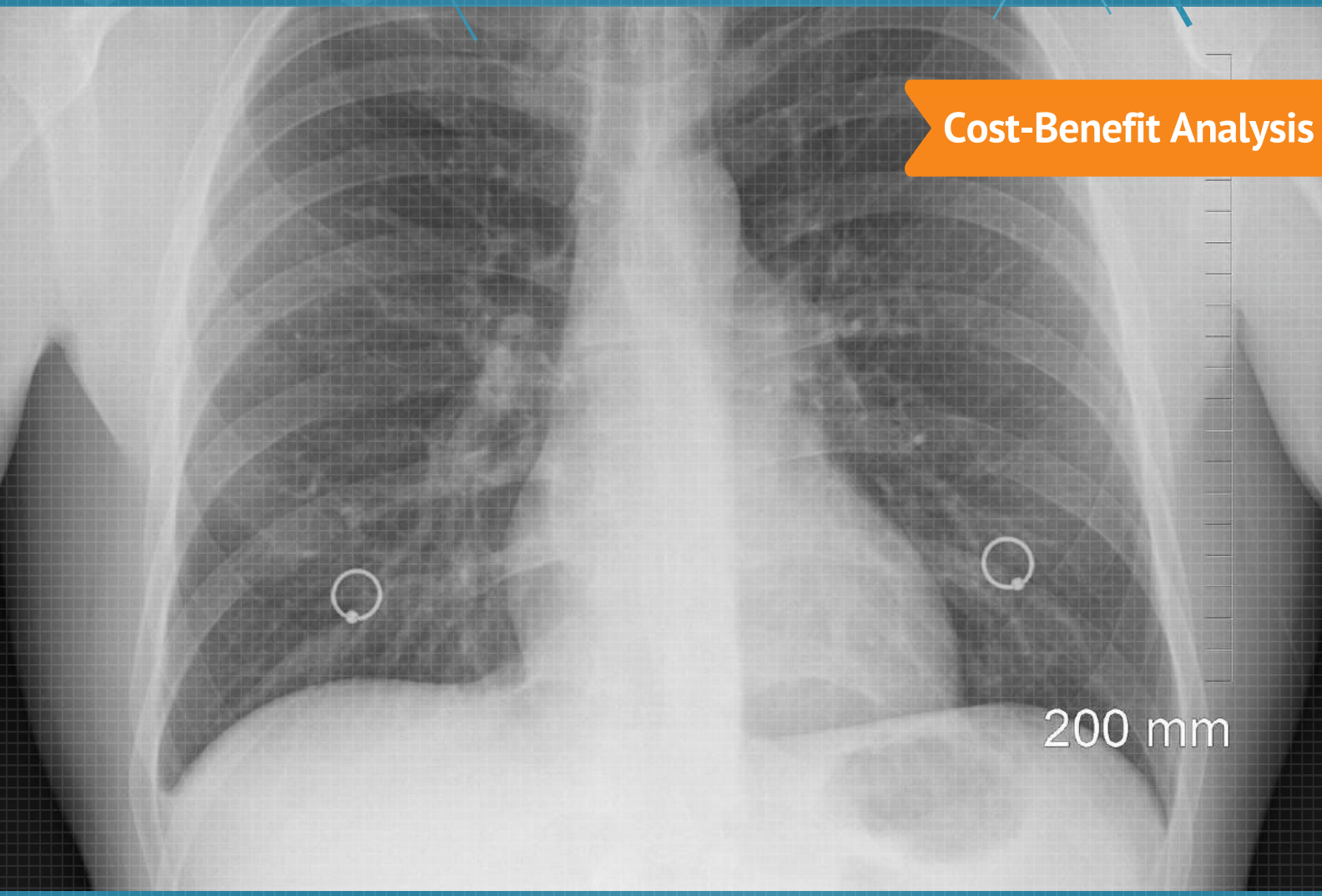
TUBERCULOSIS

Modelling the potential impact of TB interventions in Andhra Pradesh



Cost-Benefit Analysis

AUTHOR:

Nimalan Arinaminpathy
Senior Lecturer
Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London

SECTOR EXPERT REVIEWERS:

Dr. Raghuram Rao
SDADG (TB)
Dte. General of Health Services
Ministry of Health & Family Welfare, GOI

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info@copenhagenconsensus.com
www.copenhagenconsensus.com

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Andhra Pradesh Priorities
An India Consensus Prioritization Project

Nimalan Arinaminpathy

Senior Lecturer, Mathematical Epidemiology

Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, UK

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Academic Abstract

Tuberculosis (TB) is a major global health challenge, and India is the country with the world's largest TB burden. India's recent National Strategic Plan (NSP) for TB elimination, launched in 2017, sets out renewed ambition for TB control. In this context, it is important to estimate the potential impact of different interventions against TB.

The present analysis focuses on Andhra Pradesh. Importantly, TB interventions benefit not only the patients receiving the intervention (such as those receiving curative TB treatment), but also those who might otherwise have been infected. To capture these dynamics, we use mathematical modelling of TB epidemiology, coupled with cost and economic data. We use such models to examine two interventions against TB, that play a critical role in India's NSP: private sector engagement, and intensified case-finding in urban slums.

Our analysis suggests that an intervention that succeeds in engaging 50% of private healthcare providers in Andhra Pradesh, to improve their quality of TB care, will avert 2135 deaths per year and cost on average Rs 21.7 crores per year (undiscounted) between now and 2050. Overall, the benefit-cost ratio (BCR) is 112.2 (5% discounting). Moreover, a 'combined intervention' scenario, where private sector engagement is combined with case-finding to screen urban slums thrice a year, will avert 3454 deaths per year at an average cost of Rs. 43.5 crores per year (undiscounted). The BCR is 101.9 (5% discounting).

Model findings are subject to substantial uncertainty: for example, a major cost driver in the 'combined intervention' scenario is the cost per case detected by intensified case-finding. Ongoing case-finding initiatives will provide valuable information for these and other key data gaps. Nonetheless, these estimates highlight the strong value in TB investments, offering the potential to save considerable numbers of lives from TB.

Policy Abstract

The Problem

Tuberculosis (TB) is a leading infectious disease killer. In 2016 India accounted for over a quarter of estimated TB incidence and over a fifth of estimated TB mortality worldwide, the highest burden of any country (World Health Organization, 2017). Without treatment, the disease has a serious mortality toll, mostly amongst young adults. It is a disease intimately linked to poverty: on the one hand poor living conditions exacerbate the risk of TB, but on the other, those suffering from TB often face a substantial risk of falling into poverty (Oxlade & Murray, 2012). While most cases of TB are curable with a 6-month regimen, the emergence of multi-drug-resistant TB is causing increasing concern. Management of drug-resistant TB is significantly more costly and protracted than treatment of drug sensitive TB: as a result, although MDR-TB accounts for an estimated 4% of TB burden in India, it accounts for almost half of programmatic spending in India (Revised National Tuberculosis Control Programme, 2016).

Overarching all these challenges in India is the presence of a private healthcare sector that is large, fragmented and unregulated: there is strong evidence of a poor standard of TB care in this sector. First, the use of inaccurate diagnostic tests can delay the diagnosis of TB, thus permitting ongoing transmission. Evidence suggests that TB cases visit 2-4 providers, over a period of 1-2 months, before finally being diagnosed with TB and intiaiting appropriate treatment (Sreeramareddy, Qin, Satyanarayana, *et al.*, 2014; Kapoor, Raman, Sachdeva, *et al.*, 2012). Second, a general lack of treatment support means that many TB patients do not complete the 6 month standard TB regimen (Udwadia, Pinto & Uplekar, 2010). This leads to poorer treatment outcomes than in the public sector, as well as increasing the risk of multi-drug-resistance. For future TB control efforts in India, there is therefore a critical need to address these issues, so that TB patients receive high-quality TB treatment, and the best possible treatment outcomes, wherever they seek care.

Intervention 1: Private sector engagement

Overview

The intervention involves the creation of a 'Public Private Support Agency' PPSA, supported by public funds and overseen by the national TB programme, that has responsibility for engaging with private providers and facilitating diagnosis and treatment (Pai & Dewan, 2015; Wells, Uplekar & Pai, 2015). The aim of the intervention is to improve the quality of TB care in the private sector. In particular, TB symptomatics visiting the private sector will be diagnosed more quickly (as a result of more accurate TB diagnostic tests), and will have access to higher-quality TB treatment, than at present.

A PPSA aims to sensitize and engage with private providers, offering subsidies for high-quality TB diagnostic tests; free TB treatment; support mechanisms to help TB patients complete their treatment regimens; and support to the providers for notifying TB.

Importantly, unlike earlier public-private mix approaches (Dewan, 2006), the private provider continues to manage the TB patient: the purpose of the PPSA is not to 'divert' the patient to the public sector, but rather to facilitate high-quality TB care amongst the providers that they are already visiting. Moreover, providing notification support, free drugs and diagnostic subsidies are all known to be real value propositions for the private providers.

Ultimately, a PPSA aims to reach all private providers who are treating TB, thus maximizing its 'reach' amongst TB patients. However, it is difficult to project how costs may vary at such levels of scale: they may go up, as a result of the extra effort needed to each additional provider, or they may go down, as a result of efficiencies at scale. For the purpose of this exercise we consider a more conservative scenario, where this intervention attempts to engage with all providers in the state, but only successfully manages to attract sufficiently many to the program, to capture half of the TB patients being treated in the private sector.

Implementation Considerations

There are ongoing PPSA pilots in Mumbai, Patna and elsewhere. Hence we have good information on the costs involved, and on achievable scales. However, it is difficult to measure transmission effects directly (i.e. reduced TB burden as a result of PPSA interventions). In this work, we aim to estimate these interventions using mathematical models of TB transmission.

We assume an intervention starting in 2018 and scaling up in a linear way to have approached 75% of private providers across the state by 2020. A potential risk of the intervention is that private providers do not engage with the intervention in the scale required, for impact. We assume that 2/3 of providers approached are successfully engaged. It takes time for the full benefits of the intervention to be realised. Accordingly, we calculate costs and benefits over the period from 2017 to 2050, while understanding that we expect new tools to be available for TB control to be available by this time.

Success is measured principally by the TB notifications from private providers. For example on the national level, ongoing PPSA pilots have led to a substantial increase in TB notifications from the private sector.

Costs and Benefits

Costs

Figure 1 shows how the incremental cost varies over time, corresponding to a mean annual cost of Rs. 21.7 crores. The figure illustrates the breakdowns by the major cost components: the total numbers of people being tested, as well as the volumes of TB treatment (first- and second-line). As noted above, the cost of managing drug-resistant TB is disproportionate to its burden. An intervention such as private sector engagement, in controlling MDR-TB, can therefore have a strong impact on overall spending.

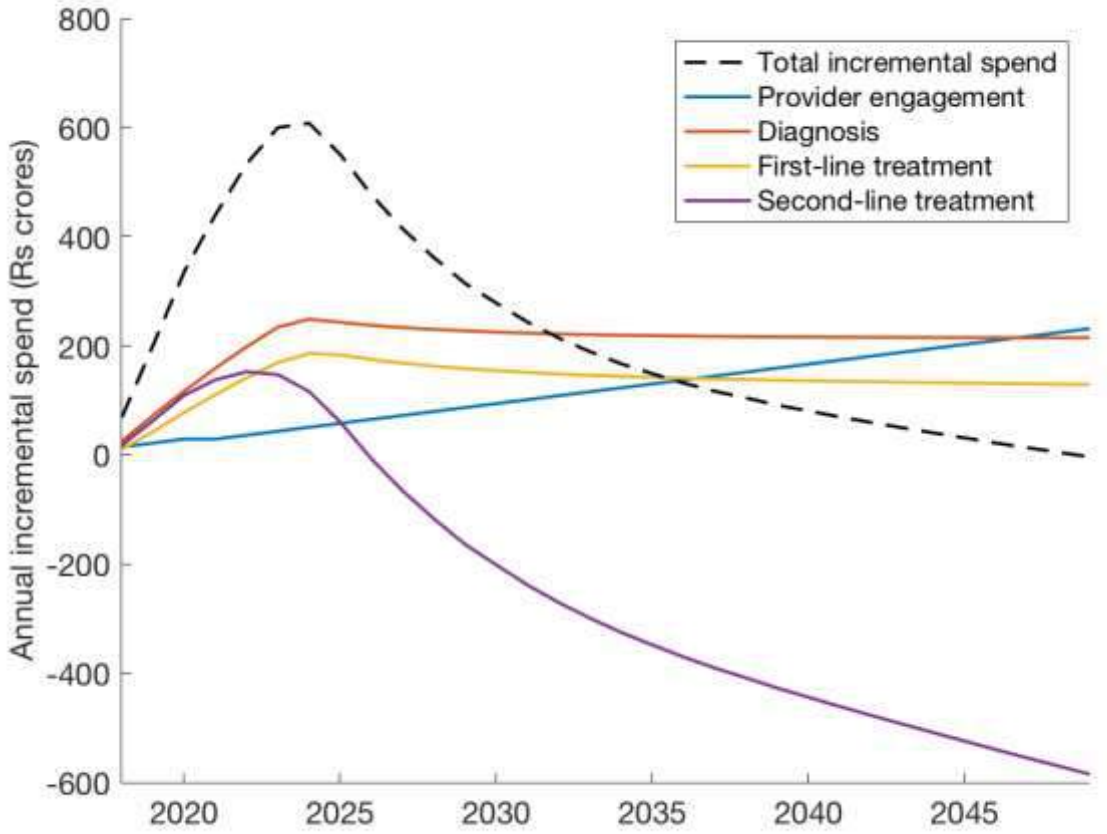

Figure 1. Summary of costs and cost drivers under private sector engagement. The horizontal dashed line shows the level of zero incremental spend. Solid lines show the main cost drivers, respectively: diagnosis, first-line (FL) treatment, and second-line (SL) treatment. Figures omit treatment initiation costs, which account for < 1% of total costs.

Benefits

Figure 2 summarises the potential epidemiological impact of the intervention, acting across urban and rural settings. The intervention increases the number of TB patients initiating high-quality treatment (either in the public sector or with 'engaged' private providers), as measured in 2040, from 35.2 thousand to 40 thousand. Through improved treatment outcomes the intervention would avert 2135 TB deaths per year on average, or 9.8% of deaths that might otherwise have occurred. Moreover, as illustrated in Figure 2, the intervention has a strong impact on MDR-TB, owing to the use of rapid molecular tests in the private sector, to facilitate the early diagnosis (and thus appropriate treatment) of MDR-TB.

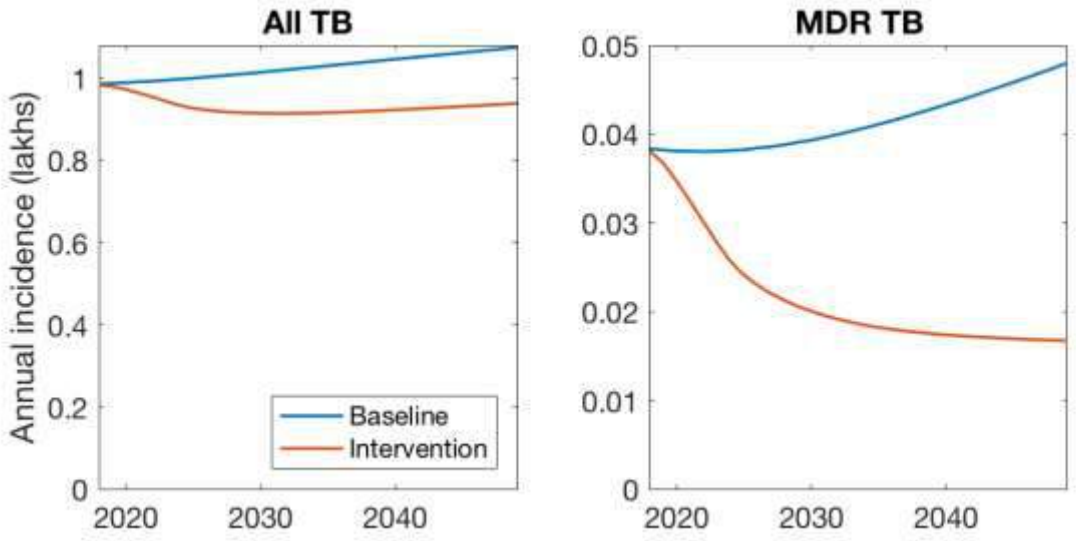

Figure 2. Potential epidemiological impact of the intervention. There is some reduction in TB incidence (left-hand panel). However, because of the use of rapid molecular tests such as GeneXpert, the intervention can turn an otherwise growing MDR epidemic into a decreasing one (right-hand panel). These epidemiological changes underpin the dynamics in cost shown in Figure 1.

Intervention 2: Private sector engagement combined with case-finding

Overview

Overview: Current TB services rely largely on 'passive' systems, that is, waiting for symptomatic patients to present for care. For further reductions in transmission, there is a need to accelerate TB diagnosis. There are several potential approaches, including measures to generate demand for TB services, as well as lowering barriers in access to care, to encourage patients to come forward sooner for care. However, these remain hypothetical. Here we concentrate on case-finding in risk groups, another important intervention in India's National Strategic Plan for TB elimination (Revised National Tuberculosis Control Programme, 2017b).

We consider an intervention with mobile units going into urban slums to screen for TB, using X-rays and symptoms suggestive of TB. Possible TB cases are diagnosed using accurate, rapid molecular tests for TB. If positive, they are referred to the public sector for treatment. This intervention is supported, staffed and implemented by the national TB programme.

Because of the intensity of effort needed, case-finding is concentrated in specific risk groups where burden is highest. Here we consider an intervention that focuses on urban slums in the state.

Implementation Considerations

We assume that urban slums account for 10% of India's population, yet 25% of India's TB burden (consistent with slums having three times the TB prevalence as in the rest of the population). We assume sustained case-finding activity that screens the whole state slum population, to identify all TB cases in that population three times a year. This scenario is consistent with India's National Strategic Plan, which calls for systematic screening of risk groups thrice a year.

Importantly, case-finding is implemented *in combination* with private sector engagement. That is, it is essential first to ensure that broken health systems are fixed as a matter of priority, before embarking on additional, novel measures such as sustained case-finding.

A risk is that case-finding activity does not produce the 'yield' that is expected: or equivalently, that it costs more to identify a single case of TB than is suggested by epidemiological estimates and operational cost estimates alone. Ongoing case-finding activities in India will go a long way towards addressing this uncertainty.

Other mathematical models suggest that case-finding could have important incidence implications. A further risk is that in practice, these impacts may not be realized, even with a significant case-finding yield. There is a lack of systematic evidence for the transmission impact that arises in real-world settings from sustained case-finding efforts. However, indirect evidence from prevalence surveys suggest that there is indeed a substantial share of TB burden that can be reached with case-finding. Again, ongoing case-finding activities in India may help in informing this gap in the evidence base. Overall the evidence for this intervention is limited, and indirect. Nonetheless, because of its potential importance for TB transmission, and its prominent role in strategic planning by the national TB programme, it is helpful to incorporate here.

Costs and Benefits

Costs

Figure 3A shows how the incremental cost varies over time, corresponding to a mean annual cost of Rs. 35.2 crores. Figures 3B – D illustrate the breakdowns by the major cost components: the total numbers of people being tested, as well as the volumes of TB treatment (first- and second-line). As above, a long-term effect of this intervention is to reduce the numbers on second-line treatment, with important implications for incremental spending (relative to baseline). However, owing to the stronger reductions in TB incidence than in intervention 1, a similar effect is also apparent in first-line treatment, as well as in diagnosis. We assume that it costs USD 2,000 per person diagnosed in the slums, covering the use of mobile diagnostic units, staff time in counselling and testing patients, and the use of rapid molecular diagnostic diagnostic tests. We assume that the intervention detects 2/3 of prevalent cases in this setting in each round of case-finding.

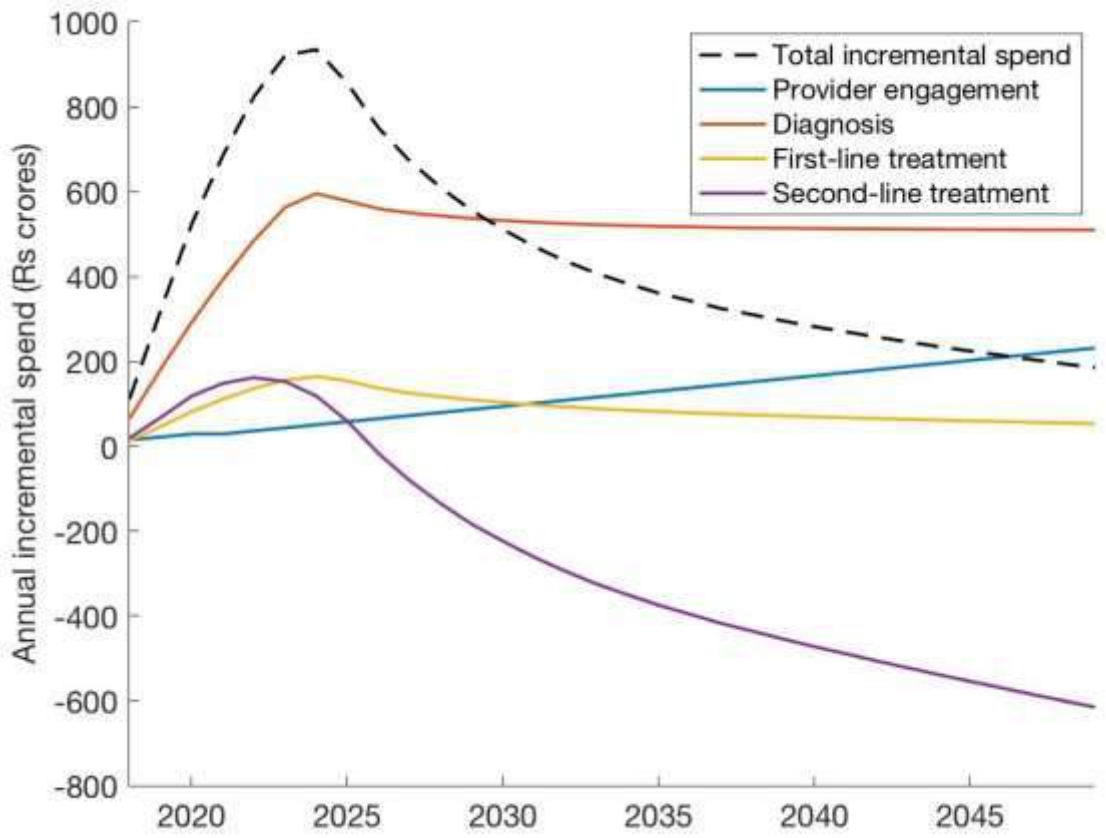

Figure 3. Summary of costs and cost drivers under private sector engagement and active case finding. Curves are as in Figure 1.

Benefits

Figure 4 summarises the potential epidemiological impact. Although the majority of TB cases in urban slums are likely to be treated in either the public or private sectors, the intervention accelerates the detection of these cases. In combination with private sector engagement, case-finding would avert an average of 3454 TB deaths per year, or 15.9% of deaths that might otherwise have occurred.

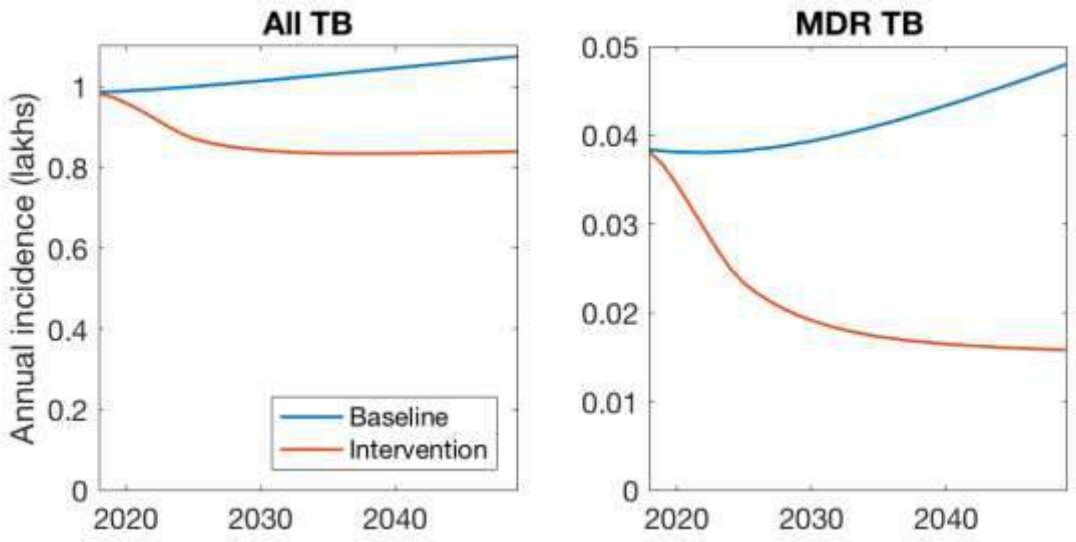

Figure 4. Potential epidemiological impact of the intervention. The strong incidence impact shown in the right-hand panel explains the long-term declines in numbers tested and treated in Figure 3.

BCR Table

Summary Table, programmatic costs only 2018-2049

Interventions	Benefit (INR crores)	Cost (INR crores)	BCR	Quality of Evidence
Private sector engagement	51598	460.06	112.2	Medium
Private sector engagement + active case finding in urban slums	84187	825.93	101.9	Limited

Notes: All figures assume a 5% discount rate

Summary Table, programmatic + patient costs (including patient time and spending) 2018-2049

Interventions	Benefit (INR crores)	Cost (INR crores)	BCR	Quality of Evidence
Private sector engagement	51598	439.63	117.4	Medium
Private sector engagement + active case finding in urban slums	84187	775.96	108.5	Limited

Notes: All figures assume a 5% discount rate

1. Introduction

Tuberculosis (TB) is a major cause of death due to infectious disease. It is estimated that in 2016, over 1.5 million people died from the disease, a mortality toll concentrated heavily in low- and middle- income countries (World Health Organization, 2016). It is a disease intimately linked to poverty, driven by factors such as malnutrition and poor living conditions. Moreover, in high burden settings, TB morbidity and mortality is borne predominantly by young adults, in what should be their most economically productive years of life.

There is increasing recognition of TB as a major global health problem. The post-2015 End TB goals call for a reduction of TB incidence rates by 90% and of TB deaths by 95% by 2035, compared to 2015 (Stop TB Partnership, 2015). However, there remain major challenges in TB control: primarily, it is not a vaccine-preventable infection. The BCG vaccine, which has been in use globally for over 90 years, has been valuable in protecting children from the severe form of the disease, but does not offer sufficiently robust immunity to block transmission on a population scale (Tuberculosis Research Centre, 1999). Nonetheless, unlike infections such as HIV, TB is curable, with cost-effective drugs. A standard regimen of anti-TB treatment consists of 6 months of combination chemotherapy, often implemented under medical supervision to ensure adherence. Overall, therefore, available tools against TB mean that the control of TB transmission (at least in the immediate term) focuses on finding infectious cases as quickly as possible, and initiating them on appropriate, curative treatment.

An added dimension is the emergence of rifampicin-resistant and multi-drug-resistant forms of TB, which we refer to here simply as ‘drug-resistant’ (DR-TB). Treating DR-TB is more costly and protracted than treating drug-susceptible TB, with poorer outcomes: a 24-month second-line regimen can cost a hundred times as much as a 6-month first-line regimen, with only 50% treatment success (Zumla, Abubakar, Raviglione, *et al.*, 2012). As a result, controlling DR-TB burden will not only improve patient outcomes, but will also have important implications for programme spending, through averted costs of managing DR-TB.

India is the country with the world's largest burden of TB, accounting in 2016 for an estimated 27% of global TB incidence (World Health Organization, 2016), despite also having the world's largest public-sector national TB programme. The reasons for the size of India's TB epidemic

are manifold, including: (i) a vast and disorganized private healthcare sector, where many patients first seek care (Kapoor, Raman, Sachdeva, *et al.*, 2012; Arinaminpathy, Batra, Khaparde, *et al.*, 2016; Sreeramareddy, Qin, Satyanarayana, *et al.*, 2014), and (ii) the presence of marginalized groups bearing a disproportionate burden of TB, including urban slums, where poor living conditions and lack of access to high-quality care facilitate transmission.

Here we estimate the potential impact of two major interventions for addressing TB burden in Andhra Pradesh, in India: private sector engagement, and case-finding in urban slums. This work comes at a time of increasing ambition for TB control, with India's recently-launched National Strategic Plan (NSP) setting out a far-reaching vision for TB elimination (Revised National Tuberculosis Control Programme, 2017b). Both private sector engagement and case-finding form critical parts of the NSP. Therefore, this analysis aims to align with existing plans, taking a 'look ahead' to estimate the potential benefits of implementing of these interventions in Andhra Pradesh.

There are other important, recent programmatic changes that are outside the scope of this work. For example, India's most recent Guideline for Programmatic Management of Drug-resistant TB (Revised National Tuberculosis Control Programme, 2017a) highlights the need for universal drug sensitivity testing (DST) for all notified TB cases. Previous modelling analysis showed how such measures could strongly impact DR-TB burden, even when limited to TB cases notified through the public sector (Sachdeva, Raizada, Gupta, *et al.*, 2015). Our present analysis complements this work, in the scenario where private sector engagement acts as a vehicle for high-quality DST in the private sector.

We note that improved TB services can save lives by improving outcomes (Glaziou, Floyd, Korenromp, *et al.*, 2011). However, they can also avert morbidity and mortality by reducing opportunities for transmission (Mandal, Chadha, Laxminarayan, *et al.*, 2017). We capture these effects using a mathematical model of TB transmission, calibrated to capture the TB epidemic in Andhra Pradesh. The model is adapted from previously published work in India (Mandal, Chadha, Laxminarayan, *et al.*, 2017; Sachdeva, Raizada, Gupta, *et al.*, 2015), and is described in further detail in the Technical Appendix.

2. Private sector engagement

2.1 Background and evidence

The private healthcare sector in India is vast, fragmented and unregulated (Pai, Daftary & Satyanarayana, 2016; Das, Kwan, Daniels, *et al.*, 2015; Satyanarayana, Nair, Chadha, *et al.*, 2011). There is widespread use of poor-quality diagnostic tests, leading to missed opportunities for diagnosis, thus extending opportunities for transmission (Sreeramareddy, Qin, Satyanarayana, *et al.*, 2014). Moreover, a general lack of treatment support means that TB patients do not often typically complete the six months' standard TB treatment regimen, as symptoms usually resolve in a matter of weeks. Such conditions increase the risk of recurrent TB disease (relapse), while also raising concerns about the generation of multi-drug-resistant (MDR) forms of TB. Second-line treatment for MDR-TB is toxic, costly and protracted, with poor outcomes.

As a result, it is widely recognised that TB control in India needs to start with improving the standard of TB care in the private sector, in order to improve both the quality of diagnosis, and patient treatment support. However, early 'public-private mix' approaches to this problem were frustrated by a lack of cooperation by private healthcare providers, driven partly by a lack of trust in the public sector (Uplekar *et al.*, 2001; Uplekar, 2016). Such approaches were often seen as taking patients away from the private sector, and therefore as threatening provider income, as well as interfering in patient choice. More recently, emerging evidence indicated that the burden of TB being managed by the private healthcare sector was even higher than previously recognised, adding urgency to the need to address this issue (Arinaminpathy, Batra, Khaparde, *et al.*, 2016).

In this context a novel mechanism, the 'Public-Private Support Agency' (PPSA), is being piloted in Mumbai, Patna and other locations in India (Pai & Dewan, 2015). This intervention aims to make high-quality TB services available wherever a patient seeks care, whether in the public or private sector. In particular, an NGO (or other similar entity) is contracted to engage with private providers, to provide training, and to offer subsidies for high-quality TB tests - principally GeneXpert, a new molecular test for TB that can diagnose rifampicin resistance at the same time as a TB diagnosis. Diagnosed TB patients receive treatment counselling and are

linked with a call centre to support treatment adherence, while cases diagnosed with DR-TB are referred to the public sector. Overall these measures aim to diagnose TB as early as possible, through high-quality diagnostics, as well as providing a mechanism (through the rapid molecular testing provided by GeneXpert) for early recognition of drug-resistant TB. Additionally, by promoting treatment completion, adherence support aims to minimise long-term risk of relapse.

Initiatives like the PPSA have led to unprecedented increases in TB notifications from the private sector over the past three years, and are forming the basis for the national programme's future plans for scaling up private sector engagement (Pai & Dewan, 2015; Wells, Uplekar & Pai, 2015).

The quality of evidence is 'Moderate': while we have some idea of the costs and potential programmatic performance of such interventions from ongoing pilots, the potential transmission impact has thus far only been possible to estimate through transmission modelling approaches, rather than being measured directly.

2.2 Description of intervention

We model a 'private sector engagement' intervention, in which private providers in the community are systematically engaged and supported, in a manner similar to PPSA activities. In line with India's National Strategic Plan, we assume an intervention that is scaled up over three years, to approach 75% of private providers in Andhra Pradesh. In practice, not all private providers will engage equally with the programme: we assume additionally that 2/3 of providers actually take up the diagnostic tests available to them, as well as linking their patients to adherence support mechanisms.

As described above, patients visiting engaged providers are offered subsidies for GeneXpert, a highly sensitive, rapid molecular test for TB that can also detect rifampicin resistance. Patients diagnosed with TB are linked to a call centre, which tracks their treatment progress and offers adherence support, offering free drugs. Patients diagnosed with drug-resistant TB are referred to the public sector, for second-line treatment.

Rather than taking patients away from private providers, this innovative approach instead allows the provider to continue managing their patients, and provides incentives for the use of

high-quality diagnostic tests, as well as providing free TB drugs and adherence support. Importantly, these approaches also provide help to providers, for notifying TB to public health authorities. Private providers appreciate these activities, which they see as supporting their work, rather than competing or interfering with it. As a result, these interventions have contributed towards an unprecedented increase in recent years, in TB notifications from the private sector (World Health Organization, 2017; Revised National Tuberculosis Control Programme, 2016).

The epidemiological impact of these interventions is: to facilitate early diagnosis through the use of rapid, sensitive diagnostic tests (thus reducing opportunities for transmission), and to improve treatment completion rates (thus reducing the incidence of relapse).

2.3 Calculation of Costs and Benefits

For programmatic costs, we include the costs of engaging private providers; provider training; subsidies for TB diagnostics; TB treatment counseling; free TB drugs; and the call centre support mechanism. All of these costs are informed by cost data from the ongoing PPSA operations in Mumbai and Patna (Arinaminpathy et al, in review). For patient costs, we include the time and travel costs for each visit to a provider, as well as for each visit for DOTS treatment. We value patient time at 50% of wages. Additionally, we incorporate the patient costs of TB care in the private sector, incorporating consultation fees, diagnosis costs, and out-of-pocket expenditure on TB drugs. For all patients initating second-line treatment, we include costs of a week's hospitalization, valued at 100% of patient's wages. To estimate benefits, we calculate the lives saved by this intervention as well as the reduction in person-years of active TB disease. We use a disability weighting of 0.331 for active disease, drawn from recent Global Burden of Disease estimates.

Figure 5 shows model projections for the epidemiological impact of this intervention, running from 2018 to 2050. It is important here to distinguish the dynamics in drug-susceptible and drug-resistant (DR)-TB: while the latter accounts only for an estimated 4% of overall TB burden in India, the management of DR-TB is disproportionately costly. Figure 5 illustrates that the intervention would bring down cumulative TB incidence by around 9.3%. Importantly, however, the use of rapid molecular tests in the private sector allows the early recognition of

DR-TB, at the point of diagnosis. This has an important effect on DR-TB burden, potentially turning an increasing DR-TB epidemic into a decreasing one.

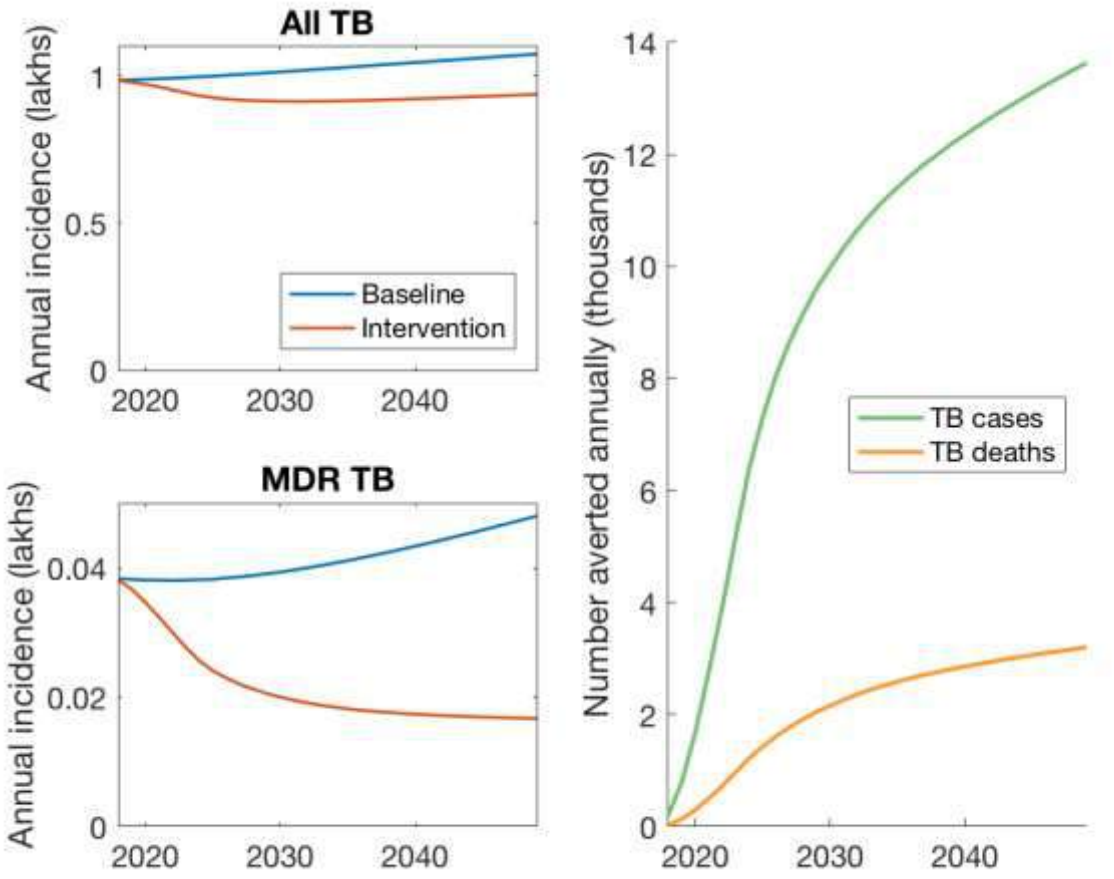

Figure 5. Projected epidemiological impact for private sector engagement. (A, B): Projections for incidence and TB mortality, comparing baseline (red curve) with intervention (blue curve) scenarios. (C) Annual numbers of TB cases and deaths averted (green, orange curves respectively).

Figure 5 (right-hand panel) additionally shows the annual TB cases and mortality averted by the intervention, between 2018 and 2050. On average in this period, the intervention will save 2135 lives per year from TB (9.8% reduction compared to baseline), and avert 9563 TB cases per year (9.3% reduction compared to baseline).

Figure 6 shows the associated programmatic spending (shown with no discounting, for illustration). Incremental costs are driven by transmission dynamics as well as by the scale of

the intervention. In particular, the DR-TB impact shown in Figure 5 is a strong driver of incremental programme spending in Figure 6 (purple line): while initial growth in programme spending is driven by investment in implementing the intervention, after 2025 there is an increasing, countervailing role from cost savings through falling DR-TB burden. Figure 7 additionally illustrates these dynamics showing programme activities, comparing intervention with baseline: while the intervention achieves increases in the long-term volumes of diagnosis and first-line treatment, it brings about substantial reductions in volumes of second-line treatment. Overall, this intervention has a benefit-cost ratio of 112.2 at 5% discounting (see BCR summary table).

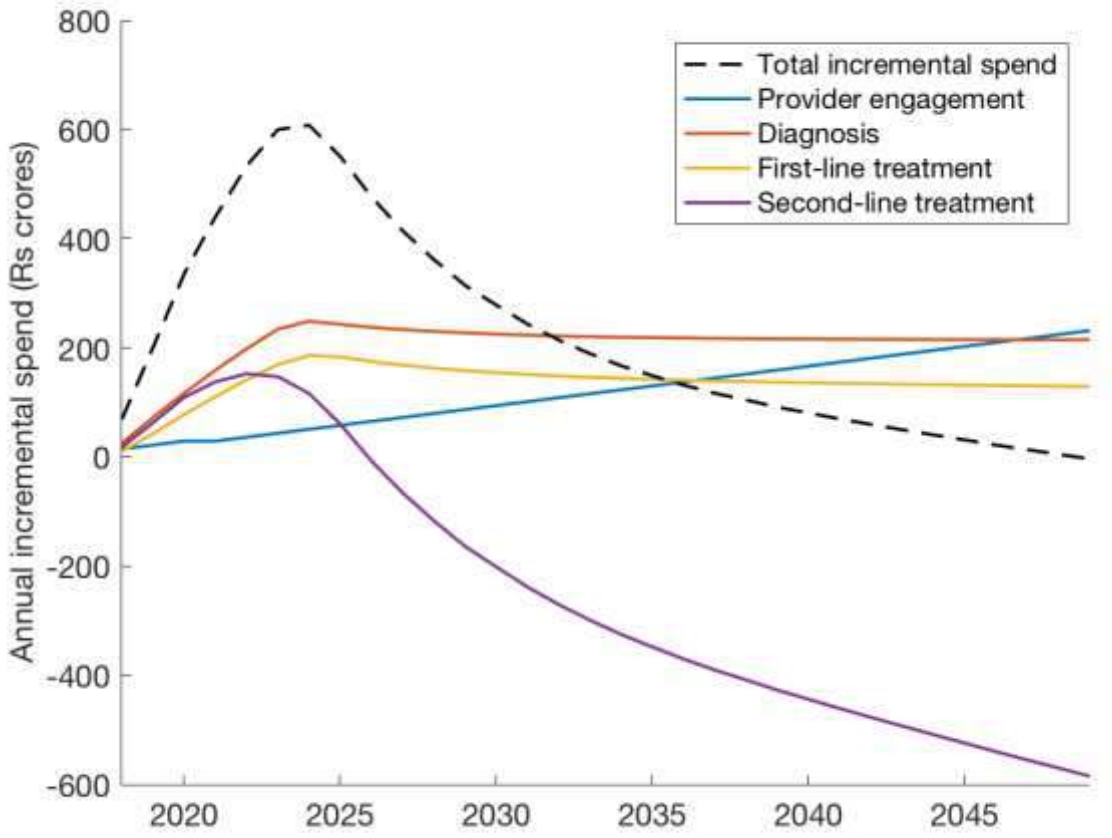

Figure 6. Projected annual programmatic spending for private sector engagement. Figure shows the total incremental spend, relative to the baseline scenario (dashed line), with break-up of individual cost components shown in solid lines. The figure does not display the cost of engaging private providers, as this accounts for ~1% of total incremental spending.

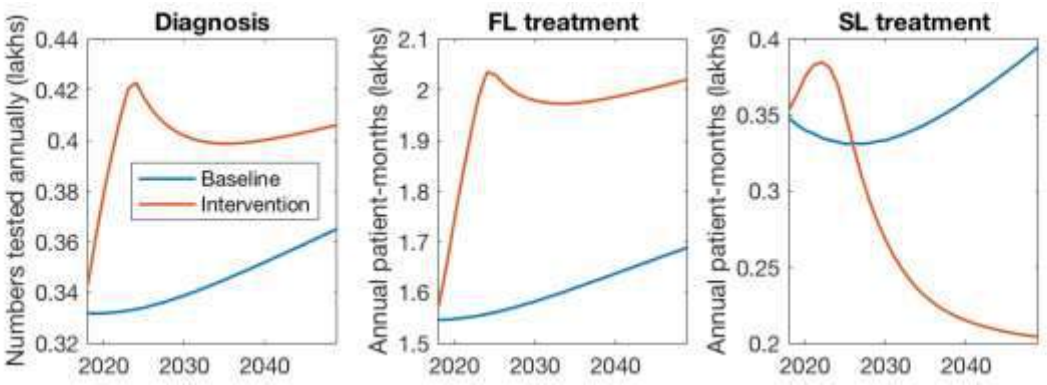

Figure 7. Annual volumes of programmatic activity (diagnosis and treatment), comparing intervention to baseline scenarios. Overall the intervention causes an increase in the amount of diagnostic tests conducted, as well as in the amount of first-line treatment: however, second-line treatment is ultimately reduced in comparison with baseline, owing to the impact of the intervention on DR-TB burden.

2.4 Sensitivity Analysis

The transmission model is informed by a wide set of parameters, relating to the clinical course of TB as well as the structure of the healthcare system in the state. Given the complexity of this system, we conduct multivariate sensitivity analysis by incorporating uncertainty in each of the model parameters in a Bayesian framework. We take plausible ranges for epidemiological parameters. For unit costs, we take relatively broad intervals of +/-50% of the point values. The Bayesian analysis varies all of these parameters simultaneously, thus giving rise to a range of model outputs for BCR, whose variation reflects the uncertainty in the underlying model parameters. By studying which parameters account for the greatest variation in BCR, we therefore identify those to which the results are most sensitive. Figure 5 shows the results of this analysis, presented as a correlation coefficient. The 'leading' parameter is the cost per case diagnosed by an engaged private provider. By way of illustration, doubling and halving this cost yields BCR values of 61.8 and 189.1 respectively, at 5% discounting. Next most important parameters relate to the baseline quality of TB care: specifically, the accuracy of diagnosis in the private sector, and the proportion of patients visiting the private sector for their symptoms.

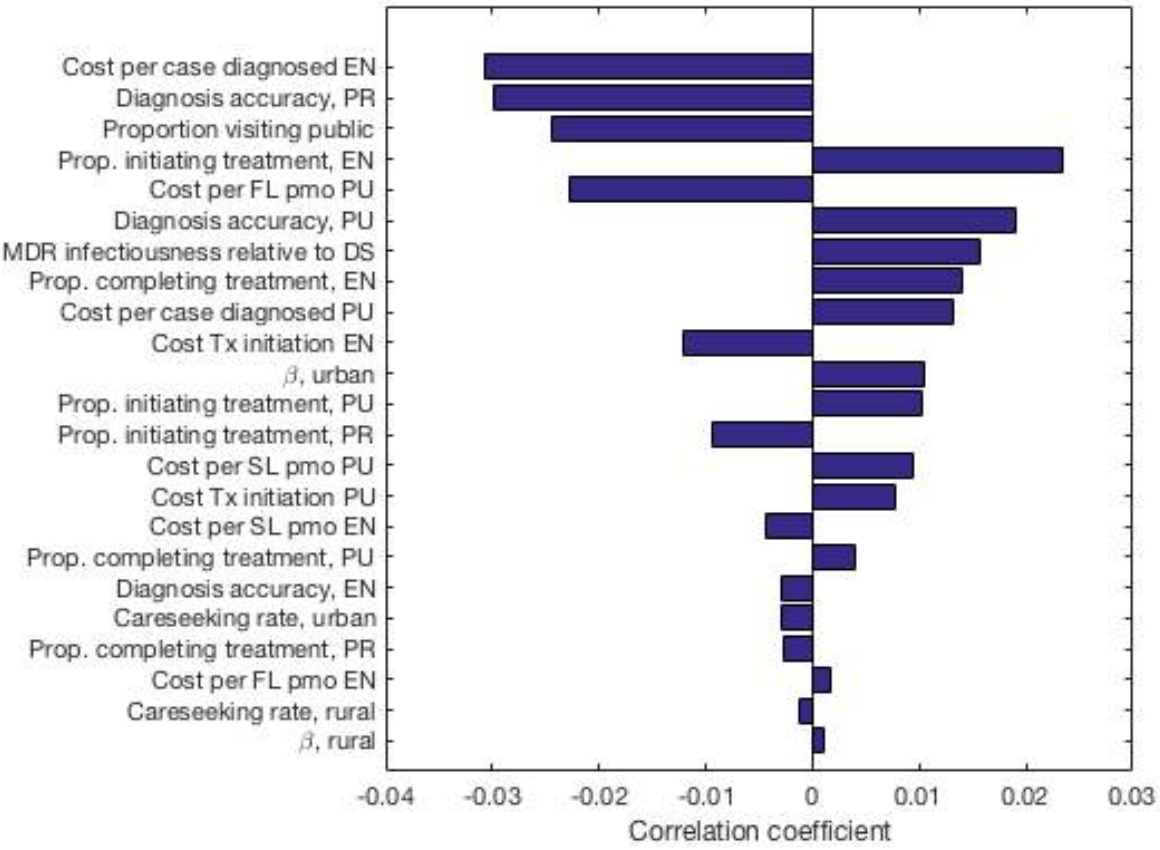

Figure 8. Multivariate sensitivity analysis of model outputs for Andhra Pradesh. Figure shows the partial rank correlation coefficient of model parameters against the projected BCR of intervention 1 (programmatic costs only), at a 5% discounting level. Parameters are shown in decreasing order of sensitivity, from top to bottom. The horizontal axis can be interpreted as the amount of variance in BCR attributable to a given parameter, once all other parameters are accounted for. Letters in capital denote the type of provider invoved: Public (PU); Private (PR); and engaged private (EN). Other abbrevations are as follows: 'FL', first-line treatment; 'SL', second-line treatment; 'pmo', patient-months of treatment; 'DS', drug-suscpetible TB; and β, the average number of infections per year per TB case.

3. Private sector engagement combined with case-finding

3.1 Background and evidence

Most current TB services are 'passive', in the sense that they rely on TB cases visiting an appropriate health facility or provider. However, these do not address the transmission that may occur during the initial period of infectivity, prior to a TB patient's first presentation for care. By actively searching for cases in the community, it should be possible to identify TB cases more quickly. Moreover, such measures could also identify TB cases that otherwise may not have presented for care (for example, because of lack of access). Such measures are referred to as 'case-finding'.

We note here that case-finding is one amongst several approaches that may give rise to the same effect: for example, the Government of India has recently announced a scheme for nutrition support amongst TB patients. These and other measures may help to generate demand for TB services, thus accelerating a patient's contact with the healthcare system. Further data on their actual effect on demand generation will be valuable in future analysis of their potential epidemiological impact.

The challenge with case-finding in the general population is that it requires intensive effort to identify cases. Even in a high-burden setting like India, the prevalence of bacteriologically positive TB amongst symptomatic individuals (e.g. with cough, fever and other symptoms suggestive of TB) is no more than 10% (Sachdeva, Raizada, Sreenivas, *et al.*, 2015). For this reason, planning around case-finding in India has concentrated on specific risk groups, where the prevalence is known to be disproportionately high (Revised National Tuberculosis Control Programme, 2017b).

The evidence for the epidemiological impact of case-finding is limited. The ZAMSTAR trial in South Africa, which combined case-finding with other interventions, did not detect a change in TB burden following the study (Ayles, Muyoyeta, Toit, *et al.*, 2013). However, it is not clear how generalisable these findings are, to settings such as India where HIV co-infection is considerably lower. A systematic review in 2012 concluded that the challenge was not 'evidence of absence', but rather 'absence of evidence', for the epidemiological impact of case-finding (Kranzer, Afnan-Holmes, Tomlin, *et al.*, 2013). Nonetheless, more recent work is

starting to fill the evidence gap for case-finding initiatives in the South-East Asia region. A recent study in Viet Nam demonstrated effective strategies for case-finding in that setting .

Moreover, indirect evidence from India points to a potentially important impact of case-finding on transmission. In a recent community prevalence survey in Gujarat state, amongst those found to have TB, 24% reported having symptoms, but had not visited a provider for those symptoms. Case-finding would address this substantial proportion of prevalent, infectious TB: as a result, it plays a major role in India's recent National Strategic Plan (Revised National Tuberculosis Control Programme, 2017b). RNTCP activities include urban slums, as well as risk groups such as those with an occupational hazard. For simplicity we concentrate here on urban slums, while recognizing that full implementation of RNTCP plans is likely to yield a still higher impact.

We also note that any case-finding activity should be considered as being in addition to private sector engagement. The latter addresses the need to fix basic TB services throughout the healthcare system, before moving onto more novel strategies such as sustained case-finding. That is, implementing a well-coordinated health system offering high-quality, basic TB services throughout, should be seen as a programmatic priority.

Overall, therefore, the quality of evidence is 'limited': there is indirect evidence suggesting that the epidemiological impact of case-finding is plausible, but as yet no direct evidence of epidemiological impact.

3.2 Description of intervention

We model the potential impact of systematic screening in urban slums in the state, assuming that these slums account for 10% of the population, but with a prevalence of TB that is three times that of the rest of the population. The epidemiological impact of these measures is to shorten the time to diagnosis and initiation on treatment, thus reducing opportunities for transmission.

In line with India's national strategic plan (Revised National Tuberculosis Control Programme, 2017b), we assume an intervention that screens the urban slum population three times a year. To allow for imperfect implementation (whether in participation, diagnosis or linkage to treatment), we assume that each single screening campaign detects 2/3 of the total TB burden

in the slums. Under this intervention, mobile diagnostic units are sent into communities to screen for symptoms suggestive of TB. All those with symptoms or X-rays suggestive of TB are asked to submit a sputum sample, for bacteriological testing with rapid molecular tests. All those confirmed to have TB are referred to the public sector for treatment. This intervention is supported, staffed and implemented by the national TB programme.

3.3 Calculation of Costs and Benefits

For programmatic costs, we incorporate the costs of running and staffing the mobile diagnostic unit, as well as the use of rapid molecular tests – together with X-ray - to diagnose TB. As well as the costs of the private sector engagement described in section 2, we include the costs of treatment for those diagnosed with TB, including both first- and second-line treatment. For patient costs, we incorporate those costs identified in intervention 1: as case-finding activities aim to identify patients in the community, we do not consider additional patient costs directly arising from this intervention. Once patients are diagnosed and initiated on treatment, they incur the same travel and time costs as identified in intervention 1. As in section 2.3, we calculate benefits in terms of averted TB deaths, and averted TB DALYs, translating these health gains into monetary terms using VSL multipliers.

Figure 9 shows model projections for the epidemiological impact of this intervention. By identifying TB cases early in their infectious period, this combined intervention scenario has a higher epidemiological impact than shown in Figure 5. Over the time horizon shown, the intervention would save an average of 3454 lives from TB per year, while averting an average of 16493 TB cases per year, corresponding respectively to reductions of 15.9% and 16.1% compared to baseline.

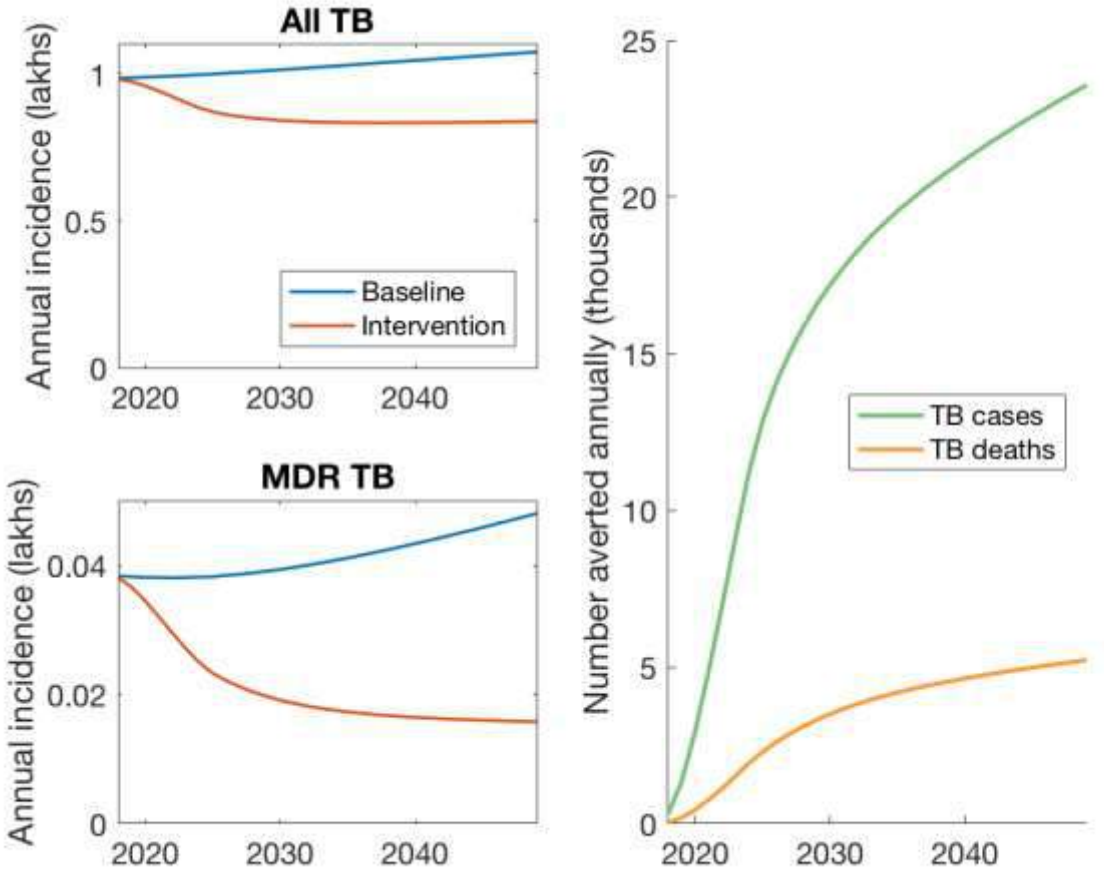

Figure 9. Projected epidemiological impact for private sector engagement + case finding. (A, B): Projections for incidence and TB mortality, comparing baseline (red curve) with intervention (blue curve) scenarios. (C) Annual numbers of TB cases and deaths averted (green and orange curves respectively).

Figure 10 shows the associated programmatic spending (shown with no discounting, for illustration). As with intervention 1 (Figure 6), incremental spending for this intervention is driven by programmatic investment, as well as by eventual cost reductions in the management of DR-TB. Figure 11 additionally illustrates these dynamics showing programme activities, illustrating once again the important cost implications of turning a growing DR-TB burden into a decreasing one.

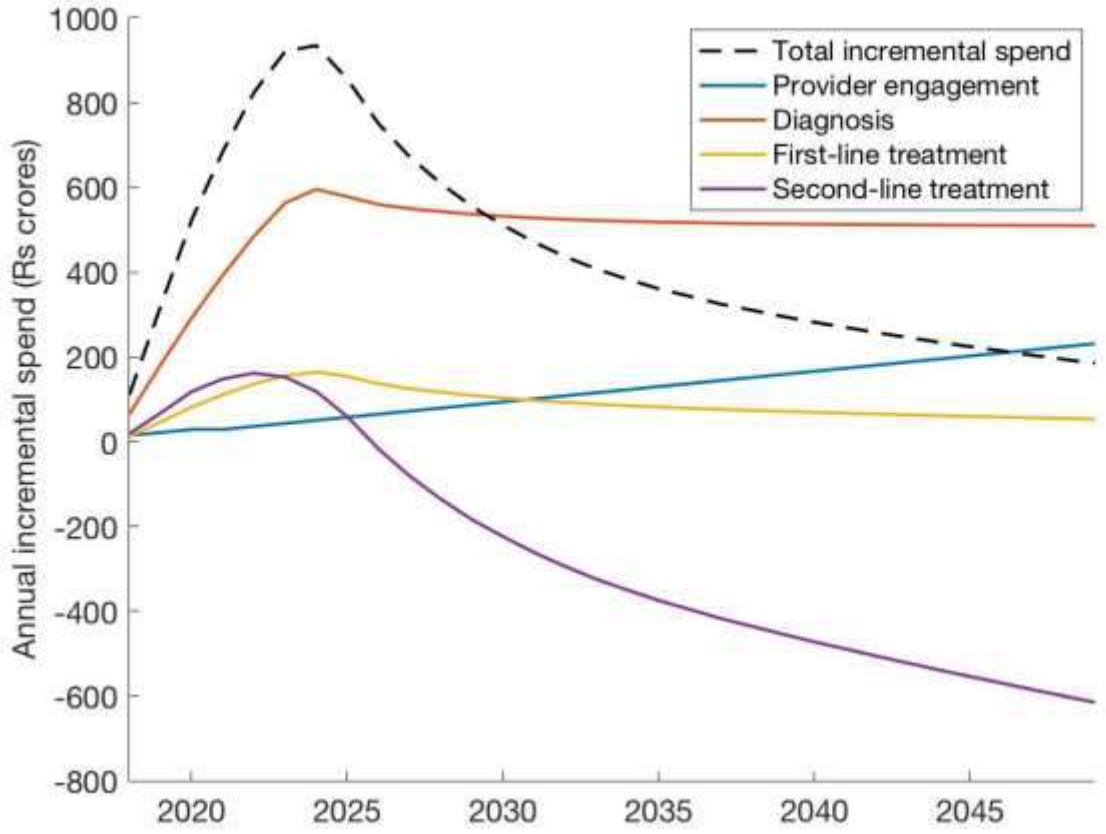

Figure 10. Projected annual programmatic spending for private sector engagement + case finding. Figure shows the total incremental spend, relative to the baseline scenario (dashed line), with break-up of individual cost components shown in solid lines. The figure does not display the cost of engaging private providers, as this accounts for ~1% of total incremental spending.

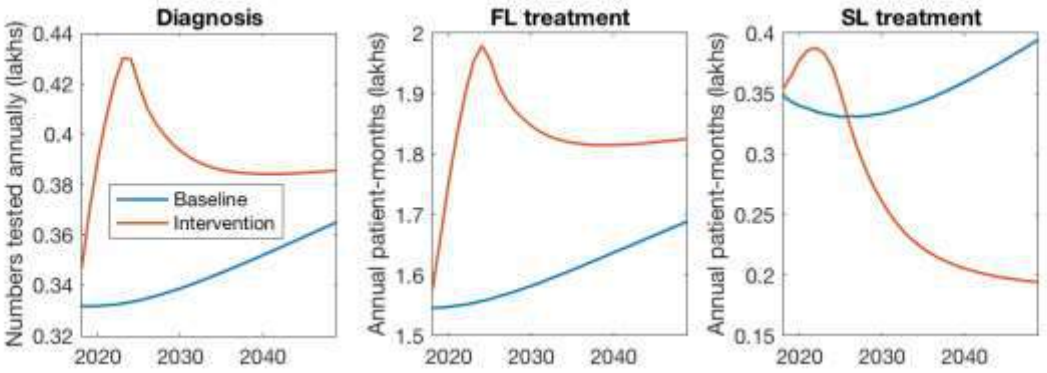

Figure 11. Annual volumes of programmatic activity (diagnosis and treatment), comparing intervention to baseline scenarios. Overall the intervention causes an increase in the amount of diagnostic tests conducted, as well as in the amount of first-line treatment: however, second-line treatment is ultimately reduced in comparison with baseline, owing to the impact of the intervention on DR-TB burden.

Overall, this intervention has a benefit-cost ratio (BCR) of 101.9 at 5% discounting (see summary table). We note that, because of the impact of the intervention on transmission, this BCR depends sensitively on the time horizon being adopted. Figure 12 illustrates how the BCR varies over different end-points for this time horizon, comparing with and without MDR costs. For example, taking a time horizon from 2018 to 2035 yields a BCR of roughly 50. This value rapidly increases for longer time horizons, as a result of the averted costs due to averted TB burden.

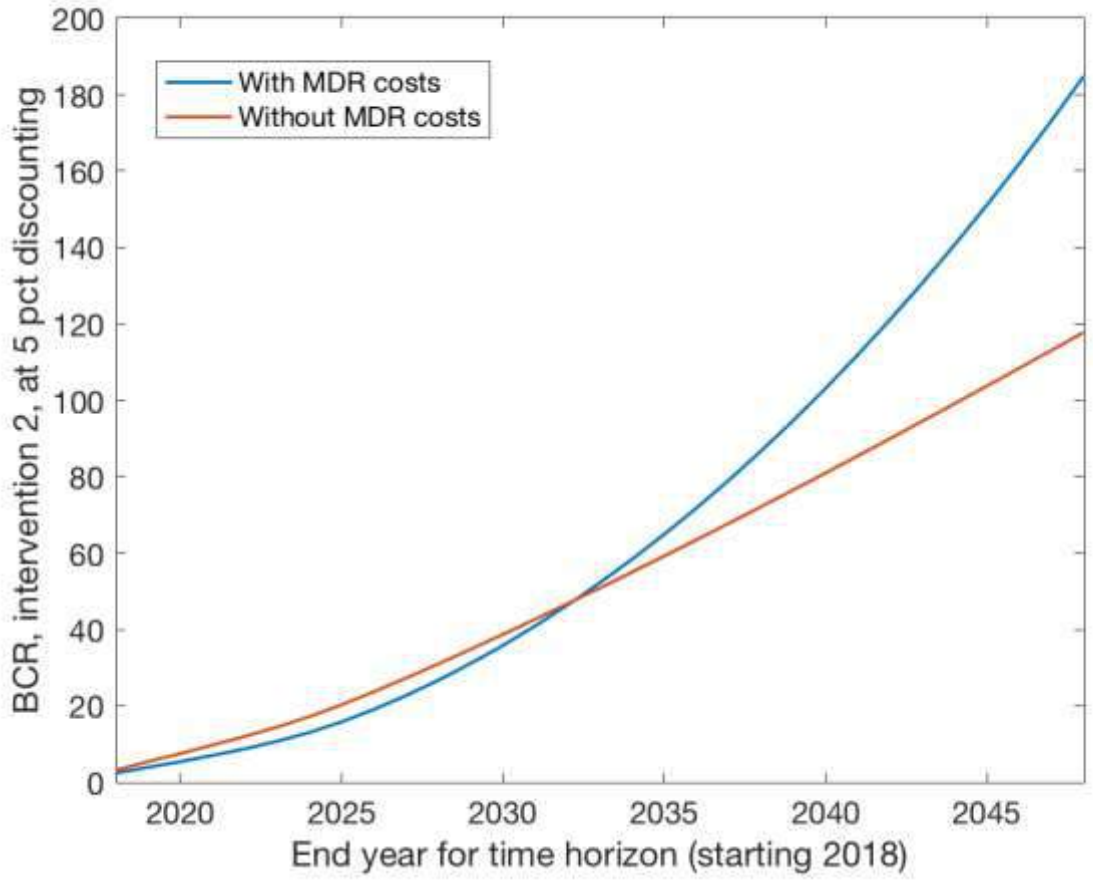

Figure 12. How the benefit-cost ratio (BCR) varies with the time-horizon taken for the analysis. Shown is the BCR for intervention 2, over a time horizon ending in the year shown on the *x*-axis. The blue curve shows BCR excluding MDR burden and costs; the red curve shows BCR including MDR benefits and costs.

3.4 Sensitivity Analysis

As described in section 2.6, we conduct a multivariate sensitivity analysis within a Bayesian calibration framework. Figure 6 shows resulting findings. The most sensitive parameter is the cost of diagnosis per case, through case-finding. By way of illustration, doubling and halving this cost leads to BCR values of 63.8 and 145.3 respectively, at 5% discounting. The next most important parameter relates to the cost of diagnosis per case amongst engaged private providers, a component reflecting the impact of private sector engagement.

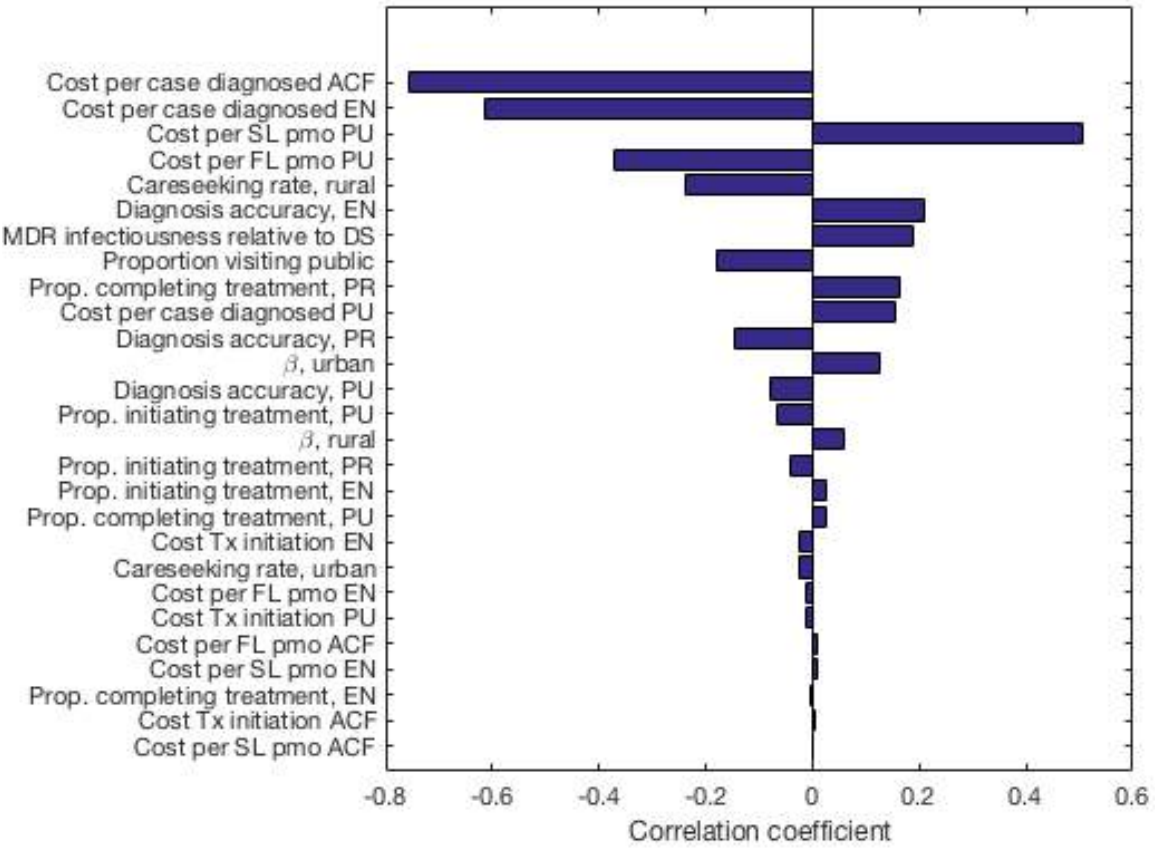

Figure 13. Multivariate sensitivity analysis of model outputs for Andhra Pradesh. As in figure 5, this plot shows the partial rank correlation coefficient of model parameters against the projected BCR of intervention 2 (using programmatic costs), at a 5% discounting level. Parameters are shown in decreasing order of sensitivity, from top to bottom. The horizontal axis can be interpreted as the amount of variance in BCR attributable to a given parameter, once all other parameters are accounted for. Letters in capital denote the type of provider invoved: Public (PU); Private (PR); engaged private (EN); and those identified through case-finding (ACF). Other abbrevations are as follows: 'FL', first-line treatment; 'SL', second-line treatment; 'pmo', patient-months of treatment; 'DS', drug-suscpetible TB; and β, the average number of infections per year per TB case.

4. Conclusion

Our findings illustrate that investment in TB services can offer substantial returns. Simply put, a fundamental reason for this potential impact is that TB is a lethal but curable disease: even in the absence of need new tools, such as better vaccines, there is much that could be achieved through optimizing the use of current, curative approaches. In particular, there is a need to fix current health systems so that patients have access to high-quality treatment wherever they seek care, as well as to accelerate the rate at which patients can be identified and initiated on therapy.

Here, we have examined private sector engagement and case-finding as interventions addressing these needs respectively. Importantly, these interventions already play an important role in India's recently launched National Strategic Plan (NSP) for TB elimination, and are already being implemented across the country. In this analysis we have aimed to 'look ahead', to address the potential benefits and costs of these existing plans, when taken to scale in Andhra Pradesh.

As with any modelling approach, there are important limitations to note. As discussed above, there are important data gaps relating to the cost and effectiveness of case-finding, in a South-Asian setting like India. However, this important gap is starting to be addressed: recent findings from Vietnam demonstrate effective approaches for case-finding (Fox, Nhung, Sy, *et al.*, 2018). There are also currently increasing efforts in case-finding across India. Ongoing and future such activities will, therefore, offer important data to inform these gaps.

Amongst other limitations, the model simplifies several aspects of TB natural history, averaging over smear status, age, and the differences between pulmonary and extrapulmonary TB. Where other data gaps exist, we have aimed to address these gaps by incorporating parameter uncertainty within a Bayesian framework (Figs. 8, 13). While offering a systematic approach, we note that such measures cannot be comprehensive.

Such limitations notwithstanding, our findings underscore the significant health gains that could arise through improving basic TB services. TB control in India has already seen massive investment in the national expansion of the country's DOTS programme in the 1990s. However, there is now a need for renewed efforts to maximise the impact of this programme. Now, in

the context of India's far-reaching national strategic plan for TB elimination, there are valuable opportunities emerging. Such renewed investment, and commitment to control TB, will have immense benefits for those bearing the burden of TB, both in India and worldwide.

Summary Table – programmatic costs only

Interventions	Discount	Benefit (INR cores)	Cost (INR crores)	BCR	Quality of Evidence
Private sector engagement	3%	89217	536.47	166.3	Medium
	5%	51598	460.06	112.2	
	8%	24598	374.02	65.8	
Private sector engagement + active case finding in urban slums	3%	145505	998.65	145.7	Limited
	5%	84187	825.93	101.9	
	8%	40162	645.01	62.3	

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Appendix: Modelling the potential impact of TB interventions in Andhra Pradesh

Model specification

Overview

We developed a dynamic, deterministic model of TB transmission, with governing equations given below. The model incorporates the acquisition and transmisson of drug-resistant; the differing quality of TB care in the public and private sectors; and the difference in burden between urban and rural TB. In doing so, the model also captures the implications of diagnostic delays and treatment outcomes, for overall transmission. For simplicity, the model ignores HIV/TB coinfection and age structure. The model does not distinguish pulmonary from other forms of TB, instead averaging the infectiousness of a TB case over these forms of TB. The model is illustrated schematically in Figure 1.

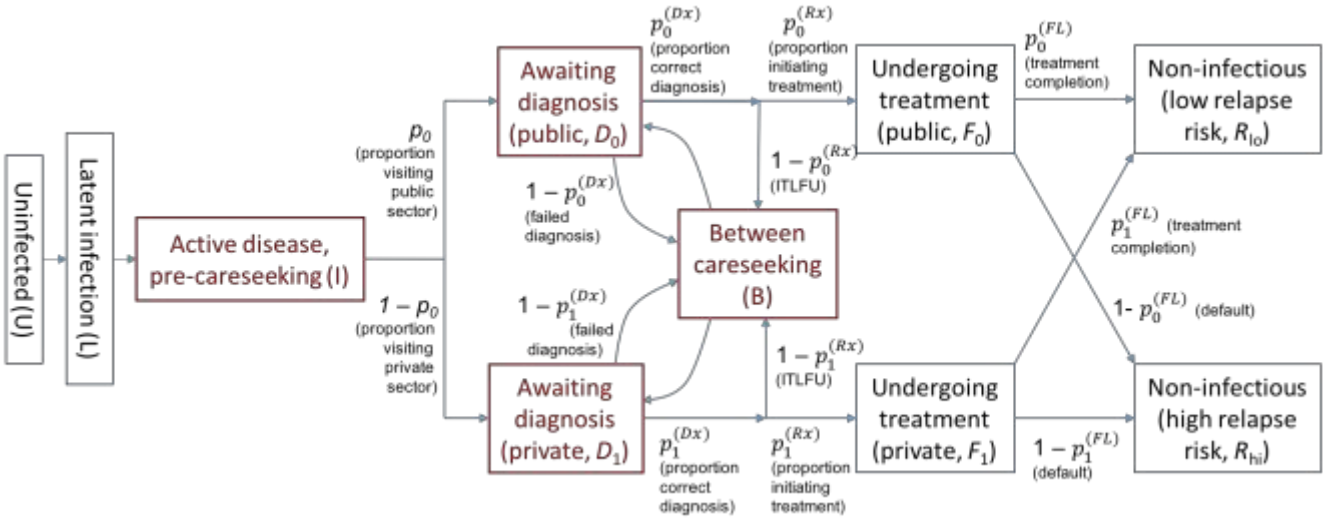

Figure 1. Overview of the model structure. Red boxes show states that are infectious, and thus contribute to the force-of-infection. Arrows show population 'flows' between different compartments: the purpose of interventions is to optimise these flows in such a way as to minimise the population in the red compartments. For conciseness, flows are labelled only with the proportions that move from one compartment to another: per-capita rates of transition are also required for the dynamical equations, and are additionally specified in table 1. This model structure is replicated by urban/rural status, and by DS/DR-TB. See appendix for the full list of equations.

Key structural elements are as follows:

Initial patient delay

We assume that, after patients develop symptoms, they undergo an initial delay before first seeking care (for example, as their symptoms develop in intensity). This delay is estimated, together with the infectiousness per case (see table 2), to yield incidence and prevalence relevant to a specific country setting. Note that, because patients in this compartment have not yet visited a provider, they can only be reached through casefinding strategies.

Public and private sectors

Upon seeking care, we assume that half of patients visit the public sector, while the remainder seek care in the private sector. Under ideal conditions (perfectly efficient healthcare systems), TB patients would be immediately diagnosed upon visiting a provider in any of the sectors, and then initiate and complete treatment appropriate to their drug sensitivity status. In reality,

there are leaks at each stage of this care cascade: we assume that such 'leaks' are greater in the private sector than in the public sector. We assume that any patients dropped from this cascade (because of failed diagnosis, initial loss to follow-up between diagnosis and treatment, or subsequent loss to follow-up or early treatment interruption) enter the compartment *B*. These patients are still infectious: they remain for an average of 1 month before seeking care again. Overall, therefore, the burden of cases in the *B* compartment is lowered by increasing the quality of diagnosis: this is achieved by private sector engagement (PSE, as described below). Quantities governing the TB care cascade in the public and private sectors are shown in table 1.

Drug resistance

We model the transmission of both drug-sensitive (DS) and drug-resistant (DR)-TB, treating these as two strains co-circulating in the population. The model captures the rate of primary acquisition of DR-TB from first-line treatment, as well as the transmission of DR-TB. We assume that a proportion *g* of cases identified in the public sector are subject to drug sensitivity testing (DST): at present this not routinely conducted, due to the expense and resources needed with current DST tools (e.g. culture, LPA): however, as described below, private sector engagement makes available the tools necessary for early DST, at the point of TB diagnosis. Those not identified as DR are assumed to undergo first-line treatment, and to remain infectious with DR-TB during this time: upon failing first-line treatment, a certain proportion are switched to second-line therapy.

Model calibration

Most parameters are drawn from the literature, or specified by assumption (see table 1). The remaining, 'free' parameters are: the average number of infections per TB case per year, specified separately for drug-susceptible and drug-resistant TB cases (β_{DS}, β_{MDR}) respectively, and the per-capita rate of initial careseeking (*d*), whose inverse represents the mean initial patient delay before first presenting for care. All parameters are stratified by urban and rural TB, giving 6 free parameters to calibrate. Parameter values are determined so that the model would yield epidemiological indicators consistent with those measured in TB burden surveys in India ('calibration'). In particular, for a given set of parameters we conduct the following steps: (i) Perturbing a disease-free state, simulate the model to endemic equilibrium in the absence of drug resistance or a public sector, (ii) Initiate the acquisition of

drug-resistance in 1980, consistent with the start of widespread use of rifampicin for TB treatment at around this time, (iii) Model the scale-up of public sector services in a linear fashion from 1997 to 2007, consistent with RNTCP expansion over this time, (iv) Simulate forward to 2016, to yield the model outputs for prevalence and force-of-infection in 2015. For given values of the free parameters, we thus find the simulated values for these calibration targets. We then perform the calibration by a simple least-squares approach, choosing parameter values to minimise the sum of squared differences between model outputs and the indicators in table 2. Resulting parameter estimates are shown in table 1.

Table 1. Parameters used in the dynamic transmission model. Footnotes: (a) Assumed parameter values in the absence of systematic evidence quantifying the care cascade in the private sector in India.

Parameter name		Symbol	Value	Note/Source
Natural history parameters				
Average infections per infectious TB case per year	Drug-susceptible TB	β	Calibrated to yield incidence and prevalence for given country setting	
	Drug-resistant TB	β_{MDR}		
Proportion of infections undergoing rapid progression		f_0	0.14	[8]
Rate of breakdown to active disease		g_0	0.001 y^{-1}	[9]
Per-capita relapse rate	High-risk (self-cures, treatment defaulters)	$\rho^{(hi)}$	0.02 yr^{-1}	[10]
	Low-risk (treatment completions)	$\rho^{(lo)}$	0.002 yr^{-1}	
Per-capita rate of self-cure, active TB		σ	0.166 y-1	Together corresponds to 50% spontaneous cure, 50% mortality in average of 3 years [11]
Per-capita mortality hazard rate, active TB		μ_{TB}	0.166 y-1	
Care cascade parameters, first-line				
Per-capita rate of first presentation to a provider following onset of symptoms		d	Governs the initial patient delay: calibrated together with β, β_{MDR} to yield incidence and prevalence	
Probability that a TB patient visits a provider of type *q*, per careseeking attempt		p_q	Calibrated for simulated treatment initiations to match reported notifications	
Per-capita rate of offering a diagnosis		h	52 y^{-1}	Assumption: corresponds to an average of 1 week to arrive at a diagnosis
Probability of successful diagnosis and treatment initiation with provider type *q*		u_q	Calculated using $u_q = p_q^{(Dx)} p_q^{(Tx)}$, for values of $p_q^{(Dx)}, p_q^{(Rx)}$ given below	
Per-capita rate of default from treatment from provider type *q*		δ_q	Calculated using $\delta_q = \tau^{(FL)} p_q^{(FL)} / (1 - p_q^{(FL)})$, for values of $\tau^{(FL)}$, $p_q^{(Dx)}$ given below	
Probability of correct TB diagnosis per visit to a provider	Public	$p_0^{(Dx)}$	0.83	[12]
	Private	$p_1^{(Dx)}$	0.7	Assumed (a)
Proportion of diagnosed cases initiating treatment	Public	$p_0^{(Rx)}$	0.88	[12]
	Private	$p_1^{(Rx)}$	0.7	Assumed (a)
Proportion completing first-line treatment	Public	$p_0^{(FL)}$	Drawn from WHO country reports [13]	
	Private	$p_1^{(FL)}$	0.6	Assumed (a)
Care cascade, second-line				

Probability of provider offering second-line testing at point of TB diagnosis (in absence of Xpert)	Public	v_0	0.2	From baseline data of GeneXpert demonstration study in India [14]
	Private	v_1	0.1	Assumption
Proportion of first-line treatment failures being switched to second-line treatment	Public	w_0	Calibrated for simulated, second-line treatment initiations to match reported RR/MDR notifications [13]	
	Private	w_1	0.1	Assumption
Proportion treatment success, second-line treatment	Public	$p_0^{(SL)}$	0.5	Taken from country reports [13]
	Private	$p_1^{(SL)}$	0.2	Assumption
Other care parameters				
Duration of first-line regimen		$\tau^{(FL)}$	2 y-1	Corresponds to a 6 month regimen [15]
Duration of second-line regimen		$\tau^{(SL)}$	0.5 y^{-1}	Corresponds to a 2 year regimen [15]
Rate of repeat care seeking for patients who have dropped out of care cascade		γ	12 y-1	Yields an average interval between careseeking episodes of 1 month [16]
Population structure				
Per-capita birth rate		b	Selected to yield projected population growth	
Per-capita 'background' mortality hazard		μ	1/66	Corresponding to a TB-free life expectancy of 66 years for India (World Bank)
Transmission coupling between urban and rural settings	c	0.3	Assumption	
Number of private doctors per 1,000 population	0.8		Drawn from ref.[17]. Note: data shows the total number of providers, which we take here as a proxy for the number of *private* providers – in reality a proportion will be in public practice. Our approach is conservative with respect to the cost of engaging with the private sector.	

Table 2. Epidemiological inputs used for model calibration

Indicator		Andhra Pradesh	Notes/source
Annual Risk of TB infection (ARTI), pct	Urban	1.3	Nationally representative infection surveys in India [18], adopting 'South' zone for AP
	Rural	0.7	
Prevalence per 100k	Urban	200	Pooled subnational prevalence surveys, taking national average for urban and rural TB (see table 1 in ref.[19], adjusted for proportion smear-positive)
	Rural	340	
MDR amongst incident cases (pct)		4	Consistent with national average [4]
Proportion population in urban settings		1/3	India Census data [20]

Table 3. Unit costs used in the model (compiled by Ross McLeod, eSys, for an earlier modelling exercise with WHO/SEARO)

Unit Cost	Value	Reference and Comments
Microscopy Diagnosis Program (X_1)	$3 per suspect tested	Sputum smear microscopy (two smears) of $3.00 from Little et al [21].
Culture + DST 1st Line Program (X_2)	$30 per suspect tested	Solid first-line DST estimated at $29.88 by Maheshwari et al (ref.[22], see Table A.1)
Screening X-ray Program (X_3)	$11 per suspect tested	From Vassal et al [23].
Treatment		
1st-line TB Treatment Program (X_4)	$10 per patient month	A first line budget estimate of $60 for first line drugs included in the Global Plan resource projections for India [24]; and expenditures in the baseline are estimated to be $70 per case. Over 6 months, the drugs component was $10 per month, and health systems/patient costs $23 per month. It is assumed $10 per month is borne by the national program.
20 month 2nd-line TB Treatment Program (X_5)	$90 per patient month	A budget estimate of $1,030 for second line drugs was included in the Global Plan resource projections for India [24], expenditures in the baseline were estimated to be $2,290 for second line in India. A lab support cost of $10 per month was also included. It is assumed $90 per month is borne by the national program.
Private Sector Engagement, PSE		
Cost of provider engagement (X_6)	$100 per private provider engaged	Average cost to recruit one provider, from BMGF pilots in Patna and Mumbai (unpublished data). Cost includes sensitisation events, followed by one-on-one provider visits to encourage providers to join the scheme.
Xpert MTB/RIF subsidy (X_7)	$15 per suspect	Includes $12 consumable, capital cost of 13% total cost from Vassal [23] and labour cost based on laboratory technician cost of 34 minutes.
Treatment support (X_8)	$11 per initiating patient	Menzies et al [25] included an incentive of $10.5 per patient per month, which included transport and administration allowance.
Free TB treatment (X_9)	See first- and second-line treatment costs, above	
Intensified case-finding, ICF		
Cost per suspect screened (X_{10})	$28	Menzies et al [25] assumed a cost of $23 per suspect for India. This accounted for incentives, all Xpert, x-ray and 3 visits. It is assumed that all suspects get verbal assessment, 30% get smear and 10% X-ray. A labor cost of $5 per suspect is included for all countries using budget expenditure from Cambodia.

Appendix: Governing equations

The model is governed by the following equations (see table S1 for definitions of state variables, and table S2 for parameter definitions and sources). First, for the states prior to a TB patient's first visit to a provider, we have:

$$\begin{aligned}
\dot{U}_r &= b_r - U_r \sum_s \lambda_{rs} - \mu U_r \\
\dot{L_{rs}} &= (1-f_r)\lambda_s \left[U + \sum_s (L_{rs} + R_{rs})\right] - (g_r + \mu) L_{rs} \\
\dot{I}_{rs} &= f_r \lambda_s \left[U + \sum_s (L_{rs} + R_{rs})\right] + g_r L_{rs} + \rho^{(hi)} R_{rs}^{(hi)} + \rho^{(lo)} R_{rs}^{(lo)} - (d + \sigma + \mu_{TB}) I_{rs}
\end{aligned}$$

where dots represent time derivatives; subscripts *r* denote the setting (denoting 'urban' and 'rural' populations); and *s* denotes the infecting strain (denoting drug-susceptible and drug resistant TB). Next, we assume that a proportion p_q of patient visits are to a provider of type *q* (denoting public and private providers). We have, for those awaiting diagnosis with provider type *q*:

$$\dot{D}_{qrs} = dp_q I_{rs} - (h + \sigma + \mu_{TB}) D_{qrs}$$

We assume that a proportion u_q of TB patients visiting provider type *q* successfully initiate TB treatment (the remainder constituting missed diagnosis as well as initial loss to followup, covered below). For those initiating first-line treatment, it is convenient to specify equations separately by drug-susceptible (*s* = 0) and drug-resistant (*s* = 1) status. Thus we have, for drug-susceptible TB:

$$\dot{F}_{qr,0} = hu_q D_{qr,0} - \left(\tau^{(FL)} + \delta_q + \alpha + \sigma + \mu\right) F_{qr,0}$$

where α represents the per-capita hazard of acquisition of multi-drug-resistance while on first-line TB treatment, only applicable to drug-sensitive TB. For drug-resistant TB, we have:

$$\dot{F}_{qr,1} = hu_q(1 - v_q)D_{qr,1} + \alpha F_{qr,0} - \left(\tau^{(FL)} + \delta_q + \sigma + \mu_{TB}\right)F_{qr,1}$$

where v_q is the proportion of TB patients presenting to a provider of type q who undergo drug sensitivity testing at the point of TB diagnosis.

For second-line treatment (only for DR-TB), we have:

$$\dot{S}_{qr,1} = hv_q D_{qr,1} + \tau^{(FL)} w_q F_{qr,1} - \left(\tau^{(SL)} + \mu\right)S_{qr,1}$$

where w_q represents the proportion of DR-TB patients with provider type q who are switched to second-line treatment after failing first-line treatment.

Next, the compartment B captures those patients who have dropped out of the care cascade and remain infectious, whether by failed diagnosis, loss to follow up, subsequent default, or failed treatment. We have, for B:

$$\dot{B}_{rs} = \sum_q \left[h(1 - u_q)D_{qrs} + \tau^{(FL)} F_{qrs} s + \left(1 - p_q^{(SL)}\right)\tau^{(SL)} S_{qrs}\right] - (\gamma + \sigma + \mu_{TB})B_{rs}$$

Those who have recovered from disease, whether from treatment or cure, have a certain risk of relapse, thought to be greatest in the first 2-5 years after recovery. Within this period we classify those who have completed curative treatment as 'low-relapse-risk' individuals ($R^{(lo)}$), and those who have either self-cured or defaulted from treatment as 'high-relapse-risk' individuals ($R^{(hi)}$), drawing from the literature for the risk of relapse amongst both. We have:

$$\dot{R}_{rs}^{(hi)} = \sum_{q} \left[\delta_q F_{qrs} + \sigma D_{qrs}\right] + \sigma(I_{rs} + B_{rs}) - \left(\mu + \rho^{(hi)} + \eta\right) R_{rs}^{(hi)}$$

$$\dot{R}_{rs}^{(lo)} = \sum_{q} \left[\tau^{(FL)} F_{qrs}(1 - s) + \tau^{(SL)} p_q^{(SL)} S_{qrs}\right] + \eta R_{rs}^{(hi)} - \left(\mu + \rho^{(lo)}\right) R_{rs}^{(lo)}$$

where the term $(1 - s)$ acts as a strain-dependent indicator function, taking value 1 when $s = 0$ (i.e. for DS-TB) and value 0 when $s = 1$ (i.e. for DR-TB). The term η denotes the rate at which high-risk individuals 'stabilise' in their relapse risk, over time.

Finally, for the forces-of-infection λ_{rs} for setting *r* and strain *s*, we have:

$$\lambda_{rs} = \beta_{rs}(I_{rs} + B_{rs} + D_{rs}) + c\beta_{(1-r),s}[I_{(1-r),s} + B_{(1-r),s} + D_{(1-r),s}],$$

where *c* denotes the transmission coupling between urban and rural settings (with, for example, *c* = 0 representing the artificial – but illustrative – case of urban and rural settings being fully isolated).

Table A1. List of state variables used in the model. Here, all 'proportions' are of the total population being modelled.

Symbol	Meaning
q	Indicator variable for provider type: q = 0, 1, 2 respectively for public providers, private providers and 'engaged' private providers, respectively
r	Indicator variable for setting: r = 0, 1 respectively for urban and rural settings
s	Indicator variable for strain: s = 0, 1 respectively for DS- and DR-TB
$\boldsymbol{U_r}$	Proportion uninfected in risk group r
$\boldsymbol{L_{rs}}$	Proportion in group r having *latent infection* with strain s
$\boldsymbol{I_{rs}}$	Proportion in group r having *active disease* with strain s, that has not yet presented for care
$\boldsymbol{D_{qrs}}$	Proportion in group r awaiting diagnosis with provider type q
$\boldsymbol{F_{qrs}}$	Proportion in group r undergoing *first-line TB treatment* with provider type q
$\boldsymbol{S_{qrs}}$	Proportion in group r undergoing *second-line TB treatment* with provider type q
$\boldsymbol{B_{rs}}$	Proportion who have temporarily dropped out of care cascade
$\boldsymbol{R_{rs}^{(hi)}}$	Proportion self-cured or defaulted from treatment, having a high relapse risk
$\boldsymbol{R_{rs}^{(lo)}}$	Proportion cured after having completed appropriate treatment

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Sector Expert Review

Andhra Pradesh Priorities
An India Consensus Prioritization Project

Dr. Raghuram Rao
DADG (TB)
Dte.General of Health services
Ministry of Health & Family Welfare,GOI

This report is a useful step to understand the cost benefit analysis for specific interventions in different States. However, it needs to be interpreted with caution considering the presence of private sector and quality assured diagnosis / treatment, the socio economic profile of the population, the health seeking behavior, the capacity of the public health system for intensified case finding activities in urban slums / vulnerable population, etc.

Even after twenty five years of being declared a global health emergency, TB continues to be a major public health challenge, particularly in India. According to the Global TB Report 2017, out of the global 104 lakh new cases per year, 28 lakh are from India, i.e., we account for one-fourth of the global burden of tuberculosis. Tuberculosis is one of the leading causes of deaths worldwide, with India accounting for 4.2 lakhs out of the 17 lakhs deaths occurring globally due to TB. In India, TB causes more deaths than any other infectious disease, including both HIV and Malaria.

Resistance to conventionally used anti-TB drugs has also emerged as an enormous public health challenge with an estimated 1,47,000 cases of DR-TB occurring annually out of the notified cases of pulmonary TB in India. India currently has the highest burden of both TB and DR TB and second highest of HIV associated TB, according to estimates reported in Global TB Report 2017. Based on the first National Drug Resistance Survey (2014-16) approximately 3% among new TB cases and 12 - 17% among previously-treated TB cases have DR-TB. An estimated 87,000 HIV associated TB occurred in 2015 and 12,000 estimated number of patients died among them.

To fight this massive public health problem, the Government of India (GoI) launched the National TB Programme in 1962. After pilot testing recommendations from an expert committee, a full-fledged Revised National TB Control Programme was started in 1997 using the Directly Observed Treatment Short-course chemotherapy (DOTS), which was fully established by 2006. In 2007, GoI introduced the Programmatic Management of Drug Resistant TB (PMDT) to combat drug resistance and achieved full geographical coverage by 2013.

The program has come a long way since then and has undergone major changes over the past few years. Much effort is being made to make the program more patient-centric and provide comprehensive treatment care and support.

- The Technical and Operational Guidelines were updated in 2016 which gives a comprehensive picture for case finding, diagnosis, treatment and care for Tuberculosis under RNTCP.
- Daily regimen through fixed dose drug combinations (FDCs) to reduce the pill burden, enhance patient autonomy and adherence without compromising on the effectiveness of treatment.
- To enhance adherence to treatment, the TB program has adopted digital technology in the form of ICT enabled patient centric adherence support called 99DOTS. It is an innovation that seeks to address issues of adherence by using basic mobile phones and augmented packaging for medication. This has further increased patients' control over their treatment and has advanced patient rights and autonomy.
- To improve case finding and 'Reaching the Unreached', the country has undertaken Active Case Finding (ACF) over three phases in 378 districts, wherein high risk and vulnerable populations were screened for TB. Through this effort, more than 25,000 additional TB patients were diagnosed.
- Provision of incentives for nutrition for all TB patients through Direct Beneficiary Transfer (DBT).
- Provision of incentives to private practitioners as well as chemists to notify tuberculosis patients to the RNTCP.
- Interdepartmental linkages through 'single window care' for TB-HIV co-ordination is in place, with all diagnosed TB patients being referred for HIV testing and all People Living with HIV/AIDS (PLHIV) being screened for tuberculosis.
- Cross referral and Linkages with the National Tobacco Control Programme (NTCP) and National Programme for prevention of Cancer, Diabetes, Cardiovascular disease and Stroke (NPCDCS) have been established.

- Public private linkages are being enhanced which may help us to extend our diagnostic, treatment and patient support services even to patients seeking care in the private sector.
- To ensure early case detection and initiation of treatment for drug resistant TB, 1135 CBNAAT machines have been put in place. These rapid molecular diagnostics have revolutionized the programmatic landscape and have enabled the Revised National TB Control Programme to decentralize Universal Drug Susceptibility (U-DST) testing services.
- The PMDT Guidelines have been revised to adopt a new and more robust diagnostic algorithm that will help in early detection and treatment initiation of DR-TB.
- To aid early detection of drug resistant TB, Universal DST (U-DST) is being implemented across India, wherein all diagnosed TB patients are being offered CBNAAT testing to detect Rifampicin resistance, at the very outset of their treatment.
- To strengthen monitoring the program has introduced web based case management system called “Nikshay” through which data access and analysis have both been made easier. Nikshay Aushadhi has been introduced to strengthen the procurement and supply chain.

These new adoptions are crucial to tackle the crisis of tuberculosis and help attain the ambitious goal to End TB, as envisaged in the National Strategic Plan (2017-2025).

As a new state, Andhra Pradesh faces a bright future, but it is still experiencing many acute social and economic development challenges. It has made great strides in creating a positive environment for business, and was recently ranked 2nd in India for ease of doing business. Yet, progress needs to be much faster if it is to achieve its ambitions of becoming the leading state in India in terms of social development and economic growth. With limited resources and time, it is crucial that focus is informed by what will do the most good for each rupee spent. The Andhra Pradesh Priorities project as part of the larger India Consensus – a partnership between Tata Trusts and the Copenhagen Consensus Center, will work with stakeholders across the state to identify, analyze, rank and disseminate the best solutions for the state. We will engage people and institutions from all parts of society, through newspapers, radio and TV, along with NGOs, decision makers, sector experts and businesses to propose the most relevant solutions to these challenges. We will commission some of the best economists in India, Andhra Pradesh, and the world to calculate the social, environmental and economic costs and benefits of these proposals

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