# Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models

*Nicolas A Menzies, Gabriela B Gomez, Fiammetta Bozzani, Susmita Chatterjee, Nicola Foster, Ines Garcia Baena, Yoko V Laurence, Sun Qiang, Andrew Siroka, Sedona Sweeney, Stéphane Verguet, Nimalan Arinaminpathy, Andrew S Azman, Eran Bendavid, Stewart T Chang, Ted Cohen, Justin T Denholm, David W Dowdy, Philip A Eckhoff, Jeremy D Goldhaber-Fiebert, Andreas Handel, Grace H Huynh, Marek Lalli, Hsien-Ho Lin, Sandip Mandal, Emma S McBryde, Surabhi Pandey, Joshua A Salomon, Sze-chuan Suen, Tom Sumner, James M Trauer, Bradley G Wagner, Christopher C Whalen, Chieh-Yin Wu, Delia Boccia, Vineet K Chadha, Salome Charalambous, Daniel P Chin, Gavin Churchyard, Colleen Daniels, Puneet Dewan, Lucica Ditiu, Jeffrey W Eaton, Alison D Grant, Piotr Hippner, Mehran Hosseini, David Mametja, Carel Pretorius, Yogan Pillay, Kiran Rade, Suvanand Sahu, Lixia Wang, Rein M G J Houben, Michael E Kimerling, Richard G White, Anna Vassall*

## Summary

**Background** **The post-2015 End TB Strategy sets global targets of reducing tuberculosis incidence by 50% and mortality by 75% by 2025. We aimed to assess resource requirements and cost-effectiveness of strategies to achieve these targets in China, India, and South Africa.**

**Methods** **We examined intervention scenarios developed in consultation with country stakeholders, which scaled up existing interventions to high but feasible coverage by 2025. Nine independent modelling groups collaborated to estimate policy outcomes, and we estimated the cost of each scenario by synthesising service use estimates, empirical cost data, and expert opinion on implementation strategies. We estimated health effects (ie, disability-adjusted life-years averted) and resource implications for 2016–35, including patient-incurred costs. To assess resource requirements and cost-effectiveness, we compared scenarios with a base case representing continued current practice.**

**Findings** **Incremental tuberculosis service costs differed by scenario and country, and in some cases they more than doubled existing funding needs. In general, expansion of tuberculosis services substantially reduced patient-incurred costs and, in India and China, produced net cost savings for most interventions under a societal perspective. In all three countries, expansion of access to care produced substantial health gains. Compared with current practice and conventional cost-effectiveness thresholds, most intervention approaches seemed highly cost-effective.**

**Interpretation** **Expansion of tuberculosis services seems cost-effective for high-burden countries and could generate substantial health and economic benefits for patients, although substantial new funding would be required. Further work to determine the optimal intervention mix for each country is necessary.**

**Funding** **Bill & Melinda Gates Foundation.**

**Copyright** **© The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license.**

*Lancet Glob Health* 2016

Published **Online** October 6, 2016 http://dx.doi.org/10.1016/S2214-109X(16)30265-0

See **Online/Comment** http://dx.doi.org/10.1016/S2214-109X(16)30268-6

See **Online/Articles** http://dx.doi.org/10.1016/S2214-109X(16)30199-1

**Department of Global Health and Population** (Prof N A Menzies PhD, S Verguet PhD, Prof J A Salomon PhD) **and Center for Health Decision Science** (Prof N A Menzies, Prof J A Salomon), **Harvard T H Chan School of Public Health, Boston, MA, USA; Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands** (G B Gomez PhD); **Department of Global Health, Academic Medical Center, University of Amsterdam, Netherlands** (G B Gomez); **Department of Global Health and Development** (G B Gomez, F Bozzani MSc, Y V Laurence MSc, S Sweeney MSc, A Vassall PhD), **TB Modelling Group, TB Centre** (M Lalli MSc, T Sumner PhD, R M G J Houben PhD, R G White PhD), **Faculty of Epidemiology and Public Health** (M Lalli, T Sumner, D Boccia PhD, R M G J Houben, R G White), **and Department of Clinical Research** (Prof G Churchyard PhD, Prof A D Grant PhD), **London School of Hygiene & Tropical Medicine, London, UK; Public Health Foundation of India, Delhi NCR, India** (S Chatterjee PhD, N Arinaminpathy DPhil, S Mandal PhD, S Pandey PhD); **Health Economics Unit,**

## Introduction

The World Health Assembly's post-2015 End TB Strategy formalises goals for aggressive action against tuberculosis, including reductions in global incidence by 50% and mortality by 75% by 2025.[1] To meet these targets, major advances are needed in high-burden countries. The TB Modelling and Analysis Consortium conducted a multimodel evaluation to assess the goals' feasibility,[2] finding that aggressive but feasible scale-up of existing approaches could achieve the reductions described by the global targets in South Africa but not in India or China.

If targets can be met, understanding whether doing so represents the best use of funding or is even affordable is crucial. Conversely, if targets cannot be met, expansion of tuberculosis services is not without value. Although the End TB Strategy provides an important consensus to invigorate the fight against tuberculosis and attract funding, Ministries of Health also need to consider local priorities and programmatic constraints. In this context, an understanding of the resources required for scale-up and a comparison of the performance of competing intervention approaches are crucial.

In this analysis, we aimed to describe the costs and health outcomes of aggressive intervention against tuberculosis, and to assess cost-effectiveness, financial implications, and patient economic burden of these interventions. Although previous studies[3–5] have assessed the cost-effectiveness of various interventions in high-burden settings, few have compared multiple interventions simultaneously and assessed affordability. Quantification of the effect of these interventions on patient-incurred costs is also important, in view of the high disease burden in low-resource settings[6,7] and the

School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa (N Foster MPH); Monitoring and Evaluation Unit (I G Baena MSc), Global TB Programme (A Siroka PhD), `, Geneva, Switzerland; School of Health Care Management and Key Laboratory of Health Economics and Policy Research of Ministry of Health, Shandong University, Jinan, China (Prof S Qiang PhD); Department of Infectious Disease Epidemiology, Imperial College London, London, UK (N Arinaminpathy, J W Eaton PhD); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (A S Azman PhD, D W Dowdy MD); Department of Medicine (E Bendavid MD), Department of Management Science and Engineering (S-c Suen MS), and Stanford Health Policy, Centers for Health Policy and Primary Care and Outcomes Research (J D Goldhaber-Fiebert PhD), Stanford University, Stanford, CA, USA; Institute for Disease Modeling, Seattle, WA, USA (S T Chang PhD, P A Eckhoff PhD, G H Huynh PhD, B G Wagner PhD); Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA (Prof T Cohen DPH); Victorian Tuberculosis Program at the Peter Doherty Institute, Melbourne, VIC, Australia (J T Denholm PhD, E S McBryde PhD, J M Trauer MBBS); Department of Microbiology and Immunology, University of Melbourne, Melbourne, VIC, Australia (J T Denholm, E S McBryde, J M Trauer); Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA, USA (A Handel PhD, Prof C C Whalen MD); Synthetic Neurobiology Group, Media Lab, Massachusetts Institute of Technology, Cambridge, MA, USA (G H Huynh); Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan (H-H Lin ScD, C-Y Wu MS); Burnet Institute, Melbourne, VIC, Australia (E S McBryde, J M Trauer); Epidemiology and Research Division,

## Research in context

### Evidence before this study

The World Health Assembly's post-2015 End TB Strategy proposes aggressive action to reduce tuberculosis incidence and mortality worldwide. Major reductions in high-burden countries will be essential for achieving these targets. Before this study, little quantitative evidence existed on the feasibility of efforts to reach these targets in high-burden settings and on the cost of implementing aggressive service expansion. We reviewed published work (English-language articles identified on PubMed, supplemented by the authors' familiarity of the relevant literature) on the cost-effectiveness of tuberculosis interventions relevant to China, India, and South Africa. Most studies addressed only one intervention area, and few investigated issues of affordability. Although the economic burden of tuberculosis on individuals and households is known to be high, few studies have estimated patient-incurred costs as part of cost-effectiveness analysis. None of the studies reviewed were designed to address the issues raised by the global End TB Strategy targets. Collaborative analysis with multiple models to assess intervention cost-effectiveness has previously been done for HIV policy changes but not for tuberculosis policy.

### Added value of this study

In this study, we found that substantial improvements in the reach and quality of tuberculosis care might be cost-effective according to conventional criteria, despite requiring substantially increased funding compared with current practice. By estimating patient-incurred costs at the same time as health service costs, we were able to understand the relative magnitude of these effects—for some interventions, patient cost savings are larger than the additional costs borne by health services, leading to net cost savings under a societal perspective. By comparing multiple intervention approaches, our findings reveal the relative efficiency of each approach in the generation of health benefits. From these comparisons, efforts to improve access to care seemed the most beneficial and cost-effective in each setting. Our findings also show substantial variation in results predicted by different models, pointing to important uncertainties in the evidence base for predicting long-term costs and health outcomes.

### Implications of all the available evidence

Combined with evidence from previous cost-effectiveness studies, the results of our analysis lend support to efforts to scale up tuberculosis services, motivated by the End TB targets. Our findings also reveal wide differences in the effect and efficiency of different approaches, implying that countries will need to carefully consider the approaches taken to service expansion. The variation in results also shows a clear need for further empirical research to strengthen the evidence base used for tuberculosis policy modelling, and thereby improve the reliability of future analyses.

growing policy interest in catastrophic health-care spending,[7,8] a concern addressed explicitly in the End TB Strategy.[1]

## Methods

### Overview

In collaboration with national tuberculosis programme representatives for each country, we defined scenarios for scaling-up existing interventions to high yet feasible coverage by 2025. We projected long-term outcomes using multiple independently developed models of tuberculosis epidemiology and health services, and estimated costs by synthesising model outputs with empirical cost data and expert opinion on implementation approaches. We estimated health effects (disability-adjusted life-years [DALYs] averted) and resource implications for the 20 year period (2016–35), and calculated costs from multiple perspectives. For each country we compared intervention scenarios with a base case in which present intervention coverage is maintained.

### Countries

We undertook this study for China, India, and South Africa because of their substantial tuberculosis burden and their contrasting HIV and tuberculosis epidemiology and organisation of tuberculosis services. In China, tuberculosis incidence is 68 cases per 100 000 population and mortality is three per 100 000 population[8] (equivalent to 3% of global tuberculosis mortality), and the country has achieved progressive reductions in tuberculosis burden in the past three decades.[9] In India, tuberculosis incidence is 167 per 100 000 population and mortality is 19 per 100 000 population (accounting for 17% of global tuberculosis mortality), and a large private sector provides roughly half of all tuberculosis care.[10] In South Africa, tuberculosis incidence is 834 per 100 000 population and mortality is 178 per 100 000 population (equivalent to 6% of global tuberculosis mortality), with both incidence and case fatality driven by the HIV epidemic.

### Intervention scenarios

With input from national tuberculosis programme representatives for each country, we defined scenarios describing scale-up of specific interventions to high coverage by 2025 (table 1), making use of currently available intervention options and considering local policy preferences and capacity. Although intervention areas were defined in advance, country experts determined whether additional scale-up of an intervention was appropriate for their country, and the anticipated scale and pace of coverage improvements. Scenario descriptions included the activities required to produce coverage changes: for example, in South Africa,

| | Activities | Timing and programme effects* | Mechanism of action for health effects |
|---|---|---|---|
| **China** | | | |
| Expand access to care | Local Centers for Disease Control and Prevention offices reimburse patients' expenses and encourage tuberculosis care in designated hospitals | Population without access to tuberculosis care reduces from 5% to 3·75% by 2025. Population accessing high-quality care increases from 80% to 95% by 2025 | Reduced duration of infectiousness and mortality risks through improved case detection |
| Introduce Xpert MTB/RIF for diagnosis | Xpert replaces smear for routine diagnosis of new and retreatment cases | Xpert MTB-RIF coverage increases from 0% to 100% by 2022 | Minor improvement in diagnosis and improvement in detection of drug-resistant cases |
| Improve treatment quality | Improve referral systems and sample transport; reimburse patient expenses; enhance mobile health, case management, and adherence support; improve management of side-effects of MDR tuberculosis treatment | Initial default decreases from 3% to 1·5% by 2025 for drug-sensitive infections, and from 50% to 15% by 2025 for drug-resistant infections. Treatment success increases from 82% to 90% by 2025 for drug-sensitive infections, and from 35% to 65% by 2025 for drug-resistant infections | Reduced initial default, and improved retention and cure rates for both drug-sensitive and drug-resistant cases |
| Combination | All of the above | All of the above | All of the above |
| **India** | | | |
| Expand access to care | Pay subsidies for tuberculosis care in the private sector and increase microscopy access in the public sector | Population without access to tuberculosis care decreases from 9·5% to 4·8% by 2022. Population accessing high-quality care increases from 50% to 90% by 2022 | Reduced duration of infectiousness and mortality risks through improved case detection |
| Active case finding in the general population† | Mobile screening units with symptom screen, x-ray, or Xpert algorithms | Achieve population coverage of 1·6% for annual screening from 2015 to 2020 | Reduced duration of infectiousness and mortality risks through improved case detection |
| Introduce Xpert MTB/RIF for diagnosis | Xpert replaces smear in routine diagnostic algorithm in the public sector | Xpert MTB-RIF coverage increases from 0% to 30% by 2019 | Improvements in tuberculosis diagnosis and detection of drug-resistant cases |
| Improve treatment quality | Improve private sector quality through provider training, supervision, regulation, and subsidies; provide patient retention incentives, nutritional support, and link to social welfare programmes | Initial default decreases from 10% to 5% by 2015 for drug-sensitive infections, and from 11% to 5% by 2020 for drug-resistant infections. Treatment success increases from 75% to 85% by 2022 for drug-sensitive infections, and from 48% to 67% by 2022 for drug-resistant infections | Reduced initial default, improved retention and cure rates for both drug-sensitive and drug-resistant cases |
| Combination | All of the above | All of the above | All of the above |
| **South Africa** | | | |
| Screening and IPT for individuals receiving ART | Screen current and new HIV-positive patients receiving ART and provide continuous IPT for all these patients without active tuberculosis | ART population on IPT increases from 5% to 80% by 2021 | Treatment of active tuberculosis detected through screening and reduced progression to active tuberculosis for individuals on IPT |
| Expand access to care | Provide outreach clinics to underserved areas and symptom screening in primary care | Population without access to tuberculosis care decreases from 5% to 0% by 2021 | Reduced duration of infectiousness and mortality risks through improved case detection |
| Improve treatment quality | Provide mobile health and patient follow-up in community, adherence counselling, and improved staffing for MDR tuberculosis | Initial default decreases from 17% to 5% by 2021 for drug-sensitive infections, and from 30% to 15% by 2021 for drug-resistant infections. Treatment success increases from 76% to 85% by 2021 for drug-sensitive infections, and from 52% to 67% by 2025 for drug-resistant infections | Reduced initial default and improved retention and cure rates for both drug-sensitive and drug-resistant cases |
| Combination | All of the above | All of the above | All of the above |

MDR=multidrug-resistant. IPT=isoniazid preventive therapy. ART=antiretroviral therapy. *Represents summary outcomes across public and private sectors. †Active case finding in specific risk groups was not considered because of modelling limitations.

***Table 1*: Intervention scenarios for China, India, and South Africa**

improving access to tuberculosis diagnosis could be achieved through outreach to underserved areas and symptom screening for individuals attending primary care. Specification of activities helped to define the feasible extent of scale-up, and allowed the costs of each scenario to be estimated (see appendix p 3 for a description of the disease course, treatment, and final outcomes).

We assessed interventions separately and also considered a scenario representing the combination of all interventions for each country. A base case scenario represented continuation of current practice, with service coverage held at existing levels. Services not specifically addressed in a scenario were held at current coverage levels, with two exceptions: for South Africa, we assumed that antiretroviral therapy (ART) coverage would increase to 77% by 2025; and for India, we assumed all retreatment tuberculosis cases would receive drug susceptibility testing by 2019. Both policies have high-level commitment in their respective countries.

## Modelling approach

We projected policy outcomes using multiple independently developed *Mycobacterium tuberculosis* transmission models.[3,11–19] Models had to represent the major mechanisms determining tuberculosis outcomes in each setting, be consistent with existing evidence on epidemiology and service provision, and simulate outcomes needed to estimate summary health and economic effects. Of 11 models in the modelling exercise, nine fulfilled these requirements and contributed inputs for the economic analysis (table 2; appendix pp 4–7), and additional details are provided by Houben and colleagues.[2]

**National Tuberculosis Institute, Bangalore, India** (V K Chadha MD); **Aurum Institute, Johannesburg, South Africa** (S Charalambous PhD, Prof G Churchyard, P Hippner MSc); **Bill &Melinda Gates Foundation, Seattle, WA, USA** (D P Chin MD); **School of Public Health, University of Witwatersrand, Johannesburg, South Africa** (Prof G Churchyard, Prof A D Grant); **Stop TB Partnership, Geneva, Switzerland** (C Daniels MA, L Ditiu MD, S Sahu MD); **Bill & Melinda Gates Foundation, New Delhi, India** (P Dewan MD);

**Africa Centre for Population Health, School of Nursing & Public Health, University of KwaZulu-Natal, Durban, South Africa** (Prof A D Grant); **Strategic Information Department, The Global Fund, Geneva, Switzerland** (M Hosseini MD); **National Department of Health, Pretoria, South Africa** (D Mametja MPH, Y Pillay PhD); **Avenir Health, Glastonbury, CT, USA** (C Pretorius PhD); **World Health Organization Country Office for India, New Delhi, India** (K Rade MD); **National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China** (L Wang MS); **and KNCV Tuberculosis Foundation, The Hague, Netherlands** (M E Kimerling MD)

Correspondence to: Prof Nicolas A Menzies, Department of Global Health and Population, Harvard T H Chan School of Public Health, Boston, MA 02115, USA
**nmenzies@hsph.harvard.edu**

See Online for appendix

## Cost estimation

Models produced standardised outputs describing service use under each scenario, and outputs to estimate the economic burden of tuberculosis on patients and households. We also did a systematic review[20] to collate and synthesise unit costs for each country. Empirical tuberculosis cost data are limited;[20] where local values were unavailable we adapted estimates from other settings using local prices, holding country consultations to ensure face validity. We developed country-specific cost models to combine service use estimates with unit costs. We divided cost categories into diagnosis (ie, active or passive screening, tuberculosis diagnosis, and drug resistance testing), first-line treatment for active disease, multidrug-resistant (MDR) tuberculosis treatment, treatment of latent infection for HIV-positive individuals (ie, isoniazid preventive therapy; South Africa only), and programme overheads (ie, high-level overheads supporting service delivery). We estimated direct intervention costs and changes in the costs of core services (eg, passive detection and treatment) indirectly affected by policy change. To estimate programme overheads, we examined past programme expenditures and consulted with WHO and country experts. Patient-incurred costs were calculated as the sum of direct medical costs (ie, fees paid to providers to receive care [eg, consultation fees] and to purchase drugs), direct non-medical costs (ie, expenses incurred to receive care, such as travel costs, excluding fees paid to providers), and indirect productivity costs (ie, income loss due to tuberculosis symptoms or treatment, and opportunity cost of productive activity forgone due to untreated active disease or time taken to receive treatment). Several intervention strategies used reimbursements or incentives paid for attending care to offset patient-incurred costs. Additional details on the costing approach and input values are shown in the appendix pp 17–31.

We report economic costs from several perspectives: a tuberculosis service perspective, representing costs borne by national tuberculosis programmes and associated service providers; a health service perspective, summing tuberculosis service costs (for South Africa, costs or cost savings associated with ART were also taken into account); and a patient perspective, including costs or cost savings realised by individuals with active tuberculosis or receiving tuberculosis care; as well as a societal perspective combining patient and health service costs. We did sensitivity analyses for unit costs and programme overheads.

## Summary health outcomes

We measured health benefits using DALYs. Models produced standardised outputs for calculating DALYs averted compared with the base case. Outputs included deaths by age and year, and the yearly population distribution across tuberculosis-related and HIV-related health states (appendix pp 8–10). Disability weights (appendix p 11) were derived from a multicountry valuation study,[21] and remaining life expectancy (appendix p 12) from country-specific life tables[22] (values not truncated at the analytic horizon).

## Scenario comparisons

In all scenarios, the assumptions were that interventions would reach peak coverage before 2025 and that they would be extended to 2035 maintaining 2025 coverage levels. This 20 year evaluation period balanced conflicting concerns: that longer-term projections would be increasingly unreliable, but that a short evaluation period

| | Institutions | Model type | Model calibration | Age structure | Population strata | Countries |
|---|---|---|---|---|---|---|
| AuTuMN | Australian Institute of Tropical Health & Medicine, University of Melbourne, Monash University, Burnet Institute | D | Algorithmic | <15 and 15+ years | MDR/non-MDR tuberculosis, tuberculosis care access. For South Africa: HIV/ART/CD4 status | China, India, South Africa |
| Harvard | Harvard University, Yale University | D | Bayesian | 15+ years | HIV/ART/CD4 status, multiple tuberculosis strains, tuberculosis treatment history, tuberculosis care access | China, India, South Africa |
| Hopkins | Johns Hopkins University | D | Manual | 15+ years | HIV/ART/CD4 status, MDR/non-MDR tuberculosis | South Africa |
| ICPHFI | Public Health Foundation of India, Imperial College London | D | Algorithmic | 15+ years | MDR/non-MDR tuberculosis, tuberculosis treatment history | India |
| IDM | Institute for Disease Modeling | I | Bayesian | By month of age, 0–100 years | MDR/non-MDR tuberculosis, provider and tuberculosis treatment history | China |
| NTU | National Taiwan University | D | Manual | 15+ years | MDR/non-MDR tuberculosis, health-care system, tuberculosis treatment history | China |
| STAMP | Stanford University | I | Grid Search | By month of age, 0–100 years | MDR/non-MDR tuberculosis, sex, tuberculosis treatment history and treatment type, time since infection and progression | India |
| TIME | London School of Hygiene & Tropical Medicine | D | Manual | <15 and 15+ years | HIV/ART/CD4 status, MDR/non-MDR tuberculosis, tuberculosis treatment history | China, India, South Africa |
| UGA | University of Georgia | D | Manual | <15 and 15+ years | HIV/ART status, MDR/non-MDR tuberculosis | South Africa |

D=deterministic compartmental model. I=individual-based, stochastic microsimulation. MDR=multidrug-resistant. ART=antiretroviral therapy. CD4=CD4 cell count.

*Table 2*: **Characteristics of participating models**

would exclude important policy consequences, as health benefits are lagged relative to implementation costs.

We summed costs and DALYs over the 20 year period (2016–35). For cost-effectiveness analyses, we discounted these outcomes at 3% per year. Costs represent 2014 US$ (equal to 6·1 Chinese Yuan, 60·9 Indian Rupees, and 10·8 South African Rand). Model results are presented individually and averaged across models. Cost-effectiveness ratios were calculated as mean incremental cost divided by mean incremental health benefits for each scenario, as compared with base case. To describe affordability, we compared annual undiscounted costs for each scenario, averaged across models with equal weights. As we estimated economic costs, annual results are a smoothed version of actual financial needs.

### Role of the funding source

DPC and PD are employees of the Bill & Melinda Gates Foundation, which funded the study. These authors were acting as subject matter experts rather than agency representatives, and did not have veto power over any study decision. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

## Results

The models for China and South Africa had fairly consistent results in terms of incremental costs (figure 1). In China, introduction of Xpert MTB/RIF seemed more expensive than expansion of access to care and improvement of treatment quality, because of high diagnostics costs and increased volume for MDR tuberculosis treatment. In South Africa, expansion of access to care had higher costs than other single-intervention scenarios, because of the high costs of expanding screening in primary care. Results for India showed clear differences between models. In particular, the results for expansion of access to care differed, with some models predicting cost savings over the 20 year period. This diversity of results points to the uncertain consequences of private sector intervention—central to several scenarios modelled for India—and different assumptions about the effect of shifting patients from low-quality care to high-quality care.

For incremental patient-incurred costs, most intervention scenarios showed cost savings compared with the base case (figure 2). These cost savings resulted from reduced disease burden and from the inclusion of social protection or incentives paid for attending care, or both, in many intervention scenarios. By contrast, incremental patient-incurred costs were positive for the scenario of introducing Xpert in China, because of improved diagnosis of MDR tuberculosis and high costs that patients incur at present to receive second-line treatment. For India and South Africa, expansion of access to care generated the greatest patient cost savings among the single-intervention scenarios.

Figure 3 presents incremental costs, health benefits (ie, DALYs averted), and cost-effectiveness ratios from both health service and societal perspectives for each intervention scenario compared with the base case (see appendix pp 13–15 for results of individual models). Results for South Africa included any costs or cost savings from changes in ART service volume. Exclusion of these costs reduced cost-effectiveness ratios by 10–20% (appendix p 16). In China, Xpert introduction averted fewer DALYs at higher cost than expansion of access to care and improvement in treatment, the results for which largely overlap. This finding might be related to the relatively minor increase in sensitivity of the Xpert algorithm over current practice and the low success rates for MDR tuberculosis treatment at present, both of which were features of the modelled scenarios. In India, expansion of access to care seemed the most attractive among the single-intervention strategies. On average, the scenario of improving treatment averted more DALYs at lower cost than Xpert introduction or active case finding, although results for this strategy vary widely. Active case finding in the general population generated minimal health benefits and comparatively high costs per DALY averted. In South Africa, tuberculosis services are predominantly publicly provided, and thus patient-incurred costs are lower relative to health service costs. Consequently, cost-effectiveness ratios differed little between health service and societal perspectives. Cost-effectiveness ratios were similar across scenarios, although the magnitude of effects was substantially greater for expansion of access to care than for other single-intervention scenarios.

Figure 4 presents average annual tuberculosis service costs for each scenario, showing the budgetary implications of aggressive scale-up. In all three countries, the combination scenario required substantially increased funding. In China and South Africa, resource requirements peaked at about three times existing tuberculosis service costs. In China and India, cost increases were projected to decline over time, whereas for South Africa high spending levels were expected to persist, which is attributable to high ongoing costs of expanding access to care.

Major sources of uncertainty relating to costs that affected our results included, for China, additional programme investments needed to support scale-up, costs of Xpert introduction, and costs of providing second-line treatment. For India, the cost of implementing public–private partnerships to expand access was the major source of uncertainty, followed by uncertainty around programme costs and Xpert introduction costs. For South Africa, the costs of implementing mobile health services to increase access was the major source of uncertainty, followed by the costs of implementing symptom screening in primary care. Full results of the sensitivity analysis are given in appendix pp 31–33.


***Figure 1:*** **Incremental tuberculosis service costs for 2016–35 for each intervention scenario, compared with the base case, by country and model**
Costs below $0 represent cost savings compared with the base case. Intervention scenarios for each country are described in table 1, and details of each model are provided in table 2 and by Houben and colleagues.[2] IPT=isoniazid preventive therapy. MDR=multidrug-resistant. *Sum of all cost categories.

## Discussion

The post-2015 End TB Strategy aims to reinvigorate action on tuberculosis control and achieve substantial and rapid reductions in incidence and mortality. In this study, we assessed the costs and cost-effectiveness of aggressive expansion of tuberculosis services with existing technology and interventions. Compared with current practice, all intervention scenarios in India and South Africa—and all but the scenario of Xpert introduction in China—had a cost per DALY averted that fell below the country's gross domestic product (GDP) per person, even before patient cost savings were considered. GDP per person is a conventional threshold for identifying highly cost-effective interventions,[23,24] yet many potential public health interventions meet this criterion.[25] Recent work has highlighted that this threshold might not adequately reflect

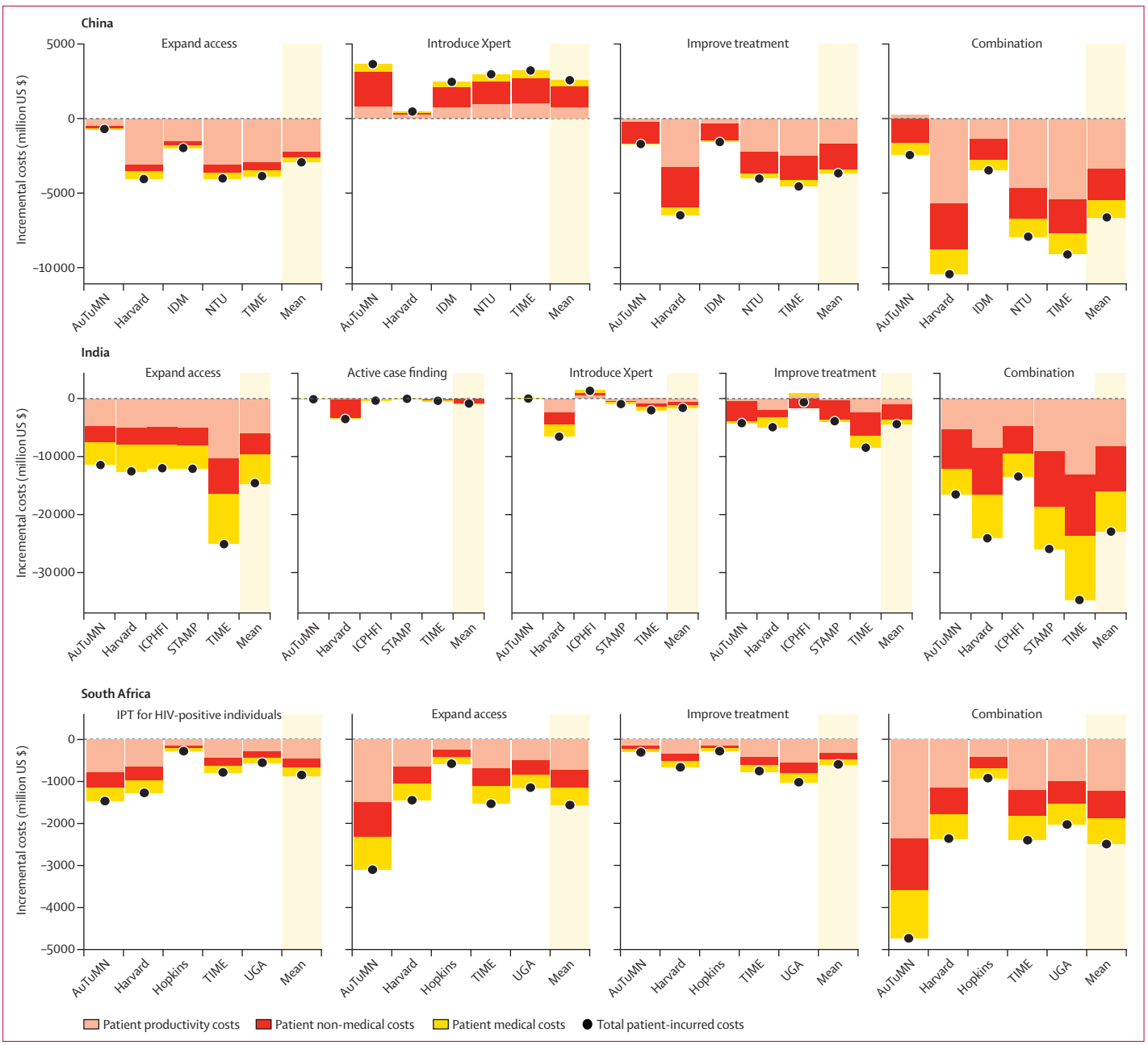


***Figure 2:*** **Incremental patient-incurred costs for 2016–35, for each intervention scenario, compared with the base case, by country and model**
Costs below $0 represent cost savings compared with the base case. Intervention scenarios for each country are described in table 1, and details of each model are provided in table 2 and by Houben and colleagues.[2] IPT=isoniazid preventive therapy.

opportunity costs in many settings.[26] However, in view of the very low costs per DALY averted for many interventions and the substantial reductions in economic burden for patients, the results suggest that some form of expansion of tuberculosis services is likely to be cost-effective for each country, and this finding is robust because it is supported by the results of every participating model.

Involvement of experts from each country was crucial for the development of realistic policy scenarios. The process of developing these scenarios revealed the importance of local epidemiology and care patterns in determining the relevant interventions for a particular setting, such that important interventions for one country (eg, private sector intervention in India and isoniazid preventive therapy for HIV-positive individuals in South Africa) were thought irrelevant or to have minimal benefit for the other countries. Therefore, the activities suggested for each scenario differed between

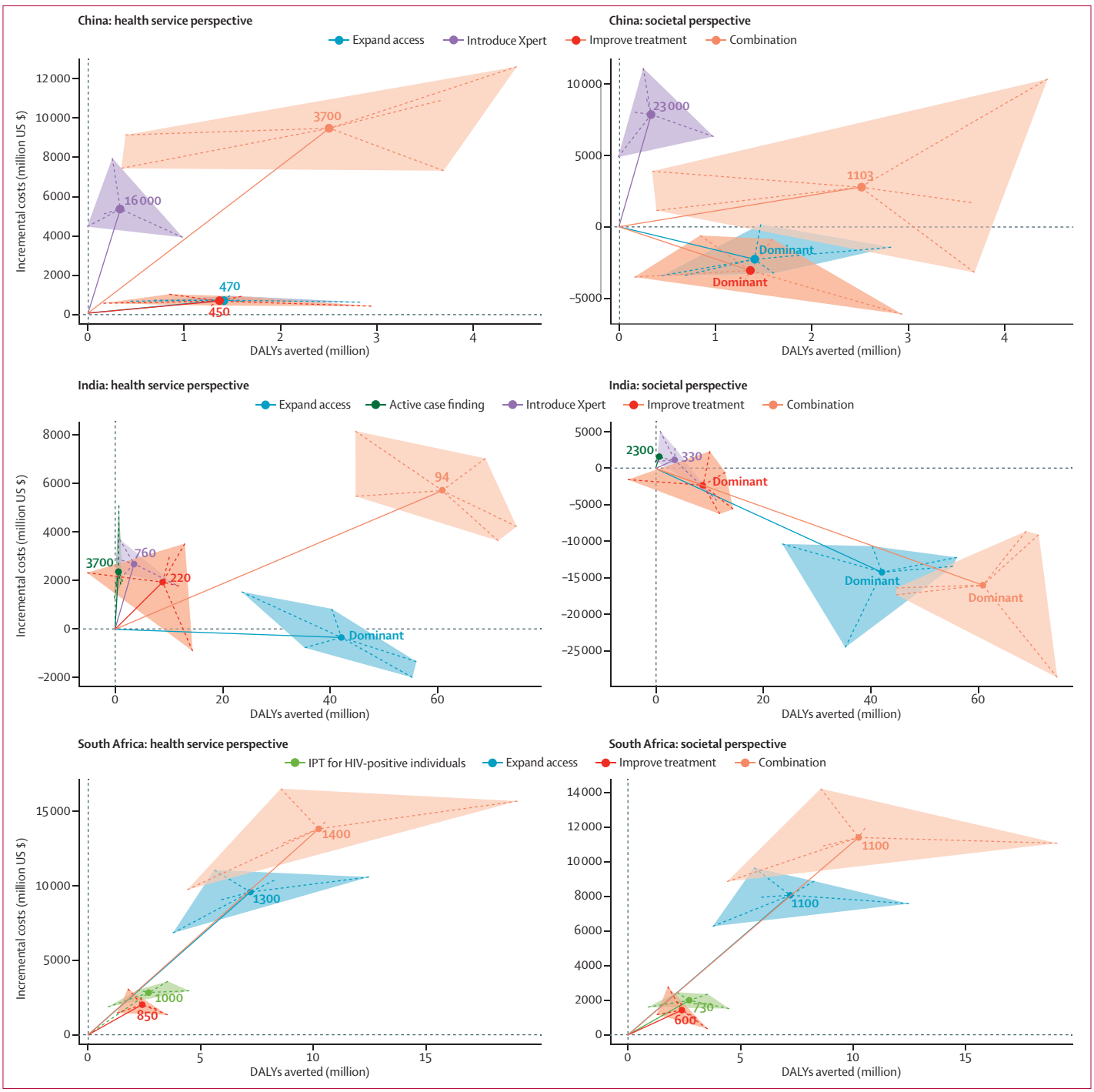


***Figure 3:*** **Cost-effectiveness ratios of intervention scenarios compared with base case**
Costs and DALYs were summed over the period 2016–35, discounted at 3% per year. Values and bold lines connected to the origin represent cost-effectiveness ratios calculated from costs and health benefits averaged across models. Dominant scenarios represent improved health and reduced costs compared with the base case. Dashed lines connect individual model results to the overall average. Shaded areas represent the region spanned by the set of model results for each intervention scenario, and reflect the relative heterogeneity of findings for a particular scenario. Intervention scenarios for each country are described in table 1. DALYs=disability-adjusted life-years. IPT=isoniazid preventive therapy.

countries. Despite this heterogeneity, a consistent finding across countries was the importance of expanding access to care, thereby reducing the duration of infectiousness and mortality risks for individuals with active infection. The combination scenario produced the largest average reduction in DALYs in each country,

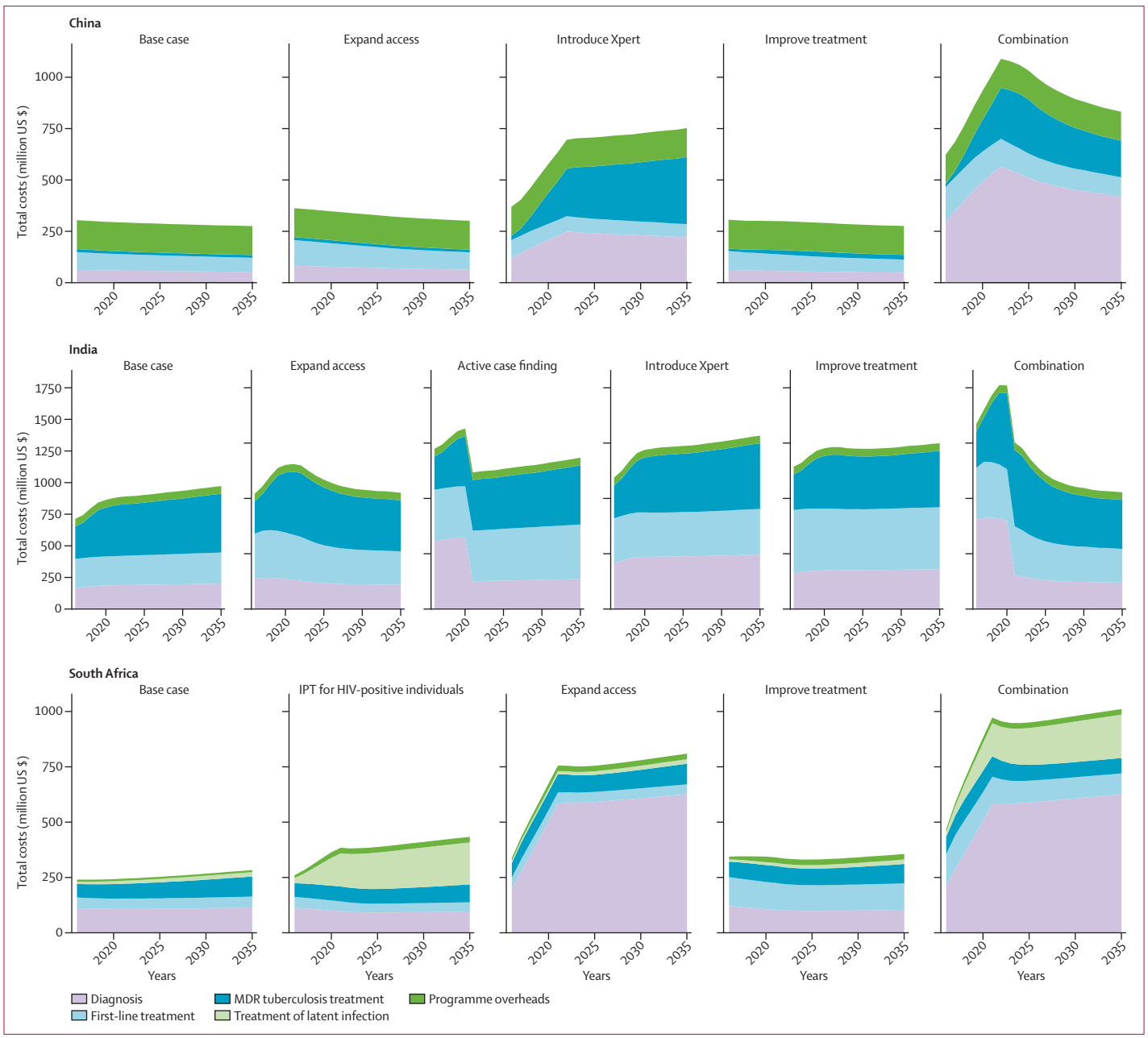


***Figure 4:*** **Time trends in annual tuberculosis service costs estimated for each scenario, 2016–35**
Shaded regions represent annual cost of each cost component averaged across models. Costs were estimated at 2014 price levels and not discounted. Intervention scenarios for each country are described in table 1. IPT=isoniazid preventive therapy. MDR=multidrug-resistant.

followed by expansion of access to care, although with a higher cost per DALY averted than other interventions in South Africa. In India and South Africa, expanding access to care had a substantially greater effect than improving treatment, whereas in China this difference was only marginal, reflecting China's past success in improving case detection.

For both India and China, Xpert introduction had a smaller health effect and higher costs than improving treatment or expanding access, despite Xpert producing major improvements in the detection of MDR tuberculosis. This finding is related to low treatment quality for MDR tuberculosis in these two countries at present, characterised by poor retention and cure rates, and by high treatment costs. If the major consequence of Xpert introduction is to expand access to MDR tuberculosis treatment (as assumed in this study), then cost-effectiveness ratios are likely to

remain high while the treatment costs of MDR tuberculosis remain high.

Despite our broadly positive cost-effectiveness findings, our results raise concerns regarding affordability. In all three countries, the annual tuberculosis service costs of the combination intervention were more than double the base case levels and remained elevated throughout the 20 year projection (figure 4). For India and South Africa, the average annual increase in spending required in the first 5 years of the combination scenario (compared with the base case) represented 3–4% of present government health sector funding, compared with only 0·15% in China. Only in India was the effect on tuberculosis burden sufficient to return the budget to the same level as the base case after 20 years. Although human resource needs and other health system constraints were not modelled explicitly, they might also present major challenges to scale-up.

Although affordability and health system constraints remain a challenge, a key finding of this study is that, across all three countries, more aggressive tuberculosis policy would substantially reduce the economic burden of tuberculosis on patients and their families. These results reflect reductions in direct costs and reductions in income loss from early identification and effective treatment and prevention. For India and China, several interventions directly targeted the costs borne by patients, using such reimbursements and monetary incentives to the patient to improve patient adherence to effective diagnosis and treatment. Factoring the effects on patient-incurred costs into the cost-effectiveness ratio will substantially strengthen the investment case for expanding tuberculosis services, with both expansion of access to care and improvement in treatment producing net savings in societal costs in the evaluation period.

Despite this study's strengths and breadth, care should be taken in drawing conclusions about the cost-effectiveness of any one intervention approach. Although we investigated a range of interventions, because of the complexity of using multiple models we considered only a restricted set of options. In reality, each intervention could be implemented at different scale and in various combinations with one another, and other interventions might also be considered. By comparing our set of intervention scenarios with the base case, we provide an initial scoping of the effects that might be achieved with each approach and highlight broad priority areas. However, ideally a full set of mutually exclusive strategies would be compared simultaneously, to identify the optimal set of services for a given budget or cost-effectiveness threshold. A consequence of our more limited approach is that even though the combination scenario seemed cost-effective compared with current practice, it is possible that another combination—potentially involving a subset of interventions or components of the intervention scenarios, more or less aggressive scale-up, or interventions not be considered in this analysis—might be optimal.

To our knowledge, we are the first to use multiple independently developed models to assess the cost-effectiveness and affordability of tuberculosis intervention options. An important benefit of this approach was the opportunity to compare model results and in so doing understand the variation in predictions across models. Research in HIV has highlighted the variation in results possible when modelling complex disease and health system dynamics,[25,27] and by using multiple models we were able to identify major uncertainties that would remain undetected by single-model analyses. We found substantial variation in the net health and economic consequences predicted for several intervention scenarios, and in the rankings of interventions implied by these results. Since we applied a standard cost model, this variation is primarily due to uncertainty in the processes of tuberculosis epidemiology and interventions in high-burden settings—realised as differences in model structure and parameterisation—as well as uncertainty about how specific programme actions will affect tuberculosis epidemiology and outcomes.[28] For costs, we had few empirical data for several interventions, and for the programme costs of supporting scaled-up service provision and addressing health system constraints and increasing use. Our results are sensitive to these uncertainties. Because of the complexity of using multiple models, we were unable to systematically investigate uncertainty in individual epidemiological parameters, yet these uncertainties are also likely to be consequential. These uncertainties are related to the nature of the scenarios we examined, which were designed to extend the reach and quality of services far above current levels. Although the use of multiple models provides some indication of the uncertainty, these projections will not include unanticipated (and therefore unmodelled) factors that will limit the health effect of interventions or increase the costs. The major coverage expansions described by the intervention scenarios are unprecedented for tuberculosis control, and the possibility of unanticipated challenges might be higher than those for more conventional policy options.

In this study, we examined the cost-effectiveness of a set of tuberculosis interventions using multiple models, bringing together a community of country experts, modellers, and economists. In view of the limitations described previously, this study is a crucial first step in supporting resource allocation to and within tuberculosis control programmes. We found that a wide range of context-sensitive interventions are likely to be cost-effective and alleviate financial burden, but at substantial cost. Further work is needed to inform tuberculosis policy. In the future, policy decisions will ideally involve country-led planning processes—exemplified by South Africa's investment case analysis in 2016—which can more fully examine the range of candidate policies and attendant implementation challenges, validate modelling assumptions, and evaluate budget needs against options for increasing funding.

### Contributors

NAM, GBG, and AV designed the study. FB, SChat, NF, IGB, YVL, SQ, AS, SSw, SV, and JAS helped to design the economic analysis. RGW and RMGJH led the epidemiological analysis, and DB, JWE, and CP provided input on the study approach. VKC, SChar, DPC, GC, CD, PD, LD, ADG, PH, MH, DM, YP, KR, SSa, LW, and MEK provided country and policy inputs. NAM, NA, ASA, EB, STC, TC, JTD, DWD, PAE, JDG-F, AH, GHH, ML, H-HL, SM, ESM, SP, JAS, S-cS, TS, JMT, BGW, CCW, C-YW, and RMGJH did the epidemiological modelling. GBG and AV did the economic analysis. NAM prepared the first draft of the report. All authors edited the report and approved the final version.

### Declaration of interests

We declare no competing interests.

### Acknowledgments

NAM received funding from the US National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH; grant 7R01AI112438-02). RMGJH and RGW are funded by the Bill & Melinda Gates Foundation (TB Modelling and Analysis Consortium OPP1084276 and SA Modelling for Policy OPP1110334). RGW is funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC–DFID Concordat agreement that is also part of the European & Developing Countries Clinical Trials Partnership 2 (EDCTP2) programme supported by the European Union (MR/J005088/1), and by UNITAID (4214-LSHTM-Sept15; PO #8477-0-600). SSw was supported by the US National Science Foundation Graduate Research Fellowship under grant DGE-114747. JDG-F was partly supported by an NIH National Institute on Aging Career Development Award (K01 AG037593-01A1), by Stanford University's Freeman Spogli Institute for International Studies and its Global Underdevelopment Action Fund, and by the Bill & Melinda Gates Foundation. GHH, BGW, STC, and PAE thank Bill and Melinda Gates for their active support of this work and their sponsorship for the Institute for Disease Modeling through the Global Good Fund. H-HL was funded by the Bill & Melinda Gates Foundation for this work. AH and CCW were partly supported by a grant from the US National Institutes of Allergy and Infectious Diseases, NIH (AI093856). JMT received funding for doctoral studies in tuberculosis from the Australian National Health and Medical Research Council. ESM received a career development fellowship from the Australian National Health and Medical Research Council. YVL is a Commonwealth Scholar funded by the UK Government.

### References

1 World Health Assembly. Post-2015 global TB strategy and targets (A67/62). Geneva: World Health Assembly, 2014.

2 Houben RMGJ, Menzies NA, Sumner T, et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *Lancet Glob Health* 2016; published online Oct 6. http://dx.doi.org/10.1016/S2214-109X(16)30199-1.

3 Suen SC, Bendavid E, Goldhaber-Fiebert JD. Cost-effectiveness of improvements in diagnosis and treatment accessibility for tuberculosis control in India. *Int J Tuberc Lung Dis* 2015; **19:** 1115–24.

4 Wang WB, Zhang H, Petzold M, Zhao Q, Xu B, Zhao GM. Cost-effectiveness of the Health X Project for tuberculosis control in China. *Int J Tuberc Lung Dis* 2014; **18:** 939–45.

5 Knight GM, Gomez GB, Dodd PJ, et al. The impact and cost-effectiveness of a four-month regimen for first-line treatment of active tuberculosis in South Africa. *PLoS One* 2015; **10:** e0145796.

6 Jackson S, Sleigh AC, Wang GJ, Liu XL. Poverty and the economic effects of TB in rural China. *Int J Tuberc Lung Dis* 2006; **10:** 1104–10.

7 Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. *Soc Sci Med* 2015; **130:** 42–50.

8 WHO. Global tuberculosis report 2015. Geneva: World Health Organization, 2015.

9 Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data. *Lancet* 2014; **383:** 2057–64.

10 Satyanarayana S, Nair SA, Chadha SS, et al. From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. *PLoS One* 2011; **6:** e24160.

11 Chindelevitch L, Menzies NA, Pretorius C, Stover J, Salomon JA, Cohen T. Evaluating the potential impact of enhancing HIV treatment and tuberculosis control programmes on the burden of tuberculosis. *J R Soc Interface* 2015; **12:** 20150146.

12 Menzies NA, Cohen T, Lin H-H, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med* 2012; **9:** e1001347-e.

13 Huynh GH, Klein DJ, Chin DP, et al. Tuberculosis control strategies to reach the 2035 global targets in China: the role of changing demographics and reactivation disease. *BMC Med* 2015; **13:** 88.

14 Trauer JM, Denholm JT, McBryde ES. Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-Pacific. *J Theor Biol* 2014; **358:** 74–84.

15 Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. *BMC Med* 2014; **12:** 216.

16 Sachdeva KS, Raizada N, Gupta RS, et al. The potential impact of up-front drug sensitivity testing on India's epidemic of multi-drug resistant tuberculosis. *PLoS One* 2015; **10:** e0131438.

17 Lin HH, Wang L, Zhang H, Ruan Y, Chin DP, Dye C. Tuberculosis control in China: use of modelling to develop targets and policies. *Bull World Health Organ* 2015; **93:** 790–98.

18 Houben RM, Lalli M, Sumner T, et al. TIME impact—a new user-friendly tuberculosis (TB) model to inform TB policy decisions. *BMC Med* 2016; **14:** 56.

19 Handel A, Whalen C. UGA model. Atlanta, GA: University of Georgia, 2015. http://http://handelgroup.uga.edu/resources_research (accessed Sept 22, 2016).

20 Laurence YV, Griffiths UK, Vassall A. Costs to health services and the patient of treating tuberculosis: a systematic literature review. *Pharmacoeconomics* 2015; **33:** 939–55.

21 Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2129–43.

22 United Nations Population Division. World population prospects: the 2010 revision, CD-ROM edition. Geneva: United Nations, Department of Economic and Social Affairs, Population Division, 2011.

23 WHO Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva: World Health Organization, 2001.

24 Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Eff Resour Alloc* 2003; **1:** 8.

25 Eaton JW, Menzies NA, Stover J, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *Lancet Glob Health* 2014; **2:** e23–34.

26 Marseille E, Larson B, Kazi D, Kahn J, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ* 2015; **93:** 118–24.

27 Eaton JW, Johnson LF, Salomon JA, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med* 2012; **9:** e1001245-e.

28 Dowdy DW, Dye C, Cohen T. Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'. *Int J Tuberc Lung Dis* 2013; **17:** 866–77.