Assessing tuberculosis control priorities in high-burden settings: a modelling approach

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Summary

Background In the context of WHO's End TB strategy, there is a need to focus future control efforts on those interventions and innovations that would be most effective in accelerating declines in tuberculosis burden. Using a modelling approach to link the tuberculosis care cascade to transmission, we aimed to identify which improvements in the cascade would yield the greatest effect on incidence and mortality.

Methods We engaged with national tuberculosis programmes in three country settings (India, Kenya, and Moldova) as illustrative examples of settings with a large private sector (India), a high HIV burden (Kenya), and a high burden of multidrug resistance (Moldova). We collated WHO country burden estimates, routine surveillance data, and tuberculosis prevalence surveys from 2011 (for India) and 2016 (for Kenya). Linking the tuberculosis care cascade to tuberculosis transmission using a mathematical model with Bayesian melding in each setting, we examined which cascade shortfalls would have the greatest effect on incidence and mortality, and how the cascade could be used to monitor future control efforts.

Findings Modelling suggests that combined measures to strengthen the care cascade could reduce cumulative tuberculosis incidence by 38% (95% Bayesian credible intervals 27–43) in India, 31% (25–41) in Kenya, and 27% (17–41) in Moldova between 2018 and 2035. For both incidence and mortality, modelling suggests that the most important cascade losses are the proportion of patients visiting the private health-care sector in India, missed diagnosis in health-care settings in Kenya, and drug sensitivity testing in Moldova. In all settings, the most influential delay is the interval before a patient's first presentation for care. In future interventions, the proportion of individuals with tuberculosis who are on high-quality treatment could offer a more robust monitoring tool than routine notifications of tuberculosis.

Interpretation Linked to transmission, the care cascade can be valuable, not only for improving patient outcomes but also in identifying and monitoring programmatic priorities to reduce tuberculosis incidence and mortality.

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Introduction

Despite being a disease of antiquity that is largely curable with affordable treatment, tuberculosis is currently the leading cause of death due to infectious disease.[1] Annually, over 10 million people develop tuberculosis disease globally, with more than 1 million dying from the disease. The expansion of the Directly Observed Treatment, Short Course (DOTS) strategy worldwide in the 1990s[2,3] involved strengthening the delivery of high-quality tuberculosis treatment through nationally coordinated tuberculosis programmes, and has achieved important reductions in mortality[4–6] through improved reporting and treatment outcomes.[1] However, despite these efforts, global tuberculosis incidence has been declining slowly over the past decade at a rate of only 1–2% per year.[1] Recent years have seen renewed global ambitions for accelerating these declines in tuberculosis burden—eg, with the End TB strategy launched in 2015, calling for reductions of 90% in tuberculosis incidence and 95% in tuberculosis mortality by 2035.[7]

For strategic planning to achieve these goals, there is a need to understand how best to focus control efforts in a given setting. A 2016 modelling study showed that available interventions for tuberculosis control (enhancing access to high-quality tuberculosis services, active case-finding, and other approaches) would not be sufficient to reach the 2025 milestones of the End TB strategy in either China or India, two of the countries with the highest burden.[8] However, the question remains as to where control and research efforts should be focused in the future to meet the End TB goals by 2035. Strategic planning in the End TB era should address where deployment of current tools should be improved (eg, optimising treatment outcomes), as well as highlighting priority areas for future research, to identify

Research in context

Evidence before this study

Mathematical models have been used to assess the potential effect of tuberculosis interventions. A study published in 2016 combined different models to assess the feasibility of meeting the 2025 End TB milestones, showing, for example, that India and China are unlikely to meet these targets using currently available tools alone. Earlier modelling work used generic, illustrative models to show the scale of activity required to eliminate tuberculosis. However, there is a need to translate the ambitions of the End TB goals into context-specific priorities for tuberculosis control efforts, whether in the improved deployment of current tools, or in identifying where innovative approaches are most needed. We additionally searched PubMed using the terms "tuberculosis" AND "strategy" AND ("End TB" OR "elimination"])', but found no additional, relevant studies. The search was done in Nov 1, 2018, with no restriction on year, but limited to papers published in English.

Added value of this study

We engaged with three national tuberculosis programmes and Kenya's HIV programme, as examples of distinct challenges in tuberculosis control: India (where tuberculosis care is fragmented between public and private health-care sectors); Kenya (with a high HIV burden); and Moldova (with a high drug-resistance burden). As an organising framework we used the care cascade, a concept initially developed to identify shortfalls in HIV care, and now increasingly being applied to improve patient outcomes in tuberculosis. Linking the care cascade to transmission, we shifted attention from individual interventions and patient outcomes, to the population level. We examined the shortfalls in the cascade, which, if addressed, would have the greatest effect on tuberculosis incidence and mortality. As well as capturing existing priorities (eg, the importance of engaging the private sector in India), our findings also cast light on problems that require attention (eg, transmission occurring before a patient's first presentation for care). Additionally, we show how indicators based on the care cascade could offer robust monitoring tools for future tuberculosis control efforts.

Implications of all the available evidence

Future tuberculosis control efforts require a combination of improvement in basic tuberculosis services (such as private sector engagement in India) and innovation to develop new, scalable approaches (eg, in all settings, to reach individuals with tuberculosis who have not sought care). Although the care cascade is conventionally applied in the context of improving patient outcomes, linking this cascade to transmission can provide a framework for synthesising diverse possible interventions, allowing systematic prioritisation and monitoring in a given country setting.

new, cost-effective approaches (eg, developing approaches for active case-finding).

In the present work, which is in support of the *Lancet* Commission on tuberculosis,[9] we present an analytical approach for addressing these issues. As an organising framework, we use the care cascade, which has been used extensively in HIV[10–12] and now increasingly in tuberculosis.[13–16] The care cascade is a framework listing the steps of care that an individual must go through to be cured (eg, linkage to treatment). Here we build on this framework, linking it to a transmission model to capture epidemiological features of a given country. We then use this model to quantify the influence of different elements of the care cascade on tuberculosis incidence and mortality. Combining key themes in the Commission,[9] this framework illustrates how to prioritise among those themes in a given setting.

We focus on three major challenges to global tuberculosis control efforts: first, many individuals with tuberculosis in south Asia seek care in the private health-care sector.[17–19] In this sector, substandard care leads to missed opportunities for diagnosis, and poor treatment outcomes.[20,21] Second, multidrug resistant (MDR) tuberculosis is a pressing problem, particularly in central and eastern European countries.[22,23] Third, the so-called syndemic of HIV and tuberculosis in sub-Saharan Africa means that tuberculosis programmes cannot operate independently of HIV control efforts.[24,25] As case studies for each of these challenges, we engaged with national tuberculosis programmes in three countries: India for public and private sectors; Moldova as a country with a high-MDR burden; and Kenya as a country with a high HIV burden. For each setting we developed a country-specific transmission model in collaboration with the respective country programmes.

Our approach focuses not on specific interventions, but on the care cascade outcomes that those interventions seek to achieve (eg, adherence support mechanisms as a means for improving treatment outcomes). Our primary objective is to establish which shortfalls in the care cascade are most important to address in order to reduce incidence and mortality in a given setting. These shortfalls can then either be mapped onto specific interventions, or used to identify research priorities for innovative approaches. Our secondary objective was to examine the potential value of the care cascade in monitoring tuberculosis control efforts. Incidence surveys are not feasible; nonetheless, we considered whether there were correlates of impact that could usefully be tracked. We examined whether elements of the cascade could offer such a correlate.

The tuberculosis care cascade is not exhaustive. It does not address preventive measures that could avert the progression from latent tuberculosis to active disease (eg, addressing malnutrition[26]), or infection control measures (eg, improved ventilation and hospital-based infection control[27]). Nor does it address intersectoral approaches, such as those addressing malnutrition, or urban development. These additional measures will be important in meeting the End TB goals.

Methods

Modelling approach

Work on patient pathways in different settings[28] and care cascade analyses[13,14] have highlighted the steps through which people must pass to be cured of tuberculosis (figure 1; table). Along this pathway, we refer to points where patients do not reach the next step as the gaps in the cascade. A second important dimension to the cascade is the delay in the transition between stages. A programme might, for example, successfully treat 100% of individuals with incident tuberculosis, but would have a small effect on transmission if successful cure occurs only after a year of undetected disease. We refer to the combined framework shown in figure 1—one quantifying both gaps and delays in a given setting—as the delay-care cascade.

For India, Kenya, and Moldova, we developed a deterministic model linking the delay-care cascade to tuberculosis transmission dynamics, as well as capturing essential features of the tuberculosis epidemic in each setting: the presence of a large private sector in India, the burden of HIV and tuberculosis in Kenya, and the burden of MDR-tuberculosis in Moldova. Drawing such stark distinctions between these country settings is somewhat artificial, as high-burden countries often face a combination of these challenges; nonetheless, as the purpose of this analysis is to be illustrative rather than prescriptive, this approach helps to simplify analysis of the priorities specific to each type of care cascade. The table lists the gaps and delays characterising the care cascade in each of the three country settings, together with examples of interventions to address each element of the cascade. Further technical details are given in the appendix (p 2,8,14).

Calibration

In each country setting, we used Bayesian melding methods[35] to estimate delay-care cascade and transmission parameters in such a way that the model captured key data simultaneously from disparate sources of evidence, while also incorporating uncertainty in model inputs. Data and sources are listed in the appendix and summarised as follows. In collaboration with country programmes, we collated WHO country burden estimates, routine surveillance data, and, when available, tuberculosis prevalence surveys. In 2016, Kenya completed a national tuberculosis prevalence survey,[36] and for India we drew from a 2011 state-wide prevalence survey in the major state of Gujarat.[37] Like other high MDR-burden countries in central and eastern Europe, Moldova has no prevalence survey to draw on. Therefore, we adopted plausible ranges for delays, and tested the model's sensitivity to these assumptions. For each country we also did a literature search to identify published sources relevant to the model parameters (table).

Combining data in this way allows estimation of elements in the delay-care cascade that might otherwise not be possible to estimate directly. An important example is the initial patient delay before presenting for care, shown in figure 1. This delay is challenging to measure directly because patient recall might be biased by the mildness of early tuberculosis symptoms, and evidence suggests that under-reporting of cough is common.[38,39] However, prevalence surveys can offer helpful, if indirect evidence. The Gujarat survey in India[37] suggested that 40% of individuals who were bacteriologically positive for tuberculosis reported symptoms, but had not yet sought care for those symptoms. Despite being a cross-sectional picture, a long patient delay in figure 1 would relate to a high proportion of prevalent tuberculosis in this compartment—the task for model calibration is to estimate this delay, to reproduce the data.

One challenging aspect of the data shown in figure 1 is that little evidence exists for what proportion of individuals who are symptomatic die or recover without ever presenting for care. We have taken a simple approach, assuming that losses at this point in the care cascade arise as a result of the mortality and spontaneous cure that occurs during the patient delay—a competing hazard[40] with the rate at which individuals who are symptomatic present for care.

We examined the sensitivity of model results to data and parameters, to highlight those inputs most strongly associated with uncertainty in model projections. Using the Bayesian framework for model calibration, we propagated uncertainty in model inputs to outputs, quantifying

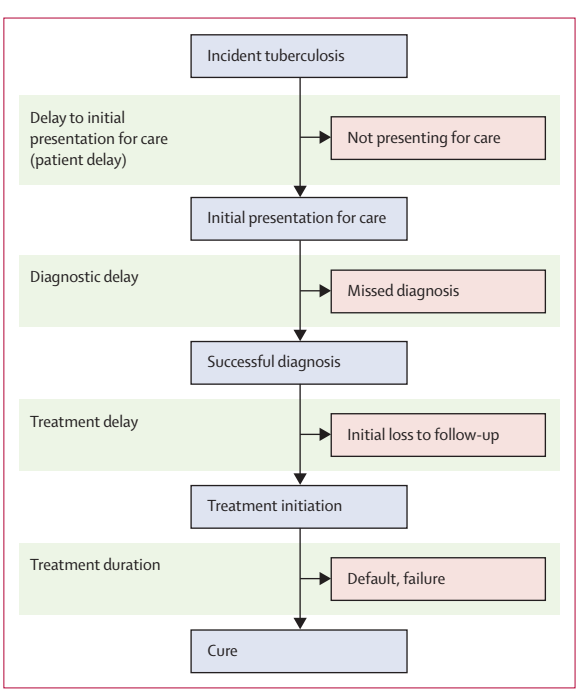

Figure 1: **The delay-care cascade**
Delays between successive stages (green) and losses at each stage (red) illustrating the delay-care cascade. For the three country settings analysed, we adapted the simple framework shown here to the epidemiological conditions prevailing in each setting. The table lists the additional gaps and delays adopted in each setting.

See Online for appendix

the uncertainty in model outputs by reporting 95% Bayesian credible intervals (CrI) on model projections.

Effect of improvements to the care cascade

The primary objective was to identify priorities for interventions. We modelled a combined cascade measures scenario, which reduces each gap in the table to an absolute level of 5% (such that 95% of patients pass through each stage), and reduces each delay in the table by 25%. These choices are arbitrary but illustrative. The choices also reflect the fact that it can be more difficult and resource-intensive to reduce delays (eg, the initial patient delay) than to close gaps (eg, loss to follow-up, among patients who are already in the cascade). Next, to address the importance of a given gap or delay, *X*, in the cascade, we simulated an all-but-one scenario, in which all shortfalls are addressed, with the exception of *X*. We defined the attributable effect of *X* as the reduction in impact, in respect of transmission and of mortality, relative to the combined measures scenario. Note that under this approach, a given gap cannot be compared directly against a given delay. We therefore treated

	Value	Relevant interventions
India		
Tuberculosis delay-care cascade		
Gap: proportion of individuals with incident tuberculosis that die or self-cure before presenting for care	10% (95% CrI 7·3–12·6)*	Case-finding in high-burden subpopulations (eg, slum dwellers); encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis); aligning the availability of tuberculosis services to where patients seek care
Delay: patient delay before first presentation for care	4·1 months (95% CrI 2·8–5·1)*	Case-finding in high-burden subpopulations (eg, slum dwellers); encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis); aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of symptomatic individuals with tuberculosis visiting the high-quality sector at each care-seeking attempt	43% (95% CrI 40–55)*	Private sector engagement;[29] aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of symptomatic individuals with tuberculosis presenting to the high-quality sector who are successfully diagnosed	83% (95% UI 80–85)[13]	Improve quality of diagnosis throughout the public health-care system, including use of rapid, accurate diagnostics
Gap: proportion of individuals diagnosed with tuberculosis in the high-quality sector who initiate treatment	88% (95% UI 86–90)[13]	Network optimisation; aligning the availability of tuberculosis services to where patients seek care
Delay: interval between diagnosis and treatment initiation in the high-quality sector	2·5 days (95% UI 1·9–3·6)[30]	Network optimisation; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of individuals with tuberculosis completing high-quality treatment	85% (95% UI 83–87)[13]	Adherence-support interventions in the public sector and among engaged private providers (eg, using new information communication technologies)
Kenya		
Tuberculosis delay-care cascade		
Gap: proportion of patients with incident tuberculosis that die or self-cure before presenting for care	22% (95% CrI 19–27)*	Case-finding in high-burden subpopulations (eg, slum dwellers); encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis); aligning the availability of tuberculosis services to where patients seek care
Delay: initial patient delay before first presentation for care among individuals who are HIV-negative	11 months (95% CrI 10·5–16·0)*	Case-finding in high-burden subpopulations (eg, slum dwellers); encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis); aligning the availability of tuberculosis services to where patients seek care
Delay: initial patient delay before first presentation for care among individuals who are HIV-positive	3·6 months (95% CrI 3·1–4·8)*	Case-finding in high-burden subpopulations (eg, slum dwellers); encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis); aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of symptomatic individuals with tuberculosis presenting who are successfully diagnosed	0·49 (95% CrI 0·35–0·64)*	Improve diagnostic capacity at health facilities, including use of rapid, accurate diagnostics; network optimisation; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of individuals diagnosed with tuberculosis who initiate treatment	0·8 (95% CI 0·77–0·82)[31]	Improve treatment capacity at health facilities where patients are diagnosed with tuberculosis; network optimisation; aligning the availability of tuberculosis services to where patients seek care
Delay: interval between diagnosis and treatment initiation	2·5 days (95% UI 1·9–3·6)[30]	Improve treatment capacity at health facilities where patients are diagnosed with tuberculosis; network optimisation; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of individuals diagnosed with tuberculosis completing high-quality treatment	87% (95% CrI 74–99)[32]	Adherence support interventions in the public sector, (eg, 99DOTS)
HIV cascade		
Gap: proportion of individuals with HIV who are on antiretroviral therapy	70% (country estimates)†	Increased rates of HIV testing and antiretroviral therapy initiation
Gap: proportion of individuals on antiretroviral therapy receiving tuberculosis preventive therapy	60% (country estimates)†	Implementation of WHO isoniazid preventive therapy guidelines; HIV and tuberculosis collaborative activities

(Table continues on next page)

	Value	Relevant interventions
(Continued from previous page)		
Moldova		
Tuberculosis delay-care cascade		
Gap: proportion of individuals with incident tuberculosis who die or self-cure before presenting for care	4% (95% CrI 2·6–10·0)*	Case-finding in key populations; contact investigation; encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis; aligning the availability of tuberculosis services to where patients seek care
Delay: initial patient delay before first presentation for care	1·5 months (95% CrI 1–4)*	Case-finding in key populations; contact investigation; encouraging demand for tuberculosis services (eg, through social protection for patients with tuberculosis; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of individuals with tuberculosis presenting who are diagnosed	93% (95% CrI 79–100; assumption to match 80% coverage 2016)[33]	Improve quality of diagnosis throughout the public health-care system, including use of rapid, accurate diagnostics
Gap: proportion of individuals with incident tuberculosis undergoing drug sensitivity testing	74%[34]	Increased use of rapid molecular tests to facilitate recognition of drug sensitivity status at the point of tuberculosis diagnosis
Gap: proportion of individuals with retreated tuberculosis undergoing drug sensitivity testing	47%[34]	Increased use of rapid molecular tests to facilitate recognition of drug sensitivity status at the point of tuberculosis diagnosis
Delay: interval between diagnosis and treatment initiation	2·5 days (95% UI 1·9–3·6)[30]*	Network optimisation; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion of individuals diagnosed with tuberculosis who initiate treatment	93% (95% CrI 79–100) (assumption to match 80% coverage 2016)[33]	Network optimisation; aligning the availability of tuberculosis services to where patients seek care
Gap: proportion individuals diagnosed with tuberculosis completing high-quality first-line treatment	80%[33]	Adherence support interventions in the public sector
Gap: proportion of individuals with tuberculosis completing high-quality second-line treatment	48% (95% CrI 41·0–55·2; cohort; all multidrug resistant tuberculosis cases)[33]	New, shortened second-line regimens

For India, high-quality denotes the public programme, along with private providers that have engaged with the public programme. For Kenya, we incorporate relevant elements of the HIV cascade in a simple way (see elements under HIV cascade). UI=uncertainty interval. CrI=credible interval. ECDC=European Centre for Disease Prevention and Control. NTP=National Tuberculosis Programme. *Model estimate. †Muthoni Karanja, National AIDS and STI Control Programme, Ministry of Health, Kenya, personal communication.

Table: **Quantification of the tuberculosis care cascade in three country settings**

delays and gaps separately, aiming to identify the most influential (highest attributable effect) of each. For a list of the interventions most relevant to each gap and delay see the table.

Our secondary objective was monitoring future control efforts. We considered how well different monitoring indicators would track progress in reducing incidence as the care cascade is strengthened. Considering three control scenarios, we compared annual notifications of tuberculosis cases against an alternative indicator, *P*—the proportion of individuals with tuberculosis undergoing high-quality tuberculosis treatment. The three control scenarios were: (1) no change in the delay-care cascade, (2) reducing gaps to 5% (leaving the patient delay unchanged), and (3) additionally reducing the patient delay by 25% (ie, reaching the full combined measures scenario). Scenarios 2 and 3 reflect the distinction between passive and active tuberculosis services (ie, services not contingent on a patient's voluntary presentation for care). Overall, these scenarios reflect increasing levels of tuberculosis control effort, with correspondingly increasing effect.

We simulated all scenarios from 2018 to 2035, the target year of the End TB goals. We assumed all care cascade measures to be scaled up in a linear way over 3 years from 2018 onwards. Model simulations were all programmed in C++.

Role of the funding source

The funders had no role in the 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

Model fits to the calibration targets for each of the country settings are shown in the appendix p 20 with the resulting model estimates of the gaps and delays for each of the three country settings. For India, the combined measures scenario corresponds to reductions of 57% (95% CrI 39–65) in incidence and 72% (95% CrI 60–79) in mortality by 2035, compared with 2015 (figure 2). The appendix (p 29) shows how these interventions influence two essential aspects of tuberculosis control: the mean length of the care cascade (ie, the duration of infectiousness) and the treatment success rate, both averaged at the population level.

To address our primary objective, figure 2 shows the attributable effect of each element. Results suggest that among the gaps considered, the proportion of symptomatic individuals visiting high-quality providers has the greatest attributable effect. As listed in the table, this parameter is improved by intervention through measures to engage with the private health-care sector,

to improve the standard of tuberculosis care in that sector. Similarly with delays, the initial patient delay before first presentation for care is associated with the greatest attributable effect. This interval is estimated to be 4·6 months (table), longer than other delays occurring in the cascade. A multivariate sensitivity analysis (appendix p 26) shows the key uncertainties in these results, highlighting in particular the importance of the infectiousness over time for an individual with tuberculosis. In a scenario in which infectiousness increases over time, the transmission influence of upstream elements in the cascade tends to be promoted (eg, the patient delay), and vice versa.

The corresponding results for Kenya show that a combined measures scenario yields reductions of 56% (95% CrI 48–66) in incidence and 77% (95% CrI 71–83) in mortality, relative to 2015 (figure 3). As well as the tuberculosis treatment cascade, this scenario includes increased antiretroviral therapy (ART) coverage and uptake of isoniazid preventive therapy (IPT) among individuals on ART (table). Although measures to improve the HIV cascade have an important role (ie, coverage of ART and of IPT among individuals on ART), the gap with the greatest attributable effect is that relating to missed diagnosis, and the most prominent delay is again the patient delay before first presentation for care. However, this delay is only important among individuals with tuberculosis who are HIV-negative; it is much shorter among HIV-positive individuals with tuberculosis (table). This difference potentially reflects the greater severity of disease among this subgroup, and the fact that a patient's existing linkage to HIV care might facilitate more rapid tuberculosis diagnosis. Overall, it is important to note that these results are context dependent. The appendix (p 27) shows corresponding results in a situation consistent with South Africa, where rates of HIV and tuberculosis co-infection are much higher (60% compared with 16% in Kenya). These results illustrate the greater transmission influence associated with the HIV cascade in this higher co-infection prevalence setting. The combined effect of these measures on the duration of infectiousness and treatment success rate, both averaged at the population level, are shown in the appendix (p 29).

In Moldova, a combined measures scenario yields reductions of 27% (95% CrI 17–41) in cumulative incidence and 52% (35–63) in mortality, between 2018 and 2045 (figure 4). The figure illustrates the importance of early drug sensitivity testing for settings with high MDR-tuberculosis burden, with similar effects attributable to levels of drug sensitivity testing in new and previously

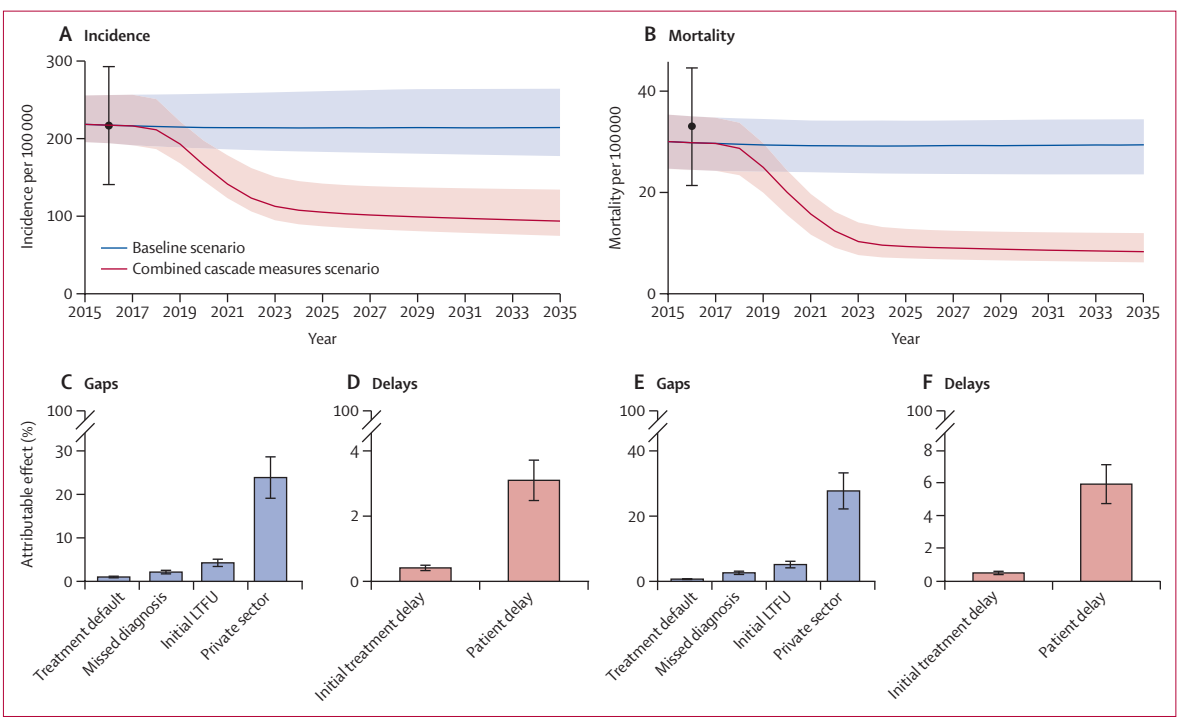

Figure 2: **Assessing tuberculosis intervention priorities in India**
Tuberculosis incidence (A) and mortality (B), comparing a baseline scenario (blue curve) to a combined cascade measures scenario in which each gap is reduced to 5%, and each delay is shortened by 25%. Shaded areas show 95% credible intervals arising from Bayesian simulation. Error bars in panels A and B show the incidence data used to calibrate the model, for comparison. (C, D) Reduction in effect on tuberculosis incidence that occurs when each element of the care cascade is dropped, singly and in turn, from the full set of interventions illustrated in panels A and B. Higher bars thus indicate a greater influence on transmission. Similarly, higher bars in panels E and F indicate a greater influence in mortality reduction. Blue bars (C, E) denote gaps, and red bars (D, F) denote delays (shown on separate axes because gaps are not directly comparable with delays). We do not show the effect of reducing the proportion of tuberculosis patients who never present for care. This gap is modelled as a consequence of the patient delay; closing this gap is thus the same intervention as reducing the patient delay (second red bar, panels D, F). LTFU=lost to follow-up.

treated cases. As with Kenya, the details of these results are context dependent. Other settings might differ in the relative importance of new and previously treated cases, depending on existing levels of coverage in these subgroups. Figure 4 also highlights the importance of second-line treatment outcomes, in the control of MDR-tuberculosis.

Although the delay-care cascade can be a helpful tool for understanding control priorities, measures to fix the cascade are not sufficient by themselves to achieve elimination in high-burden settings. This result can be shown with a hypothetical scenario, in which all gaps and delays in the cascade are eliminated—ie, patients with tuberculosis are initiated on treatment without delay or loss from the care cascade (appendix p 28). This scenario is artificial but illustrative; even with these extreme measures, it would take until 2100 to reach the End TB goals in India. As discussed in India's National Strategic Plan,[33] measures to prevent tuberculosis on a population level are clearly needed to achieve tuberculosis elimination in the coming decades.

To address our secondary objective, figure 5 examines potential approaches for monitoring future control efforts in each country setting. Under the progressively intensive tuberculosis control scenarios described (ie, no intervention, closing all gaps in the cascade, and additionally addressing the patient delay), figure 5A shows how tuberculosis notifications might change with each scenario. In the case of India, engaging the private sector improves the reporting of tuberculosis and therefore increases notifications. However, addressing the patient delay brings down incidence, therefore decreasing notifications. With a similar effect in other country settings, figure 5 illustrates challenges in using notification as a monitoring tool. Increasing or decreasing trends are not necessarily linked to programmatic success in a straightforward way.

Figure 5B illustrates an alternative metric *P*, defined as the proportion of individuals with tuberculosis who are on high-quality treatment. Based on the care cascade, this quantity can be increased either by closing gaps in the cascade, or by shortening delays, both having concomitant effects on incidence. As a result, increasing levels of *P* can be a proxy for incidence effect (figure 5B). In practice, as we discuss, monitoring *P* need not involve repeated prevalence surveys in the general population, an infeasible task.

Discussion

In an era of renewed ambition for accelerating declines in tuberculosis incidence and mortality, there is a need to understand in what areas future control efforts need to be

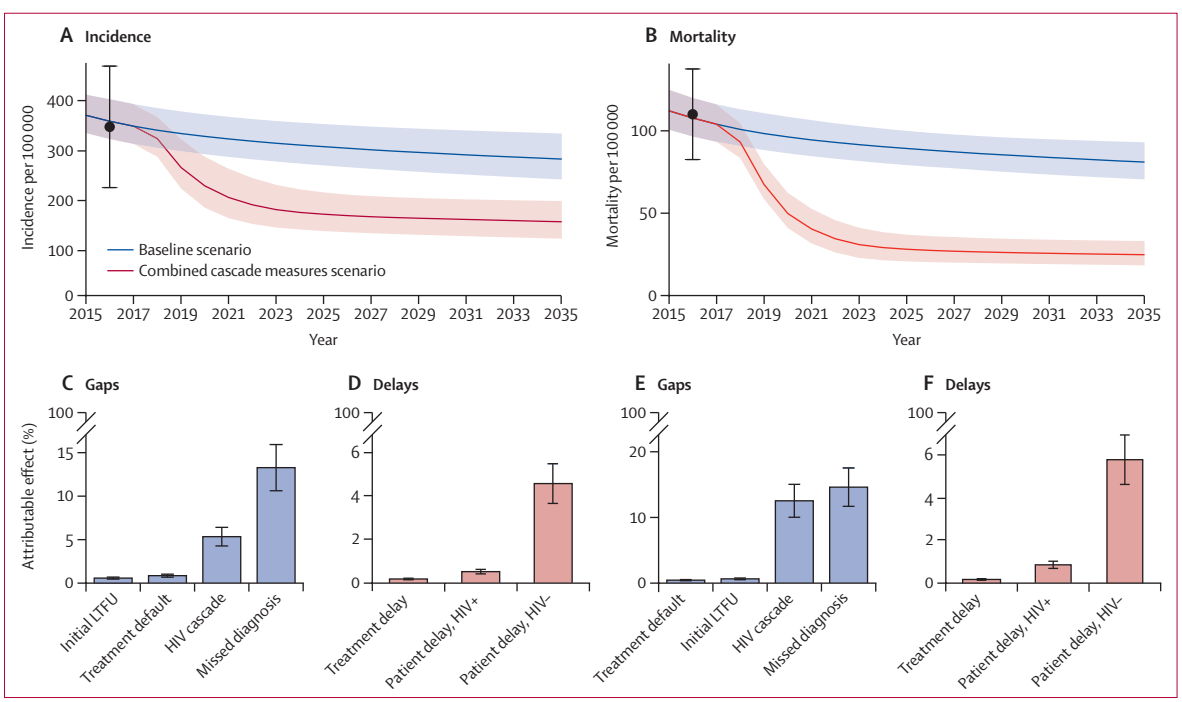

Figure 3: **Assessing tuberculosis intervention priorities in Kenya**
Tuberculosis incidence (A) and mortality (B), comparing a baseline scenario (blue curve) to a combined cascade measures scenario in which each gap is reduced to 5%, and each delay is shortened by 25%. Shaded areas show 95% credible intervals arising from Bayesian simulation. Error bars in panels A and B show the incidence data used to calibrate the model, for comparison. (C, D) Reduction in effect on tuberculosis incidence that occurs when each element of the care cascade is dropped, singly and in turn, from the full set of interventions illustrated in panels A and B. Higher bars thus indicate a greater influence on transmission. Similarly, higher bars in panels E and F indicate a greater influence in mortality reduction. Blue bars (C, E) denote gaps, and red bars (D, F) denote delays (shown on separate axes because gaps are not directly comparable with delays). We do not show the effect of reducing the proportion of tuberculosis patients who never present for care. This gap is modelled as a consequence of the patient delay; closing this gap is thus the same intervention as reducing the patient delay (second red bar, panels D, F). LTFU=lost to follow-up.

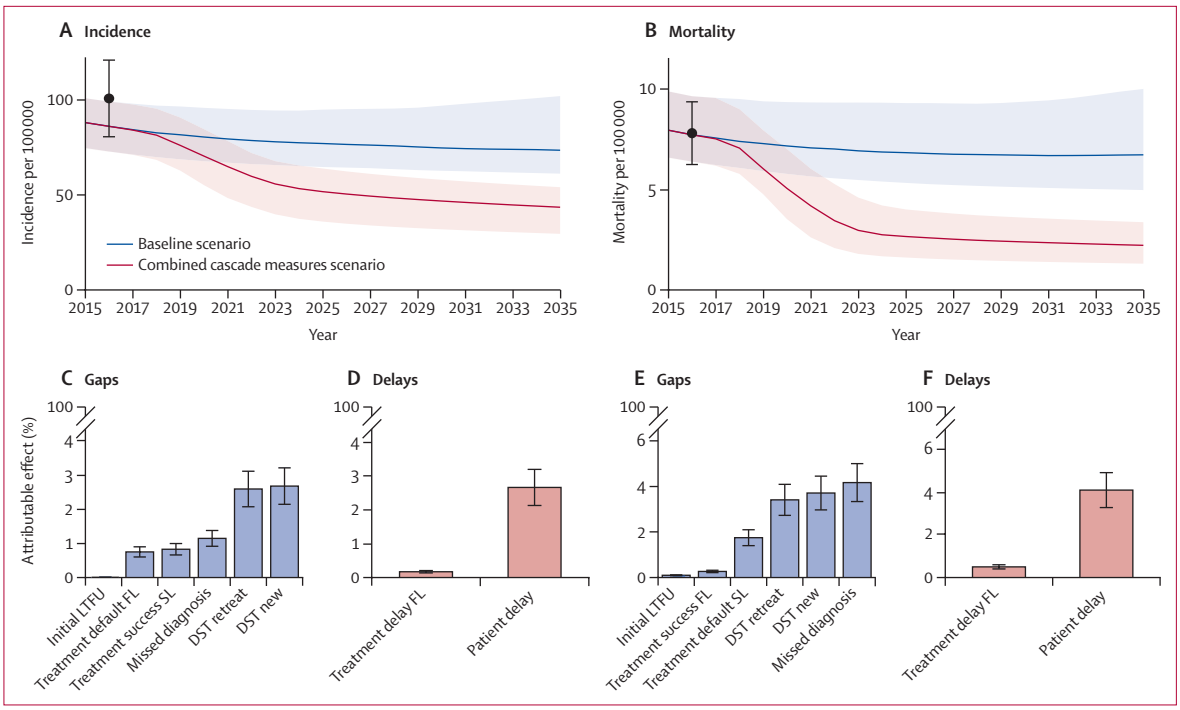

Figure 4: **Assessing intervention priorities in Moldova**
Tuberculosis incidence (A) and mortality (B), comparing a baseline scenario (blue curve) to a combined cascade measures scenario in which each gap is reduced to 5%, and each delay is shortened by 25%. Shaded areas show 95% credible intervals arising from Bayesian simulation. Error bars in panels A and B show the incidence data used to calibrate the model, for comparison. (C, D) Reduction in effect on tuberculosis incidence that occurs when each element of the care cascade is dropped, singly and in turn, from the full set of interventions illustrated in panels A and B. Higher bars thus indicate a greater influence on transmission. Similarly, higher bars in panels E and F indicate a greater influence in mortality reduction. Blue bars (C, E) denote gaps, and red bars (D, F) denote delays (shown on separate axes because gaps are not directly comparable with delays). We do not show the effect of reducing the proportion of tuberculosis patients who never present for care. This gap is modelled as a consequence of the patient delay; closing this gap is thus the same intervention as reducing the patient delay (second red bar, panels D, F). DST=drug susceptibility testing. LTFU=lost to follow-up. FL=first line. SL=second line.

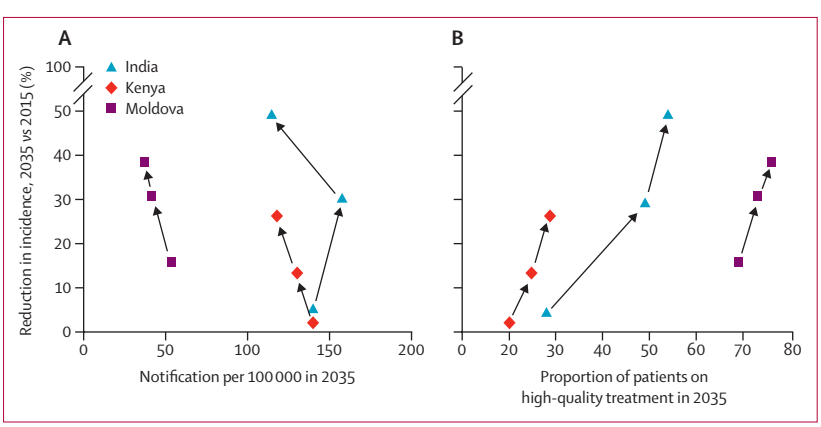

Figure 5: **Potential approaches for monitoring future tuberculosis control efforts**
Progression of effect (vertical axis) and indicators (horizontal axis) under a series of intervention scenarios: (1) baseline with no intervention until 2045; (2) improving the public sector treatment cascade; and (3) additionally shortening the patient delay. Arrows show the progression from scenario (1) to (3), with increasing transmission effect. Panels show the behaviour of two possible indicators, under this progression: (A) notifications, as currently used to monitor tuberculosis programme performance, and (B) an alternative, cascade-based indicator, the proportion of patients with prevalent tuberculosis who are on high-quality tuberculosis treatment. This indicator can be increased by any measures to reduce delays and gaps in the cascade (thus reducing the proportion of patients in other stages in the cascade). As a result, this indicator shows a closer association with effect than notifications alone.

focused. In this context, the present work accompanies the *Lancet* Commission on tuberculosis.[9] Here, we have presented a framework for bringing together the diverse themes discussed by the Commission, and for prioritising within these themes in a given setting. We have applied this analytical framework to three country settings: India, Kenya and Moldova, each capturing a distinct, important challenge in global tuberculosis control.

Our results underscore three key needs for tuberculosis control. First, ensuring the availability of coordinated, high-quality tuberculosis care throughout the health-care system (strengthening the service side of the care cascade). Second, optimising the linkage between these services and individuals who would benefit from them, whether or not they have presented for care (meeting the need for tuberculosis services). And third, recognising that strengthening the tuberculosis care cascade in these ways is only a first step, and that ultimately there will be a need for primary prevention of tuberculosis. We discuss each of these in turn.

First, regarding the service side within the care cascade, our analysis captures recognised priorities in tuberculosis care, including the need for private sector engagement in many south Asian countries, the need to assure the availability of high-quality diagnostic facilities, and the importance of universal drug sensitivity testing for control of MDR tuberculosis. These priorities are among key themes discussed in the *Lancet* Commission on

tuberculosis.[9] Our analysis illustrates the importance, for tuberculosis incidence and mortality, of addressing these gaps in basic tuberculosis service provision. However, these priorities are not universal, and will vary by country. The contrast between Kenya and South Africa is an example in which both countries are settings with a high HIV burden, but measures to improve HIV and tuberculosis services take a higher priority in South Africa than Kenya (appendix p 27). Our analysis offers a quantitative, systematic approach for resolving these priorities among a complex range of interventions in different country settings.

Second, to address the need side, our results suggest that much is still to be achieved in all of the three country settings that we have analysed. This challenge involves reaching individuals with tuberculosis who have not presented for care (figures 2–4). The evidence for how best to achieve this challenge is incomplete.[41] Active case-finding is one potential approach, for which implementation should be considered carefully, depending on local conditions. India's 2017 national strategic plan prioritises sustained, systematic screening in high-risk populations such as individuals living in urban slums, which bear a disproportionate tuberculosis burden.[42] A 2018 study in Vietnam has also highlighted the value of household contact investigation with longitudinal follow-up.[43,44] However, other, more person-centred approaches also merit attention. In practice the patient delay can arise from various factors, including barriers in access to care such as wage and time costs of seeking care or stigma. Social protection mechanisms, such as nutrition and cash support for patients with tuberculosis undergoing treatment[45] might have the secondary but important effect of encouraging individuals with symptoms to come forward for care. Such effects are as yet only speculative. Given the potential importance of these effects for controlling transmission, however, our analysis highlights these evidence gaps as key priority areas to address for future prioritisation.

Third, addressing the care cascade is important but ultimately falls short of the magnitude of impact that is needed for the End TB goals, which is an important limitation of the care cascade (appendix p 28). In particular, and in agreement with previous work,[46] measures will ultimately be required to prevent tuberculosis. Wider deployment of preventive therapy is one possible approach, and could become more feasible with ongoing development in preventive regimens.[47] Other approaches to preventing tuberculosis include infection control measures in the household, hospital, and other settings. Looking beyond vertical disease programmes, the End TB strategy recognises the need for multisectoral approaches including measures to address comorbidities such as nutritional status[26] and diabetes,[48] and the role of overcrowding, ventilation, and the built environment in tuberculosis transmission.[49] All of these factors lie outside the scope of the tuberculosis care cascade, but, through their role in preventing tuberculosis transmission and progression, could become essential in reaching the End TB goals.

Our findings also illustrate the challenges in monitoring tuberculosis control efforts with existing standard approaches (figure 5). Notifications currently play a central role in assessing programme performance. Here we propose a complementary indicator—the proportion of individuals with tuberculosis on high-quality treatment—that can only be enhanced by closing gaps in the care cascade and by accelerating the rate at which individuals with tuberculosis are diagnosed and initiated on treatment. By shortening delays, the numbers of individuals with tuberculosis in other stages of the cascade are reduced. This proposed indicator is therefore potentially a more robust correlate of impact, than notifications. A clear challenge is that such measures depend on prevalence surveys, which, being so resource-intensive, are ill-suited for routine surveillance. Nonetheless, focused efforts in high-risk populations, such as in urban slums, could be as informative. If tuberculosis burden is low in these populations, it is likely to be lower in other, lower-risk populations. Sustained, systematic screening efforts have already begun in high-risk populations in India. Ongoing collection of treatment status data from patients with tuberculosis thus identified would be valuable in monitoring ongoing control efforts. In the longer term, however, such measures should only be an interim solution. Evolving health data systems would afford invaluable opportunities for monitoring through routine data collection. In particular, a well-functioning vital registration system, fully integrated with data for health-care use, would allow monitoring to shift from prevalence-based to mortality-based approaches.

As with any modelling approach, the transmission framework has some limitations. Being illustrative and not prescriptive, the models we have presented here are deliberately simplified. For ease of presentation, they are not fully representative of each country setting, but rather they are focused on a specific issue in each setting. Therefore, this approach should be seen as a framework that can be developed as necessary for a given setting, to capture all of the key concurrent challenges (eg, HIV burden and MDR tuberculosis). In doing so, future applications of this approach could benefit from incorporating additional data sources, including notifications and mortality data, especially in settings where these sources reflect tuberculosis burden in a stable way. Additionally, it has been necessary to address gaps and delays separately in the model, recognising that they cannot be directly compared with one another.

Among other simplifications, the models presented here ignore age and sex structure, and the difference between different forms of tuberculosis (eg, pulmonary *vs* extrapulmonary tuberculosis), instead taking an average transmission potential. The models also ignore subnational heterogeneity, such as the heterogeneities

across different counties in Kenya highlighted by patient pathway analysis.[50] Similarly, urban and rural settings in India are likely to call for different approaches.[51] In the example of Kenya, for simplicity we have not aimed to capture the dynamics of HIV, taking it as a model input; our estimate of the influence of the HIV cascade (figure 3) might therefore be an underestimate. We have not addressed cost, as the analysis is intentionally unrestricted to any specific interventions. Instead, we have focused on identifying the outcomes for which cost-effective interventions are required. A next step is to estimate the upper limits on unit costs, for any future activity to be cost-effective. Other modelling analysis has, for example, addressed this question in the case of active case finding.[52] Finally, model findings are subject to substantial uncertainty. This uncertainty reflects important data gaps relating to health systems, and to the natural history of tuberculosis. Multivariate sensitivity analysis (appendix p 26) shows the importance of the temporal variability in infectiousness, in the relative effect of late-stage versus early-stage cascade effects. Addressing these factors and other data gaps will have important implications for refining our understanding of priority interventions.

In summary, tuberculosis is a complex and multifactorial disease. Although a global problem, priority needs in specific settings vary widely depending on local epidemiology, and on the combination of activities already in effect. In the face of this complexity, there is a pressing need for evidence to identify in what way and at what stage current efforts are falling short, and where future efforts should be focused. Here we have presented one possible approach for doing so. Guided by the available evidence, future programmatic change could realise new opportunities for achieving true declines in tuberculosis burden.

Contributors

NA, TBH, and MJAR conceived and designed the study. JFV, TBH, and NA did the analysis. Country coauthors (KSS, RR, SK, PD, and KR from India; MK, EOm, EM, NO, EOn, PO, MK, and RK from Kenya; and SA, VV, VC, SB, and CC from Moldova) provided country data and helped to validate and interpret the respective models. JFV and NA wrote a first draft of the manuscript, and all co-authors contributed to the final draft.

Declaration of interests

We declare no competing interests.

References

1 WHO. Global Tuberculosis Report 2018. 2018. http://www.who.int/tb/publications/global_report/en/ (accessed May 1, 2018).

2 Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA* 2000; **283:** 2537–45.

3 Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* 2005; **293:** 2767–75.

4 Dye C, Hosseini M, Watt C. Did we reach the 2005 targets for tuberculosis control? *Bull WHO* 2007; **85:** 364–69.

5 Glaziou P, Floyd K, Korenromp EL, et al. Lives saved by tuberculosis control and prospects for achieving the 2015 global target for reducing tuberculosis mortality. *Bull WHO* 2011; **89:** 573–82.

6 Mandal S, Chadha VK, Laxminarayan R, Arinaminpathy N. Counting the lives saved by DOTS in India: a model-based approach. *BMC Med* 2017; **15:** 47.

7 Uplekar M, Weil D, Lönnroth K, et al. WHO's new end TB strategy. *Lancet* 2015; **385:** 1799–801.

8 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; **4:** e806–15.

9 Reid MJA, Arinaminpathy N, Bloom A, et al. Building a tuberculosis-free world: *The Lancet* Commission on tuberculosis. *Lancet* 2019; published online March 20. http://dx.doi.org/10.1016/S0140-6736(19)30024-8.

10 Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis* 2011; **52:** 793–800.

11 Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *Plos Med* 2011; **8:** e1001056.

12 Fox MP, Rosen S. A new cascade of HIV care for the era of "treat all". *PLoS Med* 2017; **14:** e1002268.

13 Subbaraman R, Nathavitharana RR, Satyanarayana S, et al. The tuberculosis cascade of care in India's public sector: a systematic review and meta-analysis. *PLoS Med* 2016; **13:** e1002149–38.

14 Naidoo P, Theron G, Rangaka MX, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. *J Infect Dis* 2017; **216:** S702–13.

15 Cazabon D, Alsdurf H, Satyanarayana S, et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. *Int J Infect Dis* 2017; **56:** 111–16.

16 Subbaraman R, Nathavitharana RR, Mayer KH, et al. Constructing care cascades for active tuberculosis: a strategy for program monitoring and identifying gaps in quality of care. *PLoS Med* 2019; **16:** e1002754.

17 Kapoor SK, Raman AV, Sachdeva KS, Satyanarayana S. How did the TB patients reach DOTS services in Delhi? A study of patient treatment seeking behavior. *PLoS One* 2012; **7:** e42458.

18 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.

19 Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis* 2016; **16:** 1255–60.

20 Das J, Kwan A, Daniels B, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. *Lancet Infect Dis* 2015; **15:** 1305–13.

21 Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? *PLoS One* 2010; **5:** e12023.

22 Acosta CD, Dadu A, Ramsay A, Dara M. Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward. *Public Health Action* 2014; **4:** S3–12.

23 Zumla A, Abubakar I, Raviglione M, et al. Drug-resistant tuberculosis—current dilemmas, unanswered questions, challenges, and priority needs. *J Infect Dis* 2012; **205** (suppl 2)**:** S228–40.

24 Chaisson RE, Martinson NA. Tuberculosis in Africa—combating an HIV-driven crisis. *N Engl J Med* 2008; **358:** 1089–92.

25 Abdool Karim SS, Churchyard GJ, Karim QA, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet* 2009; **374:** 921–33.

26 Bhargava A. Undernutrition, nutritionally acquired immunodeficiency, and tuberculosis control. *BMJ* 2016; **355:** i5407.

27 Bock NN, Jensen PA, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. *J Infect Dis* 2007; **196** (suppl 1)**:** S108–13.

28 Hanson C, Osberg M, Brown J, Durham G, Chin DP. Finding the missing patients with tuberculosis: lessons learned from patient-pathway analyses in 5 countries. *J Infect Dis* 2017; **216:** S686–95.

29 Pai M, Dewan P. Testing and treating the missing millions with tuberculosis. *Plos Med* 2015; **12:** e1001805.

30 Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014; **18:** 255–66.

31 Tollefson D, Ngari F, Mwakala M, et al. Under-reporting of sputum smear-positive tuberculosis cases in Kenya. *Int J Tuberc Lung Dis* 2016; **20:** 1334–41.

32 WHO. Global tuberculosis report, annex II. Geneva: WHO; 2018. https://www.who.int/tb/publications/global_report/gtbr2018_annex2.pdf?ua=1 (accessed Jan 10, 2019).

33 WHO. WHO TB country profile, Moldova 2017. https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=md&outtype=pdf (accessed March 13, 2019).

34 European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2016. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/ecdc-tuberculosis-surveillance-monitoring-Europe-2016.pdf (accessed Oct 12, 2018).

35 Poole D, Raftery AE. Inference for deterministic simulation models: the bayesian melding approach. *J Am Stat Assoc* 2012; **95:** 1244–55.

36 Enos M, Sitienei J, Ong'ang'o J, et al. Kenya tuberculosis prevalence survey 2016: challenges and opportunities of ending TB in Kenya. *PLoS One* 2018; **13:** e0209098.

37 Chadha VK, Anjinappa SM, Dave P, et al. Sub-national TB prevalence surveys in India, 2006–2012: results of uniformly conducted data analysis. *PLoS One* 2019; **14:** e0212264.

38 Spinou A, Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? *J Thorac Dis* 2014; **6:** S728–34.

39 Raj AA, Birring SS. Clinical assessment of chronic cough severity. *Pulm Pharmacol Ther* 2007; **20:** 334–37.

40 Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011; **6:** e17601.

41 Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013; **17:** 432–46.

42 Revised National Tuberculosis Control Programme. National strategic plan for tuberculosis elimination 2017–2025. 2017. https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020 20.02.2017%201.pdf (accessed June 16, 2017).

43 Fox GJ, Nhung NV, Sy DN, et al. Household-contact investigation for detection of tuberculosis in Vietnam. *N Engl J Med* 2018; **378:** 221–29.

44 Lung T, Marks GB, Viet Nhung N, et al. Household contact investigation for the detection of tuberculosis in Vietnam: economic evaluation of a cluster-randomised trial. *Lancet Glob Health* 2019; **7:** e376–84.

45 van Hoorn R, Jaramillo E, Collins D, Gebhard A, van den Hof S. The effects of psycho-emotional and socio-economic support for tuberculosis patients on treatment adherence and treatment outcomes—a systematic review and meta-analysis. *PLoS One* 2016; **11:** e0154095.

46 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; **34:** 271–86.

47 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365:** 2155–66.

48 Pan S-C, Ku C-C, Kao D, Ezzati M, Fang C-T, Lin H-H. Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis: a modelling study. *Lancet Diabetes Endocrinol* 2015; **3:** 323–30.

49 Dowdy DW, Grant AD, Dheda K, Nardell E, Fielding K, Moore DAJ. Designing and evaluating interventions to halt the transmission of tuberculosis. *J Infect Dis* 2017; **216:** S654–61.

50 Masini E, Hanson C, Ogoro J, et al. Using patient-pathway analysis to inform a differentiated program response to tuberculosis: the case of Kenya. *J Infect Dis* 2017; **216:** S714–23.

51 Pandey S, Chadha VK, Laxminarayan R, Arinaminpathy N. Estimating tuberculosis incidence from primary survey data: a mathematical modeling approach. *Int J Tuberc Lung Dis* 2017; **21:** 366–74.

52 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.