis prevalence focused on adults (appendix). For China, the calibration (aged ≥15 years), calibration targets and results also the participating models only included adult groups.

Table 1: Description of mathematical models

| Country   | Model type | Model calibration | Age structure | Sex strata | Population strata | Results reported | Interventions modelled* |
|-----------|------------|-------------------|---------------|------------|-------------------|------------------|-------------------------|
| NTU       | China      | D Manual          | 15+ years     | No         | MDR, health-care sector, treatment history | Single          | All                     |
| ICPHF      | India      | D Algorithmic     | 15+ years     | No         | MDR, treatment history, HIV (2 strata), health-care sector | Single          | All                     |
| STAMP      | India      | I Grid Search     | 1-month age groups | Yes       | MDR, treatment history, health-care sector, time since infection and activation | Stoch           | All                     |
| Hopkins    | South Africa | D Manual       | Single age group (15+ years) | No         | MDR, health-care sector, treatment history, HIV/ART/CD4 status (5 strata) | Single          | All                     |
| IRD        | South Africa | D Manual       | 1-month age groups | Yes (HIV only) | HIV/ART/CD4 status (5 strata) | Single          | IPT for ART              |
| SIPTM      | South Africa | D Manual       | <15, 15-19, 19+ years | No         | HIV/ART/CD4 status (5 strata) | Single          | IPT for ART              |
| UGA        | South Africa | D Manual       | <15 and 15+ years | No         | MDR, health-care sector, HIV/ART/CD4 (3 strata) | Single          | All                     |
| IDM        | South Africa, China | I Manual   | Explicit age | No         | MDR, health-care sector, treatment history, HIV/ART/CD4 | Stoch           | All                     |
| Harvard    | South Africa, China | D Bayesian | Single age group | No         | MDR, health-care sector, treatment history, HIV/ART/CD4 (9 strata) | Single          | All                     |
| AuToMN     | South Africa, China | D Algorithmic | <15 and 15+ years | No         | MDR, health-care sector, South Africa: HIV/ ART/CD4 ($5 strata) | Single          | All                     |
| TIME       | South Africa, India | D Manual      | <15 and 15+ years | No         | MDR, treatment history HIV/ART/CD4 status (11 strata) | Single          | All                     |

D=deterministic compartmental model. I=individual-based, stochastic model. Sex strata: Yes=natural history or care pathway parameters different for male and female patients; No=no sex stratification in models. MDR=multidrug-resistant. ART=antiretroviral therapy. Single=single parameter set. Stoch=average (mean or median) of stochastic simulations. *See table 2 for details of interventions.

Table 2 summarises national tuberculosis programme levels of scale-up within those intervention scenarios.

The first intervention scenario looked at improvements in access to high-quality care, defined as individuals with tuberculosis disease having access to the best level of care available in their local context. Tuberculosis care in China and India is provided through many health-care providers. Since the quality of care is known to differ strongly between providers, the intervention scenarios explored what could be achieved if a higher proportion of the population of patients with tuberculosis disease

Figure 1: TB Care and Prevention framework

The patient care pathway from disease to completion of treatment (blue boxes and arrows). Areas affected for enhancing current tuberculosis programme activities (ie, intervention scenarios) are shown in grey boxes and arrows, with the number (#x) to link them to activities in table 2 and the appendix section 3.

New Delhi, India
(P Dewan MD); Aurum Institute, Johannesburg, South Africa (P Hippner MSc, S Charlabous PhD, Prof G Churchyard PhD); School of Public Health, University of Witwatersrand, Johannesburg, South Africa (Prof G Churchyard); National Department of Health, Pretoria, South Africa (VP Pillay PhD, D Mamelja MPH); and Bill & Melinda Gates Foundation, Seattle, WA, USA (currently KNCV Tuberculosis Foundation, The Hague, Netherlands, M E Kemerling MD)
| Activities | Base value | Target value† |
|------------|------------|---------------|
| #1 Increase access to high quality care‡ | Government subsidises tuberculosis care, and compensates patients for incurred costs | 5% 75% (NTP), 0% (A) | Government subsidises diagnostic and treatment costs in private sector, expanding number of clinics and opening times of tuberculosis care | 9% 75% (NTP), 0% (A) |
| Of those with care access, increase proportion accessing high quality care | Same technology and approaches available in hospital and CDC sector | 80% 95% (NTP), 100% (A) | Government subsidises use of high-quality tools and protocols in private sector | 50% 90% (NTP), 100% (A) |
| Improve geographical access through outreach clinics | | | Tuberculosis symptom screening for all health-clinic attendees to ensure all in need receive tuberculosis diagnosis | 20% 100% (NTP), 100% (A) |

| Activities | Base value | Target value† |
|------------|------------|---------------|
| #2 Diagnosis of disease and MDR§ | Replacement of smear microscopy with molecular diagnostic in facilities | 0% 100% (NTP), 100% (A) | Replacement of smear microscopy with molecular diagnostic in facilities | 0% 30% (NTP), 100% (A) |
| #3 Improve post-diagnosis care§ | Compensation for patient costs | 3% 15% (NTP), 0% (A) | Provide patient incentives for treatment initiation | 10% 5% (NTP), 0% (A) |
| #4 Active case finding in general population | Compensation for patient costs, improvements in speed of diagnosis and referral | 50% 15% (NTP), 0% (A) | Linkage to social welfare programmes, including nutritional support | 11% 5% (NTP), 0% (A) |
| #5 Active case finding followed by treatment of latent tuberculosis | Implement patient support strategies including health and case management | 82% 90% (NTP), 95% (A) | Provide incentives and linkage to welfare programmes | 75% 85% (NTP), 90% (A) |
| #6 Continuous IPT for ART-receiving population | Improve patient monitoring (mhealth) and side-effect amelioration | 35% 65% (NTP), 80% (A) | As above | 48% 67% (NTP), 80% (A) |
| #7 Combination | As general description | 0% 0% (NTP), 30% (A) | As general description | 0% 3% 6% (NTP), 0% (A) |

**Table 2: Summary of modelled intervention scenarios and target values for China, India, and South Africa**

Information describes the general intervention effects to be modelled, which were adapted to fit within specific model structures (see appendix section 3 for details). Target value=absolute value. NTP=national tuberculosis programme scenario. A-advocacy scenario. PLWHIV=people living with HIV. CDC=Centers for Disease Control. mhealth=mobile health. MDR=multidrug resistant. LTBI=latent tuberculosis infection. IPT=isoniazid preventive treatment. ART=antiretroviral therapy. *Summarises the activities proposed by the NTP scenario-setters to enhance current programme performance. †Scale-up to target value started in 2015 and usually reached in 2020. High quality care describes the best performing sector of all tuberculosis care providers—eg, public sector in India, CDC sector in China. Intervention scenarios for diagnosis (‡) and care (§) apply to population accessing high quality care only.
received the higher quality care as provided in the Centers for Disease Control (China) or the public sector (India). For South Africa, models explored a new policy of expanded screening of health-centre visitors for symptoms of tuberculosis disease.

A second set of intervention scenarios modelled improvements in the tuberculosis care pathway, which included replacing sputum smears with a molecular diagnostic test such as GeneXpert as the first laboratory test, increasing linkage to care for individuals diagnosed with tuberculosis disease, and improved treatment outcomes for those linked to care. We also estimated the effect of active case finding for tuberculosis disease in the general population, implemented as simple screening of a proportion of the population for disease (table 2, appendix), either on its own, or as screening for active disease along with preventive therapy for individuals with latent tuberculosis infection. For South Africa, an additional intervention scenario estimated the impact of providing continuous isoniazid preventive therapy, with screening for active disease before initiation for individuals receiving ART. A combination intervention scenario estimated the overall impact of all interventions run simultaneously. Only models that contributed results to all individual interventions reported the combined intervention.

Under the advocacy scenarios, models estimated the potential effect on tuberculosis incidence and mortality if countries were able to screen and treat 30% (India and China) or 50% (South Africa) of the general population (as a proxy for identifying a similar proportion of the burden through active-case finding in high-risk groups) for tuberculosis disease and latent tuberculosis infection twice a year (table 2). With the exception of the active case finding and preventive therapy for the general population, each intervention scenario was operationalised as specific programmatic activities tailored to each country context (table 2). Modellers were asked to reflect these activities as closely as possible using their respective model structure and parameterisation (see appendix section 3 for guidance provided and the implementation of the intervention scenarios for each model).
Economic development and related investments in universal health coverage, components of Pillar 2 in the End TB Strategy were considered critical enablers of other intervention scenarios—eg, for access to high-quality care and treatment success (table 2, appendix section 3). Thus, we did not model separately potential benefits for interventions such as achievement of universal health coverage, cash-transfer programmes, or the preventive effect of poverty-reduction efforts on tuberculosis outcomes.

Models reported on tuberculosis incidence, mortality, and prevalence for the period 1990–2025. Because half the models captured adults only (table 4), our main outcomes were the change in adult (aged ≥15 years) incidence and mortality between 2015 and 2025 in the baseline scenarios. Additionally, we recorded the incremental impact of individual intervention scenarios and the overall impact of the baseline plus the combination intervention scenarios, and the cumulative cases and deaths averted. Additional outcomes reported...
by modellers included MDR tuberculosis prevalence in new or retreatment cases, latent tuberculosis infection prevalence, and the proportion of disease after recent infection. These outcomes were used to understand the differences between models and ensure internal model consistency. After fitting to the calibration targets, modelling groups were provided with guidance on how to implement the intervention scenarios (appendix section 3) in view of the differences in model structures. Additionally, we established minimum requirements to model structure for contribution to each scenario (appendix section 3).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The modelling took place between March and December, 2014. Of 11 participating models, six provided projections for China, five for India, and eight for South Africa. Three modelling groups (Harvard, AuTuMN and TIME) contributed results for all three countries and one model (IDM) modelled the China and South Africa epidemics. Of 11 models, nine provided results for all interventions (table 1).

Figure 2 shows baseline calibration and projections for incidence and mortality. In China, where models were calibrated to 2000 and 2010 prevalence targets (appendix sections 1 and 4), historical and projected trends were similar between models. For India, the historical uncertainty was propagated in the projections, although most models predicted a declining incidence trend consistent with recent WHO projections. In South Africa, models were calibrated to an epidemiological burden and trend in 2012, but diverged over time as the projected baseline change in incidence between 2015 and 2025 ranged from 0 to 25%. For China and India, baseline changes in incidence were 11–27% and 0–19%, respectively, suggesting that with tuberculosis-programme activity, the tuberculosis burden was most likely to continue its decline.

In the national tuberculosis programme scenarios, the incremental contribution of individual intervention scenarios (compared with the baseline) differed strongly between countries. In China, the additional impact of individual interventions on tuberculosis incidence and mortality was small for all scenarios (figure 3, appendix section 4). By contrast, for India, improving access to high-quality care substantially reduced tuberculosis incidence beyond baseline trends by a median of 20% (range 5–41%). In the same setting, activities solely aimed at further improving care for patients already accessing high-quality care made little difference to baseline trends. In South Africa, although we noted some between-model variation, most intervention scenarios showed substantial impact, with prevention (#6: continuous isoniazid preventive therapy for individuals receiving ART), case finding (#1: screening at primary-health clinics), and improvements in linkage to care and treatment success (#3) reducing tuberculosis incidence by a further median of 16% (range 8–51%), 20% (7–35%), and 8% (0–25%), respectively.

In South Africa, the 2025 End TB Strategy targets seem feasible, because the model projections showed that a combination of prevention, case finding, and improvements in care (figure 4) reduced incidence and mortality with a median of 55% (range 31–62%) and 75% (65–82%), respectively, and averted a cumulative 1·2 million (0·7 million–1·8 million) cases of tuberculosis and 298 000 (193 000–453 000) deaths from tuberculosis between 2015 and 2025. In China, median cases and
deaths averted by the combination intervention scenarios were 312 000 (range 420 000–764 000) cases of tuberculosis and 65 000 (10 000–93 000) deaths from tuberculosis. In India the corresponding figures were 3·1 million (1·2 million–5·8 million) cases of tuberculosis and 1·1 million (0·8 million–2·1 million) deaths from tuberculosis. Despite these projected substantial health gains, the proportional reductions between 2015 and 2025 were estimated to fall short of the post-2015 End TB Strategy targets for China and India (figure 4).

The impact of annual screening for active disease (#4 active-case finding in the general population) was small when compared with the effect of treating latent tuberculosis infection, particularly for China where #5 (active-case finding followed by treatment of latent tuberculosis infection) achieved a median of 64% (range 52–81%) reduction in tuberculosis incidence (figure 3), and the impact of the combined intervention exceeded the 2025 global targets.

Discussion

Using multiple, independently developed tuberculosis transmission models, we explored the feasibility of achieving the post-2015 End TB Strategy targets in three high-burden countries, each with different epidemiology and existing levels of tuberculosis control. By projecting the impact of combinations of existing tools in China, India, and South Africa, we showed the importance of country context in assessing whether and how these global targets might be achieved at a country level. For South Africa, the 2025 milestones of 50% reduction in incidence and 75% reduction in mortality appear feasible with existing tools, whereas for India and China, these targets appear unfeasible.

Contrasting results between countries reflect the differences between epidemiological context and responses of local tuberculosis epidemics. Whereas in China, two decades of steady improvement in reach and quality of basic tuberculosis services have led to nearly a two-thirds reduction in tuberculosis prevalence between 1990 and 2010,7 South Africa’s tuberculosis programme was overwhelmed by the effects of HIV,18 and is only just turning a corner.20 The room for further improvement with current tools differs widely between countries, which leaves high-performing tuberculosis programmes, such as the one in China, with the question of how to achieve additional reductions. India faces specific challenges around private providers of tuberculosis care, who are common throughout the southeast Asia region, and our results show that improving the quality of tuberculosis care in the private sector is essential. This process is underway, partly through an expansion of government subsidies to pay for individuals to access effective tuberculosis diagnosis and treatment through the private sector.20

The post-2015 End TB Strategy targets are laudable in their ambition, and describe what would be a great achievement in tuberculosis control, but our results show that the targets and the tools enlisted to achieve them will need adapting to provide countries with a path that is both ambitious but also feasible. Achievement of the targets at a global level will be challenging, because more modest contributions from one country will need to be compensated by other countries going beyond these already highly ambitious targets. Additionally, for countries where the standard package of interventions is likely to be insufficient, new strategies need to be developed that tackle country-specific drivers, such as the ageing population of individuals with tuberculosis in China21 and high levels of undernutrition in India.22,23

As they stand, the advocacy scenarios would involve community-based tuberculosis screening for substantial parts of the population, twice a year. With current tools, this raises substantial issues around feasibility, resources, and evidence for impact.24 Also, we did not quantify potential negative effects, including false-positive treatment, and regimen side-effects. However, the advocacy scenarios illustrate a key point of addressing the latent tuberculosis infection reservoir in the population, particularly for settings like China where current high levels of tuberculosis programme performance (and resulting relatively minor contribution of transmission to tuberculosis incidence25) means substantial gains can be made in this area. Tools are needed to reduce the volume (and associated costs) of screening for active disease and treatment of latent tuberculosis infection, such as a postexposure vaccine, or a screening test that detects individuals with latent tuberculosis infection who are likely to progress in the next 5–10 years,26 all of which are part of Pillar 3 of the End TB strategy.27

We collated the best available data from published reports and country experts, but emphasise that improved information about tuberculosis epidemiology and the current tuberculosis care pathways is still needed. For example, substantial uncertainty exists about tuberculosis incidence and mortality in India, prevalence of latent tuberculosis infection, and treatment volume provided in public and private sectors, which can affect model projections.28,29 The epidemiological effect of activities often relied on expert opinion in the absence of reliable data, which adds uncertainty to model projections. Further evidence about efficacy of interventions activities is needed to inform policy discussions at a global and national level.

In this project we aimed to examine the impact of major policy options in the tuberculosis response. As such, some specific interventions that might be considered for specific settings were not included such as addressing undernutrition in India and age-specific screening for latent tuberculosis infection in China, which have been explored in other models.19,20 Also, we did not include scenarios that focused on active case finding in high-risk groups, such as miners or people living in informal settlements. To
adequately capture these dynamics, and the impact of targeted interventions in these populations in a reasonable way, we believe that epidemiological models require specific model structure, and credible data on size and tuberculosis burden in each population, as well as a reasonable estimate of mixing within and between the general and high-risk populations. When more data become available, these choices can be revisited.

We did not report parametric uncertainty, or the relationship between model structure and predicted outcomes. These issues represent areas for future research. What is clear is that, as models aim to capture greater complexity, the structural and parametric uncertainty that can be expressed increases. One illustration is the more pronounced divergence in baseline model projections for South Africa where HIV is a key driver of the tuberculosis burden. Models that capture the interaction between tuberculosis and HIV and the effect of ART create additional opportunities for model differences and resulting divergence of baseline projections. However, since there is no one true model structure, multimodel exercises such as ours are important to identify findings robust to the structural uncertainty, as we have here.

Our study provides unique insights on the feasibility of these global epidemiological 2025 targets at the country level, and illustrates the challenges ahead. In further work, these epidemiological projections have been linked to costs to explore cost-effectiveness, affordability, and poverty alleviation. Such information is vital as policy makers and the global tuberculosis community assess the health gains and economic costs that would come with scaling up existing tools to meet the first targets of the End TB Strategy.

Contributors

RGW and RMGJH conceived the study and were responsible for the overall design. RMGJH, NAM, TS, GHH, NA, JG, DD, TC, JAS, JE, GBG, AV, and RGW contributed to the design of the study. RMGJH coordinated and analysed the results of the epidemiological model simulations and wrote the first draft of the report. RMGJH, TS, HHL, NP, SCS, ASA, NB, ASR, AH, GHH, BGW, STC, JMT, and NAM led the analysis of the epidemiological models. CHW, SM, SP, EB, DD, CCW, P ae, MAW, MWF, JTD, ESM, TC, JAS, CP, MI, and PH contributed to the development and analysis of the epidemiological models. DB, MH, SS, CD, LD, DC, LW, VKC, KR, DP, CS, AG, GC, YP, DM, and MK contributed information for the intervention scenarios. All authors approved the final version of the report for submission.

Declaration of interests

We declare no competing interests.

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