Advancing Mathematical Models of *Mycobacterium tuberculosis* Transmission to Support Vaccine Introduction

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Declaration of Authorship

I, Chathika Krishan Weerasuriya, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Chathika Weerasuriya
15 December 2021

Abstract

Introduction Tuberculosis causes substantial morbidity and mortality, with 10 million new cases and 1.5 million deaths per year worldwide. We may acquire a new tuberculosis prevention tool in the foreseeable future as the anti-tuberculosis vaccine candidate M72/AS01$_E$ is poised to enter phase III trials. If phase III trials demonstrate efficacy, we must ensure that models and model evidence are rapidly and reliably available to support decision making around whether to introduce the new vaccine.

Prior mathematical models of tuberculosis vaccination have aimed to inform vaccine *development*, for example, by investigating the impact of varying vaccine durability and efficacy, or the host-infection status required for vaccine efficacy in low and high burden settings. These studies have identified vaccine characteristics most likely to achieve global tuberculosis control goals, providing core evidence for the World Health Organization (WHO) Preferred Product Characteristics for New Tuberculosis Vaccines. Collectively, this evidence has provided direction for vaccine research and development efforts, including the identification of indications and clinical trial endpoints. However, work to substantiate vaccine *introduction*, bridging the gap between development and broad-scale adoption, is limited.

I address two aims in this thesis, corresponding to two research needs that we should meet to advance models to support vaccine introduction:

1. Estimate the epidemiologic impact, cost-effectiveness and affordability of new tuberculosis vaccines in India and China, incorporating drug-resistance transmission and acquisition. This aim reflects the need to adapt models to include locally important features of, and uncertainty in, tuberculosis epidemiology and health systems.

2. Describe how different assumptions of adapting social contact structures to long-term demographic trends in India—as a country undergoing the demographic transition—might affect vaccine impact estimates. This aim reflects the need to establish whether vaccine impact estimates are robust to structural decisions in model design.

Methods I constructed an age-, drug-resistance, and treatment-history stratified difference equation-based dynamic transmission model of *Mycobacterium tuberculosis*, set in India and China, calibrated to epidemiologic data over 2000–2017. To this, I attached a

country-specific cost model of programmatic tuberculosis control—including multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) diagnosis and treatment—and vaccine delivery. The calibrated model was used to estimate the epidemiologic impact and cost-effectiveness of a prevention-of-disease vaccine modelled on M72/AS01$_E$, with 50% efficacy, conferring 10-years of protection over 2027–2050.

To assess the affordability of vaccine deployment, I estimated the total cost of untargeted mass vaccination of all adults and adolescents (ages ≥ 10y) compared to 10-year wide age bands in India and China, while valuing the health benefits of vaccination at cost-effectiveness thresholds based on country-specific healthcare opportunity costs.

Finally, I developed a second transmission model of tuberculosis to investigate whether adapting age-specific social contact patterns to evolving demography—using multiple update methods, each preserving different properties of social mixing matrices—affected model-based estimates of vaccine impact in an India-like scenario.

Results Vaccination was found to substantially reduce future MDR/RR-TB in China and India, reducing incidence rate by 73% (uncertainty interval: 66–76) and 72% (UI: 65–77) in 2050, with a similar impact on drug-susceptible tuberculosis. In both countries, vaccination was found likely to be cost-effective at country-specific willingness to pay thresholds.

Untargeted yet cost-effective large scale adult mass vaccination was estimated to require $21 billion (uncertainty interval: 16–27) and $15 billion (UI: 12–29) by 2050 in India and China, respectively. In India and China, targeting 50–59-year-olds and 60–69-year-olds, respectively, was found to avert the most disability-adjusted life-years per vaccine course delivered. Targeted yet cost-effective mass vaccination of these age groups was estimated to require $5 billion (UI: 4–6) and $6 billion (UI: 4–7) in India and China, respectively.

Vaccine epidemiologic impact estimates remained robust to different methods of updating age-specific social contact structures to match secular trends in demography. Across a range of methods that spanned no updates to match demography, to methods that preserved both contact reciprocity (balanced total contacts between age groups) and assortativity (inherent preference for contact by age-group with another), the maximum difference in vaccine-mediated incidence rate reduction in 2050 was found to be 7%.

Conclusions In this thesis, I develop mathematical models that provide evidence to support decision making around tuberculosis vaccine introduction. This thesis makes three unique contributions to the tuberculosis vaccine modelling literature: estimating the impact of new tuberculosis vaccines on MDR/RR-TB, incorporating both direct and transmission effects of a vaccine, estimating the total maximum cost of large scale adult tuberculosis vaccination at country-specific healthcare opportunity cost-based thresholds, and investigating whether structural assumptions around how social contact patterns change with evolving demography affect estimates of vaccine impact.

Vaccines are predicted to substantially and cost-effectively reduce the future burden of drug-resistant (and drug-susceptible) tuberculosis in India and China and could be an integral tool in MDR/RR-TB control efforts. The expected total cost of cost-effective untargeted mass adult vaccination for tuberculosis is likely to be substantial at current willingness-to-pay thresholds, but age-targeting may improve affordability. Funding for tuberculosis vaccines will require a careful situating within that for wider tuberculosis control efforts. Vaccine impact estimates may be reasonably robust to different methods of updating social contact patterns to evolving demography. This finding improves confidence in existing estimates of vaccine impact from long time-horizon models and increases the utility of model results in vaccine decision making. Overall, this thesis adds evidence in favour of tuberculosis vaccine introduction, contributing to the initial knowledge base that decision-makers may build on to address further context-specific questions regarding vaccine feasibility and implementation.

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Finally, thank you to my family: my mother, my father, my brother Iranga, and my beloved wife Kim. Your unwavering faith, unlimited patience, constant support, and steady encouragement made this all possible and worthwhile. This thesis is dedicated to you.

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Abbreviations

AIDS Acquired Immune Deficiency Syndrome

BCG bacillus Calmette-Guérin

CCDC Chinese Centres for Disease Control

CEA cost-effectiveness analysis

CET cost-effectiveness threshold

DALY disability adjusted life year

DOTS directly observed treatment, short-course chemotherapy

DST drug susceptibility testing

DSTB drug susceptible TB

GDP gross domestic product

HCOC healthcare opportunity cost

HIV Human Immunodeficiency Virus

ICER incremental cost-effectiveness ratio

LMIC low- and middle-income country

LTBI latent tuberculosis infection

MDR/RR-TB multidrug-resistant or rifampicin-resistant TB

MDR-TB multidrug-resistant TB

mITT modified Intention to Treat

Mtb *Mycobacterium tuberculosis*

NICE National Institute for Health and Care Excellence

NTEP National Tuberculosis Elimination Programme

NTP national tuberculosis programme

P&PI pre- and post-infection efficacy

POD prevention of disease

PP Per-Protocol

PRI pre-infection efficacy

PSI post-infection efficacy

RNTCP Revised National Tuberculosis Control Programme

RR-TB rifampicin-resistant tuberculosis

TB Tuberculosis

TPT tuberculosis preventive therapy

WHO World Health Organization

XDR-TB extensively drug-resistant TB

1 Overview

In this chapter, I briefly introduce the research context of this thesis, its rationale, general aims, and specific objectives.

To aid the reader in navigating this work, I then outline the thesis structure, summarizing the forthcoming chapters and how they relate to the stated aims of the work.

1.1 Introduction

Tuberculosis (TB) remains a major source of global infectious disease morbidity and mortality, leading to approximately 10 million new cases and 1.5 million deaths each year[1]. The causative agent, *Mycobacterium tuberculosis* (*Mtb*), infects around one quarter of the global population and it is estimated that *Mtb* infection carries around a 10% lifetime risk of disease[2]. TB control and elimination are therefore ongoing global health priorities. Global aspirations for TB control are embodied in the World Health Organization (WHO) End TB Strategy[3], which sets targets for the global community to reduce TB incidence and mortality rates by 90% and 95%, respectively, by 2035 (compared to 2015)[3].

The mainstay of TB control is a four drug regimen first introduced in the 1980s[4] that remains successful in 85% of treated cases under optimal conditions. In addition, a TB vaccine—bacillus Calmette-Guérin (BCG)—has existed since 1921[5,6]. Approximately 100 million doses BCG are administered to children annually, which confer >70% protection against severe TB, TB meningitis and miliary TB in childhood[7]. However, the estimated efficacy against pulmonary TB in adults is highly variable, ranging 0–80%[8–11].

Despite the availability of drug treatment and BCG, we are not on course to meet global TB control targets, as TB incidence is declining globally by only 1.5–2% per year[12]. Even with optimal use of existing technology, global TB control targets are unachievable. New tools, including new vaccines and vaccine strategies, are required.

We may have a new candidate for such a vaccine. In a recent phase IIb trial, subunit vaccine M72/AS01$_E$ containing mycobacterial antigens Mtb39A and Mtb32A and the AS01$_E$ adjuvant[13] was found to have 50% efficacy against TB disease[14]. M72/AS01$_E$ is expected to progress to a phase III trial, raising the prospect of a new efficacious TB vaccine in the foreseeable future.

However, there is a substantial gap between developing a safe and effective vaccine and using it as an effective and affordable tool for TB elimination. When deciding whether to adopt and roll out a new vaccine, decision-makers must consider many factors, including the expected impact of a new vaccine, resource requirements for vaccine introduction and delivery, optimal vaccine implementation strategy, and local public health priorities. Additionally, some factors, for example, future changes to programmatic (non-vaccine) TB control, may be completely or partially unknown (or unknowable).

We must urgently develop modelling tools to address these issues, as our focus shifts from questions around vaccine development to those around vaccine adoption.

1.2 Rationale for this Thesis

Piot et al[15] describe four 'valleys of death' that a prospective vaccine must traverse in its progression from preclinical concept to broadly accepted public health intervention. Each valley could prevent the progression of a vaccine candidate to sustained implementation. The first 'valley of death' represents the transition from discovery to early clinical development, testing for clinical proof-of-concept and safety. The second represents the transition from early clinical development to large efficacy trials and licensure; this is most often the expensive and high-risk phase of development. The third 'valley' occurs between licensure and wide adoption. Adoption requires that country-specific decision-makers decide the new vaccine is suitable for their respective setting, given the health system and epidemiologic context, leading to a policy recommendation for its use. This stage also requires that implementation capacity is readily available to deploy the vaccine as recommended. The final 'valley' represents the challenges involved in maintaining a sustained vaccination effort, including the sustainability of supply and demand, and sociopolitical acceptance of immunisation.

Prior mathematical models of tuberculosis vaccination have aimed to inform vaccine *development*—i.e., the challenges of the first and second aforementioned 'valleys'. For example, population-level models have investigated the impact of varying vaccine durability and efficacy[16], or the host-infection status required for vaccine efficacy in low[17] and high[17,18] burden settings; these studies have identified vaccine characteristics most likely to achieve global tuberculosis control goals, providing core evidence for the WHO Preferred Product Characteristics for New Tuberculosis Vaccines[19]. At the within-host level, the emergent discipline of immunodynamics and immunostimulation[20] aims to apply established pharmacokinetics and pharmacodynamics methods to vaccine dose finding. Collectively, this evidence provides direction for vaccine research and development efforts, including the identification of indications and clinical trial endpoints.

However, modelling studies that investigate the third 'valley'—the anticipated gap between potential licensure and introduction—have been limited, in part due to a lack of candidates in or approaching phase III. While vaccine clinical trials can establish individual-level

safety and efficacy, they cannot account for epidemic dynamics within populations, nor predict second-order phenomena such as drug resistance. These broader or distal effects are important considerations in vaccine introduction and can be readily approximated by mathematical models; however, to do so accurately, we must adapt models to local epidemiology and priorities.

One key priority is multidrug-resistant TB (MDR-TB) control in India and China. In 2019, India accounted for 26% of all global TB burden and 27% of all multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB)[1]. China accounted for 8.4% of all global TB and 14% of MDR/RR-TB[1].

Although we assume a priori that a new TB vaccine will reduce MDR/RR-TB burden in India and China, we lack quantitative estimates of this effect. Further, we have no evidence to characterise how planned scale-up of programmatic (non-vaccine) TB management—including for MDR-TB—by national tuberculosis programmes (NTPs) might affect vaccine impact. As MDR-TB is rare at the population level, vaccine trials powered to directly detect reductions in MDR-TB incidence are unlikely. Taken together, there is a need for dynamic TB vaccine models that explicitly model MDR-TB acquisition and transmission that can estimate vaccine impact on MDR-TB burden **(Research Gap 1)**.

It is unknown how the cost-effectiveness of potential TB vaccines might be impacted by combined uncertainties in (i) MDR-TB epidemic dynamics; (ii) TB management costs, new vaccine costs, and vaccine characteristics; and (iii) changes (MDR-)TB programmatic management. Further, the impact of heterogeneous willingness to pay thresholds on the resulting price and, therefore, risk for developers and purchasers are also unknown. These gaps identify a need for economic evaluation of new TB vaccines that integrates these sources of uncertainty **(Research Gap 2)**.

Before adopting TB vaccines, decision makers in India and China must assess whether vaccination programmes will be affordable. Affordability will reflect both the willingness-to-pay for unit health benefit by purchasers (e.g. countries) and the total scale and strategy of implementation. To date, we can estimate how much vaccine programmes may cost at given (hypothetical) vaccine prices. However, vaccine prices are not necessarily fixed and suppliers and health systems may negotiate prices specific to particular contexts. To inform these pricing strategies, decision makers must know the expected costs of TB vaccine programmes whose health benefits are valued at prevailing cost-effectiveness thresholds. **(Research Gap 3)**.

Finally, decision-makers require that model evidence is robust. We can improve the reliability of modelling evidence by investigating whether model-based conclusions are sensitive to structural choices that we make during model construction. A recent structural development in TB vaccine models is the implementation of inter-age-group social contact (mixing) matrices, which aim to better capture age-specific burden and transmission patterns. These matrices assume that the model has a specific demographic composition. However, demography can vary substantially over the long time horizons

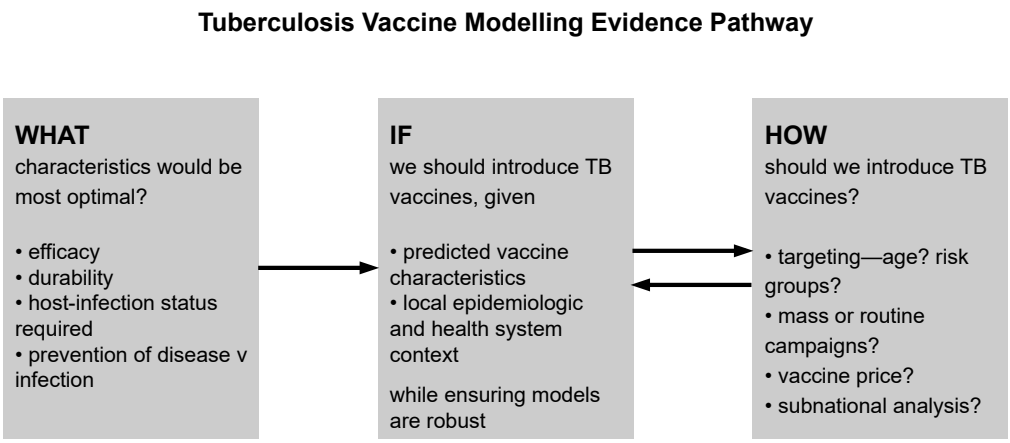

Figure 1.1: TB Vaccine Modelling Evidence Pathway

of TB vaccine models. Long time horizons are necessary in vaccine models to adequately capture vaccine impact, which lags behind delivery as dynamic effects propagate through the population. This lag is especially long—years to decades—for TB vaccines as TB latency introduces a gap between infection and disease. Over these timescales, model demography may deviate substantially from that assumed by model contact matrices. Any resulting error may be amplified over time and may propagate through the dynamic effects of the vaccine. To date, there has not been any systematic study of if—and how—adapting contact structures to match changing demography might affect estimates of vaccine impact **(Research Gap 4)**.

This thesis aims to address the research gaps above and contribute to the wider modelling literature that supports TB vaccine adoption.

Figure 1.1 shows a schematic of the TB vaccine decision-making pathway and the points at which mathematical modelling may contribute. Research questions progress from basic vaccinologic considerations ("what"), through to macroscopic feasibility and impact assessment ("if"), to granular questions regarding vaccine delivery strategies and financing ("how"). As described above, most published TB vaccine models have addressed "what"-related questions.

This thesis contributes evidence further along the pathway, pertaining to "if"-related questions. In contrast to prior work, the focus is to generate mathematical modelling evidence that incorporates context-specific epidemiologic and health economic features and to assess whether structural decisions in model design substantially affects the policy-relevant conclusions drawn from them. In doing so, I aim to contribute to the beginnings of evidence generation to inform TB vaccine introduction.

1.3 Aims

This thesis has two broad aims, reflecting two research needs that we must meet to advance models to support vaccine introduction:

1. Estimate the epidemiologic impact, cost-effectiveness and affordability of new TB vaccines in India and China, incorporating drug-resistance transmission and acquisition. This aim reflects the need to adapt models to include locally important features of, and uncertainty in, TB epidemiology and health systems (research gaps 1–3).

2. Describe how different assumptions of adapting social contact structures to long-term demographic trends in India—as a country undergoing the demographic transition—might affect vaccine impact estimates. This aim reflects the need to establish whether vaccine impact estimates are robust to structural decisions in model design (research gap 4).

1.4 Research Objectives

To define these aims fully, I first undertook a systematic review of the TB vaccine modelling literature (chapter 2) to (a) determine what features of TB epidemiology, TB vaccines, demography (including social contact), and health systems are integrated within currently published TB vaccine models and (b) characterise the extent to which current dynamic TB vaccine models include drug resistance, cost-effectiveness analysis, and affordability analysis.

Following this review, this thesis sets out four objectives to achieve the specified research aims.

I address Aim 1 through the following specific objectives:

1. Develop a transmission model of *Mtb* including dynamic acquisition and transmission of drug resistance, calibrated to overall and drug-resistant TB epidemiologic data from India and China, with an attached country-specific cost-model of TB programmatic control and vaccination.

2. Using the calibrated model to assess the epidemiologic impact of new vaccines on drug-resistant TB and TB overall in India and China; and

    a) assess the cost-effectiveness of new TB vaccines, incorporating costs of drug-resistant TB diagnosis and management; and

    b) integrate country-specific plans to scale up programmatic (non-vaccine) TB control in both India and China to investigate how these might interact with estimates of vaccine epidemiologic impact and cost-effectiveness.

3. Using the calibrated model and country-specific willingness to pay thresholds, estimate total maximum cost of—and affordability of—large scale adult TB vaccination programmes that are considered cost-effective based on their value to the health system

    a) Investigate age targeting as a strategy to improve affordability.

The following objectives address Aim 2:

4. Develop *Mtb* transmission models calibrated to an India-like epidemiologic scenario and

    a) incorporate a more precise representation of long-term future demographic trends;

    b) implement different methods to update social contact matrices to match evolving demography; and

    c) investigate whether different contact matrix update methods result in different estimates of vaccine impact by 2050.

1.5 Thesis Structure

This document conforms to the structure guidelines and regulations for a "research paper" style thesis at the London School of Hygiene and Tropical Medicine. Typeset versions of published manuscripts are included as-is without further editing. Submitted manuscripts, technical appendices, and online supplementary materials are also included, however, these are reformatted as appropriate to conform to typographic conventions and pagination in the rest of the thesis. Manuscripts and supplementary material are accompanied, where appropriate, by additional introductory and discussion material to construct unified chapters.

A summary diagram that presents the mapping between research gaps, aims, and objectives is presented in Figure 1.2.

In chapter 1 (this chapter), I provide a brief introduction to the research context of this thesis, a rationale for the work, aims and objectives, and an outline of the forthcoming chapters.

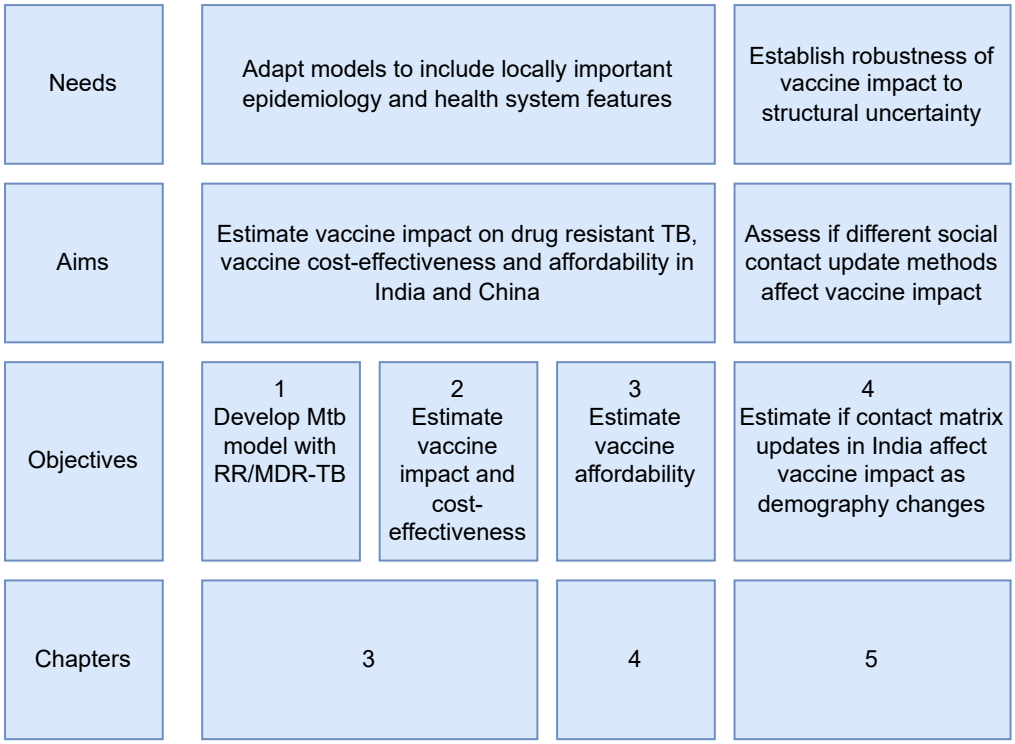

Figure 1.2: Layout of thesis

Chapter 2 presents a brief summary of the burden and natural history of TB relevant to vaccination. It includes background to the epidemics of TB and drug-resistant TB in India and China. I include a published systematic review, which summarises (i) the current status of the TB vaccine development pipeline; and (ii) the current state of the TB vaccine modelling literature. In the latter, I which identify new vaccine characteristics, targeting strategies, epidemiologic features, and economic evaluations are included in recent studies. This chapter identifies the research gaps described in section §1.2

> Weerasuriya, CK, Clark, RA, White, RG, Harris, RC New TB vaccines: advances in clinical development and modelling (Review Symposium). *J Intern Med*, 2020; 288: 661– 681. https://doi.org/10.1111/joim.13197

Chapter 3 addresses objectives one and two. It includes a published manuscript and its associated technical appendix. This study presents a dynamic transmission model of *Mtb*, stratified by age-, drug-resistance-, and treatment history- calibrated to historical epidemiologic data from India and China, with an attached country-specific cost-model of programmatic (non-vaccine) TB control and vaccine delivery. I project two future baseline (no new vaccine) scenarios for each country—one where programmatic (non-vaccine) TB control continues unchanged from 2018 (known as "Status Quo") and the other where programmatic control is scaled up according to country-specific plans per

published national strategies and expert input (known as "Policy"). Using the calibrated model, I estimate the epidemiologic impact of vaccines on both drug-resistant TB and overall TB, and vaccine cost-effectiveness.

> Weerasuriya, C.K., Harris, R.C., McQuaid, C.F. , Bozzani, F., Ruan, Y., Li, R., Li, T., Rade, K., Rao, R., Ginsberg, A.M., Gomez, G.B., White, R.G. The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China. *BMC Med* **19**, 60 (2021). https://doi.org/10.1186/s12916-021-01932-7

Chapter 4 addresses objective three. First, I discuss how commonly used cost-effectiveness thresholds do not reflect health system budget constraints or the affordability of health interventions. Then, I briefly review how the cost-effectiveness threshold against which vaccines should be appraised might change as the proposed total cost of vaccine deployment changes. Finally, I present a published study where, using the calibrated model in chapter 3, I estimated the total maximum cost at which vaccine programmes in India and China would remain cost-effective, if the health benefits gained by vaccination were valued at country-specific cost-effectiveness thresholds.

> Weerasuriya, C.K.; Harris, R.C.; Quaife, M.; McQuaid, C.F.; White, R.G.; Gomez, G.B. Affordability of Adult Tuberculosis Vaccination in India and China: A Dynamic Transmission Model-Based Analysis. *Vaccines* **2021**, *9*, 245. https://doi.org/10.3390/vaccines9030245

In chapter 5 I address objective four. This chapter includes a manuscript under review and its associated technical appendix. This study estimates the impact of TB vaccines in four simplified *Mtb* transmission models calibrated to an India-like epidemiologic scenario. Each model uses a different method to update contact structures to match evolving demography. I compare vaccine impact on TB burden in 2050 between the update methods. This manuscript builds on the work of Arregui et al.[21], who describe methods to update social contact matrices to match long-term demographic trends in dynamic transmission models.

Finally, in chapter 6, I synthesize and discuss the main findings of this thesis, the implications for vaccine adoption and methodological limitations of the work. I conclude by outlining new research questions identified by this work that may warrant further research.

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2 State of the Art

This chapter presents essential background on the natural history and burden of TB, including drug resistance and economic impact. It identifies current research gaps through a published review of recent TB vaccine trials and vaccine modelling literature.

2.1 The Natural History of Tuberculosis

The natural history of TB is complex and multifaceted. The following summary highlights those aspects of TB natural history that are important from a vaccine perspective.

Active TB typically presents as a potentially infectious pulmonary disease with a classic triad of fever, night sweats, and weight loss[1,2], often with cough, haemoptysis and lymphadenopathy. However, disease can also take an extrapulmonary non-infectious form, either in other organs or disseminated throughout the body. Extrapulmonary TB is considerably less common, accounting for 16% of all globally notified cases in 2019[3].

TB is caused by the bacillus *Mycobacterium tuberculosis* (*Mtb*). In most cases, *Mtb* is transmitted when airborne bacilli—expelled when an infectious person coughs—are inhaled by another individual. Infection generally leads to one of two outcomes:

1. **Fast progression:** The first outcome is *"fast progression"* to active symptomatic disease. If *Mtb* can be identified in expectorated sputum ("smear-positive"), active disease is considered infectious. If *Mtb* cannot be identified in sputum ("smear-negative") and the patient is diagnosed with TB on clinical or radiologic grounds[1], active disease is considered to be substantially less infectious[4]. A proportion of "smear-negative" cases may subsequently be microbiologically confirmed through mycobacterial culture or molecular assays. Non-infectious disease may progress to infectious disease. The risk of developing active disease is highest in the first twenty-four months after infection and declines continuously over time.

2. **Latent tuberculosis infection:** Alternatively, infection can lead to an asymptomatic, non-infectious state known as latent tuberculosis infection (LTBI). LTBI can persist for years to decades, but in a proportion of individuals, *Mtb* may "reactivate" to active disease[1,5].

Currently, we cannot accurately predict whether a given person will develop LTBI or active disease after *Mtb* infection. Most people develop LTBI after infection; the lifetime risk of progression to disease after infection is approximately 10%[1]. Progression to disease is more likely with advanced age, immunocompromise, infection with specific virulent *Mtb* strains, and previous history of *Mtb* infection or TB disease[6,7]. Similarly, advanced age and immunocompromise increase the risk of reactivation from LTBI[8,9].

Untreated active disease may spontaneously cure ("natural cure") or progress, ultimately leading to death. In HIV-negative persons, the estimated lifetime case fatality rates for untreated smear-positive and smear-negative TB are approximately 70% and 20%, respectively[10]. Case fatality in persons with AIDS, or other complicating factors such as diabetes, is substantially higher[11–13].

Individuals may also "relapse" back to active disease after natural cure or successful treatment; thus, latent infection and the recovered state act as long term reservoirs of *Mtb* in the population. Both groups of persons can also be reinfected with *Mtb*, which can then fast-progress to disease. However, the experience of prior infection in latently infected or recovered individuals confers incomplete immunity, reducing the risk of fast-progression on subsequent reinfection by 59–75%[14–16].

2.2 Tuberculosis Burden and Control

Over the last decade, TB has killed more people than any other infectious disease. In 2019, TB caused an estimated 1.6 million deaths worldwide[3]. Ten million new cases of TB occur each year, overwhelmingly in low- and middle-income countries. In 2019, approximately 7.1 million new cases of TB were diagnosed and notified, suggesting that 2.9 million cases remained unreported or undiagnosed[3]. Two-thirds of the global TB burden occurs in eight countries: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%)[3].

Globally, key risk factors for TB include HIV/AIDS, advanced age, diabetes mellitus, alcohol misuse, malnutrition, structural lung disease including silicosis, indoor air pollution, and smoking. Most risk factors are associated with socioeconomic deprivation; unsurprisingly, TB follows a socioeconomic gradient and disproportionately affects society's poorest and most vulnerable members[17].

The current first-line drug treatment regimen for drug susceptible TB (DSTB) was established in the 1980s. It is highly effective, attaining cure rates of approximately 85%[3,18]. This all-oral regimen lasts six months and consists of two phases: rifampicin, isoniazid, ethambutol, and pyrazinamide for two months, followed by rifampicin and isoniazid for four months[19,20]. Recent evidence suggests that a four-month regimen comprising rifapentine, isoniazid, pyrazinamide, and moxifloxacin is at least as safe and effective as the standard six-month regimen[21]. World Health Organization (WHO) plans to include

the new four-month regimen as an alternative to the standard regimen in the 2021 update to the consolidated guidelines on TB[22].

2.2.1 Drug-resistant Tuberculosis

Global TB control efforts are threatened by antimicrobial resistance. rifampicin-resistant tuberculosis (RR-TB) and its subtype multidrug-resistant TB (MDR-TB)—the latter defined as resistance to both rifampicin and isoniazid—lead to poor disease outcomes and require treatment with drug regimens that are longer, more complex, cause more adverse effects, and have poor success rates[23,24].

Approximately 465,000 new cases of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) occurred in 2019 worldwide, of which 78% were MDR-TB. Among notified TB cases, MDR/RR-TB constituted 3.3% (95% confidence interval [CI]: 2.3–4.3%) of new and 18% (95% CI: 9.7–27%) of previously treated cases of TB[3].

MDR/RR-TB is most frequently identified in people who have previously had TB or received treatment for TB[25,26]. Other risk factors vary by context and geographic setting and include advanced age, HIV/AIDS, lung disease including chronic obstructive pulmonary disease, infection with the Beijing strain of *Mtb*, a history of incarceration, male gender, smoking, and alcohol use[27–30].

At the cellular level, most *de novo* drug resistance in *Mtb* arises through mutations in bacterial genes that encode drug targets rather than via horizontal transfer from other (myco)bacteria[31]. Once a resistance-conferring mutation is acquired, antimicrobial selection pressure favours the survival of resistant organisms at the expense of drug-susceptible organisms.

Where a drug-susceptible infecting *Mtb* strain gains resistance through de novo mutations, this is termed "secondary resistance". Alternatively, MDR/RR-TB may be due to "primary resistance", where the patient is infected with drug-resistant *Mtb*[23]. The pathways to clinical MDR/RR-TB include primary resistance, secondary resistance, reinfection with a drug-resistant strain during or after treatment for DSTB, or mixed initial infection with drug-resistant and susceptible strains, with treatment unmasking resistance[23,32].

Until recently, established dogma held that secondary resistance caused most MDR/RR-TB, consistent with the higher rate of disease observed in persons who have had or had been treated for TB. Specifically, secondary resistance was attributed to treatment non-adherence during the six-month treatment regimen for DSTB. However, phylogenetic analysis of drug-resistant *Mtb* isolates is challenging this consensus. Authors across a range of settings have demonstrated high levels of clustering and relatedness in drug-resistant *Mtb* isolates[33–36] using methods such as IS6110 restriction-length polymorphism fingerprinting[37], mycobacterial interspersed repetitive units-variable numbers of tandem repeat typing[38], and whole-genome sequencing[39]. High levels of clustering suggest a substantial proportion of MDR/RR-TB is due to primary resistance[23,40]. Moreover, the

dominant driver of secondary resistance may not be non-adherence but factors such as insufficient tissue and serum concentrations of anti-TB drugs[41].

Health systems typically group RR-TB and MDR-TB together as the recommended treatment for both are identical[42]. The WHO consolidated guidelines for the management of drug-resistant TB[42] recommendations include both standard long regimens lasting 18–20 months and a shorter standardised regimen (indicated for a subset of patients) lasting 9–12 months. Drug composition in long MDR/RR-TB regimens varies per local treatment protocols, the specific antimicrobial resistance patterns of the *Mtb* isolate, and patient response. Unlike first-line therapy, most second-line regimens include at least one parenteral agent, necessitating in-patient or in-facility treatment[42]. Treatment outcomes remain poor: globally, only 57% of people who began MDR/RR-TB treatment in 2017 successfully completed treatment[3]. This estimate is heterogeneous, with treatment success rates ranging from 52% in the WHO South-East Asia region to 64% in the WHO Eastern Mediterranean and African regions[3].

Drug resistance beyond MDR-TB is classified as extensively drug-resistant TB (XDR-TB), defined as resistance to rifampicin, isoniazid, a fluoroquinolone (moxifloxacin or levofloxacin), and either bedaquiline or linezolid[43]. Fortunately, XDR-TB remains relatively rare: 12,350 cases were notified in 2019, predominantly in Eastern Europe[3].

Several recent and ongoing developments in TB diagnosis and management may substantially alter future programmatic and clinical MDR/RR-TB management.

First, the delivery of drug susceptibility testing (DST) to TB patients is increasing, leading to improved rates of MDR/RR-TB diagnosis. Universal DST is a goal of the WHO End TB strategy and DST coverage has increased from 2012 to 2019, rising from 7% to 61% of all globally notified pulmonary TB cases[3]. This increase has been driven mainly by the routine use of molecular assays for TB diagnosis—notably Xpert MTB/RIF—that can simultaneously detect rifampicin resistance[3].

Second, drug treatment for MDR/RR-TB has progressed substantially. Several new (e.g. bedaquiline[44], delamanid[45], and pretomanid[46]) and repurposed drugs (e.g. clofazimine[47]) are under investigation as new components of second-line treatment regimens. Some of these are oral agents currently in, or recently completed, trials as part of standardised all-oral short (6–9 month) treatment regimens[47–50]. However, local resistance patterns to existing second-line drugs vary, and new resistance to new drugs emerge over time. Together, these facts likely preclude a universal second-line regimen for MDR/RR-TB; programmatic control of MDR/RR-TB is likely to remain an ongoing challenge despite improved diagnosis and treatment.

2.3 The Cost of Tuberculosis

Besides the human cost, TB imposes a substantial financial burden on health systems and patients, both directly and indirectly.

The programmatic costs of DSTB control encompass those for drugs, surveillance, diagnosis and monitoring, dedicated human resources, facilities and hospitalisation (where necessary). Some modes of TB care delivery—e.g. Private-Public Financing strategies or directly observed treatment, short-course chemotherapy (DOTS), where trained healthcare providers directly supervise the administration of each dose to the patient—incur additional costs. Accurately estimating these costs is challenging as the methodological quality of studies that report them is very heterogeneous. Nonetheless, in a comprehensive systematic review, Laurence et al.[51] estimated the costs of treating DSTB from a provider perspective. They estimate that, per patient, high-income countries spend $14,659, upper-middle-income countries spend $840, lower-middle-income spend $273, and low-income countries spend $258. In total, WHO has estimated that $4.2 billion was mobilised in 2020 for TB prevention, diagnosis, and treatment over the low- and middle-income countries (LMICs) that accounted for 98% of all notified TB cases. Despite these costs, programmatic TB control has been demonstrated to be cost-effective over a range of settings[52].

Patients and their families also incur substantial direct and indirect costs due to TB. For example, Tanimura et al.[53] estimated that patients in low- and middle- income countries suffered a total mean cost of $847 (range $55–$8198), comprising 20% direct medical costs, 20% non-medical costs and 60% income loss. Similarly, other studies have consistently demonstrated patients often experience catastrophic costs[53–56]—defined as costs that exceed 20% of annual household income[57]—from TB.

2.3.1 The Cost of Drug-resistant Tuberculosis

While the burden of MDR/RR-TB is smaller than DSTB, the former imposes greatly disproportionate costs on health systems from additional diagnostic tests, drug sensitivity testing, expensive drugs, and long hospitalisation. MDR/RR-TB control required $2.26 billion of the $6.5 billion available globally for TB in 2020[3], despite constituting less than 5% of all incident TB. In their systematic review, Laurence et al. estimated mean provider costs of $83,365, $5,284, $6,313, and $1,218 per MDR-TB case treated in high-, upper-middle-, lower-middle- and low-income countries respectively[51].

MDR-TB is also very expensive for patients. One study from India estimated that MDR/RR-TB patients with an annual income of $608 ($228–$912) spent $171 ($72–$432) out-of-pocket before treatment[58]. Similarly, a study in Ethiopia, Indonesia, and Kazakhstan found that patients spent $1,838, $2,342, and $3,125, respectively, out-of-pocket, for MDR-TB diagnosis and treatment[59].

Changing epidemic dynamics may affect the health system costs of MDR/RR-TB . Health systems have invested in improving adherence for DSTB treatment, working on the assumption that most resistance is secondary. However, as primary resistance increasingly underlies MDR/RR-TB[23,60], these strategies will decline in effectiveness, necessitating investment into (more costly) early diagnosis and treatment of MDR/RR-TB .

2.4 Country Selection Rationale

This thesis modelled epidemiologic and health systems scenarios set in China and India (chapters 3 and 4), or an India-like setting (chapter 5).

Modelling across these two countries is valuable for at least three reasons. First, the results will inform policy in high MDR/RR-TB and overall TB burden settings. Second, India and China have substantially different TB epidemiology and health systems that provide TB care; modelling across heterogeneous contexts may improve the generalisability of results. Third, it may elucidate how epidemiologic differences affect the importance of particular vaccine characteristics.

TB incidence in China and India accounted for approximately 34.4% of the global total in 2019. What follows is a brief description of the context in each country.

2.4.1 India

It is challenging to accurately characterise TB epidemiology and burden in India. To date, granular, empirically derived, nationally representative estimates are unavailable. The country's first national TB prevalence survey was expected to report in 2021 but is currently on hold due to the COVID-19 pandemic. The best available countrywide estimates are derived from routine surveillance data, extrapolated from pooled subnational estimates[61–63], or inferred from other sources, such as the National Family Health Survey[64].

Per WHO estimates, India experienced 2.64 million (uncertainty interval [UI] 1.80–3.63) incident TB cases in 2019, equivalent to 192 (UI: 132–266) cases per 100,000 population and accounting for 26% of the global total[3,65]. Of these, 71,000 (UI: 49,000–98,000) cases—equivalent to 5.2 (UI: 3.6–7.2 cases per 100,000)—occurred among people living with HIV. While we do not currently have reliable empirical data to characterise the age distribution of TB in India, model-based estimates suggest that TB incidence is concentrated between ages 15–64 years[3]. Treatment coverage is estimated at 82% (UI: 60–120), suggesting that approximately a fifth of incident cases are not notified. Finally, the case fatality ratio is estimated at 17% (UI: 12–24), corresponding to approximately 445,000 (UI: 413,000–478,000) deaths in 2019.

MDR/RR-TB accounted for 124,000 (UI: 73,000–189,000) of incident TB cases in India in 2019, corresponding to 9.1 (UI: 5.3–14) cases per 100,000 population and 27% of global burden[3]. High-quality estimates of the distribution of multidrug/rifampicin resistance by treatment history were generated by the first national anti-tuberculosis drug resistance survey[66]. This survey, conducted 2014–2016, found MDR/RR-TB among 2.8% (95% CI: 2.3–3.5%) of new, 11.6% (CI: 10.2–13.2%) of previously treated, and 6.2% (95% confidence interval, CI: 5.6–6.96%) of overall TB patients.

Within India, tuberculosis epidemiology is heterogeneous, with variation by urbanisation, gender, and socioeconomic status. That poverty and lower socioeconomic status are associated with a higher risk of, and poorer outcomes from, TB is well established across a range of settings[17]. This relationship is complex, likely representing an interconnected set of risk factors—social, environmental, and biological—that are more prevalent in lower-income groups. Estimates of the differential burden by wealth groups in India vary, ranging from 242 vs 149 (per 100,000 population) in those below vs above the poverty line[67] to 201 per 100,000 population (95% CI 142–260) among the wealthiest population quintile to 1105 per 100,000 population (95% CI 919–1291000) in the poorest quintile[68]. Similarly, the degree of urbanisation is associated with differences in burden and outcomes. One study estimated the nationwide annual risk of tuberculosis infection at 2.2% and 1.3% in urban and rural areas respectively[69]. Findings regarding treatment outcomes are mixed, with some studies finding poorer Revised National Tuberculosis Control Programme (RNTCP) outcomes in remote tribal areas[70] and others reporting worse treatment outcomes with increasing urbanisation[71,72]. Finally, consistent with global findings[3], multiple studies have demonstrated an approximately 2:1 male:female ratio in TB burden in India[73,74]. This discrepancy has been attributed to a range of causes including biological factors, occupational risk, contact patterns, and care-seeking behaviour[75,76].

Many aspects of programmatic TB control have progressed in the last two decades. The National Tuberculosis Elimination Programme (NTEP), formerly the RNTCP, achieved nationwide coverage of DOTS in 2006. Programmatic management of drug-resistant TB was initiated in 2007 and scaled nationwide in 2013[66]. Following the initiation of a national TB case reporting platform ("Nikshay") in 2012, TB case notifications rose from 1.2 million in 2013 to 2.2 million in 2019[3]. As a result, treatment outcomes for DSTB in the public health sector have improved, although outcomes for drug-resistant TB remain poor[3].

Further progress in TB control is complicated by the complex structure of the Indian healthcare system. Supplementing publicly funded healthcare, India has a large, heterogeneous, and variably regulated private healthcare sector whose contribution to national TB control is not known accurately. Consensus holds that the private sector delivers at least half of all TB treatment, but analyses of private sector sales of anti-tuberculosis drugs and community surveys[77] suggest this proportion may be up to two-thirds. Patients treated for TB in the private sector are less often notified to the national tuberculosis

programme (NTP), less likely to receive appropriate diagnostic testing (including drug sensitivity testing), more likely to be treated empirically with broad-spectrum antibiotics, less likely to receive appropriate first-line anti-tuberculosis therapy, and suffer from worse treatment outcomes[78–81]. Inappropriate private sector management may also contribute to increasing levels of antimicrobial resistance.

India's RNTCP published the National Strategic Plan for Tuberculosis Elimination 2017–2025 (NSP)[82]in 2017. The NSP acknowledges the challenges above and sets out wide-ranging strategic goals over all aspects of programmatic TB management. Includes specific aims to (1) improve diagnostic capabilities, increase overall case detection rates; (2) increase drug sensitivity testing coverage to 100% by 2025; (3) increase private sector engagement, improving rates of notification from the private sector. The document also identifies the challenges posed by MDR/RR-TB, noting that MDR/RR-TB management is responsible for 40% of RNTCP expenditure.

In summary, India is a setting with a high burden of TB, including MDR/RR-TB. MDR/RR-TB imposes a substantial health burden on the populace and a substantial financial burden on the NTP. In addition, many of aims of the NSP may impact MDR/RR-TB burden. Taken together, there is a clear need to quantify the potential impact of a new TB vaccine in India, incorporating the uncertainties introduced by the planned scale-up of programmatic TB management.

2.4.2 China

TB diagnosis and control in China have made substantial progress in the past three decades. Smear positive TB prevalence fell by 80% from 1990 to 2010, corresponding to the initiation and national scale-up of the DOTS programme by the Chinese Centres for Disease Control (CCDC)[83,84].

Despite this, China experienced 833,000 (UI: 717,000–957,000) incident cases of TB in 2019, equivalent to 58 (UI: 50–67) cases per 100,000 population and corresponding to 8.4% of the global total[3]. TB caused 31,000 (UI: 28,000–34,000) deaths, corresponding to a rate of 2.2 (UI: 2.0–2.4) per 100,000 and a case fatality ratio of 4% (UI: 3–5). In general, treatment coverage is high, estimated at 87% (UI: 76–100), with >90% new and relapse cases registered in 2018 treated successfully[65].

Improvements in diagnosis and treatment outcomes for MDR/RR-TB lag behind DSTB. The NTP initiated its MDR/RR-TB component in October 2006, with sites in only two prefectures. The programme had expanded to 92 of 333 prefectures (28%) by 2014 and continues to expand[85]. However, China still accounts for 14% of global MDR/RR-TB burden, corresponding to 65,000 (UI: 49,000–83,000) incident cases in 2019, when it was identified in 7.1% (UI: 5.6–8.7) of new and 23% (UI: 23–24) of previously treated cases of TB[3,86,87]. MDR/RR-TB burden as a fraction of overall TB has remained relatively stable, or declined slowly, over the last two decades[86,88,89]. With only 54% of cases treated

successfully in 2018, MDR/RR-TB treatment outcomes remain poor, albeit consistent with global averages[3].

Heterogeneity in TB epidemiology by urbanisation, gender, and socioeconomic status also exist in China. Robust data from repeated national prevalence surveys have demonstrated a higher burden of disease in rural compared to urban populations[83]: in 2010, bacteriologically-positive prevalence was reported at 163 (95% CI 143–185) per 100,000 population in the former, compared to 73 (95%CI 51–105) per 100,000 in the latter. Gender disparities also follow global patterns, with 183 (95%CI 157–215) per 100,000 bacteriologically-positive cases in men, compared to 64 (95%CI 52–79) in women[83]. Finally, income has been reported to be negatively correlated with per capita net income in rural areas and indices of consumption in urban areas[90].

Per national TB control policy, diagnosis and treatment for uncomplicated DSTB are available nominally free of charge in China, delivered through a system of "TB dispensaries" affiliated with CCDC. Patients can also access care at "TB specialist hospitals", which are similar to TB dispensaries but tend to treat severe TB, or through an integrated care pathway, where they receive free diagnosis and care at a TB clinic run within a general public hospital[91,92]. In contrast, neither the NTP nor basic health insurance (social health insurance) provide comprehensive coverage of MDR/RR-TB diagnosis and treatment costs[93]; many patients incur substantial out-of-pocket expenditure and experience catastrophic costs[94]. Nevertheless, $401 million of $994 million available in the 2020 NTP budget was required for MDR/RR-TB management, highlighting the financial burden on the public health sector[3].

In sum, DSTB detection and treatment in China has improved over the last few decades. The burden of MDR/RR-TB is either constant or declining very slowly. MDR/RR-TB represents a substantial source of morbidity and financial burden to both the health system and patients. Given the scale of MDR/RR-TB in China, characterising the contribution of a new vaccine to its control is of particular importance.

Summary of Background

In the preceding sections, I have described the background and context of TB natural history and epidemiology, both globally and specifically in India and China, focusing on MDR/RR-TB and the costs to health systems posed by (drug-resistant) TB. Given the scale of the problem and the potential future impediment to global TB control, these aspects must be adequately integrated into mathematical models that aim to inform the adoption of new TB vaccines.

In the next section, I present a published review which includes a systematic review of the current TB vaccine modelling literature, and review the state of TB vaccine candidates in clinical trials.

2.5 Advances in Tuberculosis Vaccines

2.5.1 Research Paper 1

This research paper is cited as:

> Weerasuriya, CK, Clark, RA, White, RG, Harris, RC New tuberculosis vaccines: advances in clinical development and modelling (Review Symposium). *J Intern Med*, 2020; 288: 661– 681.
> https://doi.org/10.1111/joim.13197

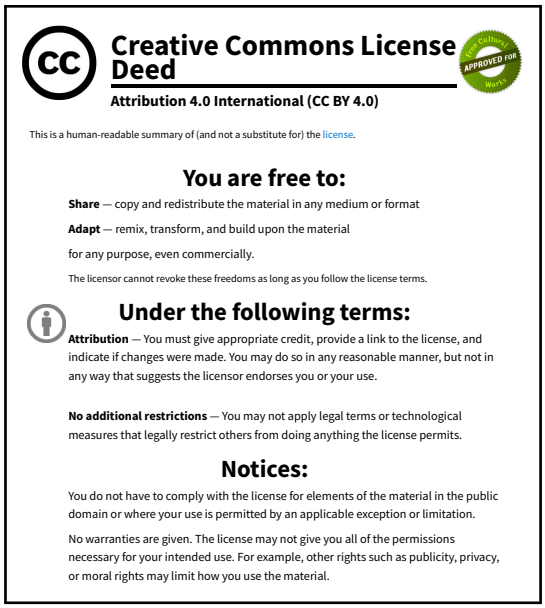

Figure 2.1: Research Paper 1: Creative Commons License

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SECTION A – Student Details

Student ID Number	1604836	**Title**	DR
First Name(s)	CHATHIKA KRISHAN		
Surname/Family Name	WEERASURIYA		
Thesis Title	ADVANCING MATHEMATICAL MODELS OF MYCOBACTERIUM TRANSMISSION TO SUPPORT VACCINE INTRODUCTION		
Primary Supervisor	PROFESSOR RICHARD G WHITE		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JOURNAL OF INTERNAL MEDICINE		
When was the work published?	31 OCTOBER 2021		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the structure of, and scope of the review. I undertook the systematic literature search relevant to the TB Modelling literature, identified relevant publications, screened results, included and excluded papers, and extracted data as one of two co-extractors. I synthesized the results of the literature search and review, analysed and tabulated the results. I also contributed to data collection relevant to TB vaccine trials, including data tabulation and synthesis. I wrote the first full draft of the introduction, TB modelling review and discussion. I generated all visualisations. I co-wrote the first full draft of the TB vaccine trial section. I edited the first full draft of the complete manuscript and all subsequent drafts, submitted the manuscript to the journal for publication, corresponded with the editorial team, responded to reviewer comments, revised and resubmitted the manuscript for publication.

SECTION E

Student Signature	[redacted]
Date	12 DECEMBER 2021

Supervisor Signature	[redacted]
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New tuberculosis vaccines: advances in clinical development and modelling

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Abstract. Weerasuriya CK, Clark RA, White RG, Harris RC (London School of Hygiene and Tropical Medicine, London, UK. New tuberculosis vaccines: advances in clinical development and modelling (Review Symposium). *J Intern Med*; 2020; **288**: 661–681. https://doi.org/10.1111/joim.13197

Tuberculosis remains a major source of morbidity and mortality worldwide, with 10 million cases and 1.5 million deaths in 2018. Achieving 'End TB' prevention and care goals by 2035 will likely require a new tuberculosis vaccine. The tuberculosis vaccine development pipeline has seen encouraging progress; however, questions around their population impact and implementation remain. Mathematical modelling investigates these questions to inform vaccine development and deployment strategies. We provide an update on the current vaccine development pipeline, and a systematic literature review of mathematical modelling of the epidemiological impact of new tuberculosis vaccines. Fourteen prophylactic tuberculosis vaccine candidates are currently in clinical trials. Two candidates have shown promise in phase II proof-of-concept efficacy trials: M72/AS01$_E$ demonstrated 49.7% (95% CI; 2.1, 74.2) protection against tuberculosis disease, and BCG revaccination demonstrated 45.4% (95% CI; 6.4, 68.1) protection against sustained *Mycobacterium tuberculosis* infection. Since the last modelling review, new studies have investigated the epidemiological impact of differential vaccine characteristics, age targeting and spatial/risk group targeting. Critical research priorities for M72/AS01$_E$ include completing the currently in-design trial, powered to improve the precision of efficacy estimates, include uninfected populations and further assess safety and immunogenicity in HIV-infected people. For BCG revaccination, the priority is completing the ongoing confirmation of efficacy trial. Critical modelling gaps remain on the full value proposition of vaccines, comparisons with other interventions and more realistic implementation strategies. Using carefully designed trials and modelling, we must prepare for success, to ensure that new vaccines will be promptly received by those most in need.

Keywords: clinical trial, mathematical model, systematic review, tuberculosis, vaccine.

Introduction

Tuberculosis (TB) was the leading cause of death due to a single infectious pathogen worldwide in 2018, with an estimated 10 million new cases and approximately 1.5 million deaths [1]. Over two-thirds of cases are found amongst eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. Global TB control efforts are hindered by the emergent epidemic of drug-resistant tuberculosis. Approximately 500 000 cases of rifampicin-resistant tuberculosis (RR-TB) arose in 2018, of which 78% were multi-drug-resistant tuberculosis (MDR-TB).

The global community has set ambitious TB control and elimination targets. The World Health Organization (WHO) End TB Strategy defines milestones and targets for TB control by 2035, which aim to reduce TB deaths by 95% and incidence by 90% compared with 2015 [2]. Despite these goals, progress has been slow. TB incidence declined only 1.6% per year between 2000 and 2018, and TB deaths declined 11% between 2015 and 2018. To

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affirm its commitment to TB control, in 2019, the UN General Assembly issued a political declaration following the first-ever high-level meeting on TB, which included targets to mobilize at least USD 13 billion towards TB diagnosis, care and prevention by 2022, and at least USD 2 billion towards TB research.

The End TB Strategy recognizes that a lack of optimal tools to prevent TB, including a vaccine, is a key barrier for TB control, and calls for intensified research and innovation in this area. Encouragingly, the TB vaccine pipeline has recently seen rapid development. There are prophylactic vaccine candidates at all stages along the clinical development pathway [3,4], including three in phase I, eight in phase II and three in phase III, reflecting a diverse array of antigens and proposed mechanisms of vaccine effect. Two recent phase II efficacy trials have reported promising results. A trial of adolescent bacille Calmette–Guérin (BCG) revaccination in South Africa demonstrated 45.4% reduction in sustained *Mycobacterium tuberculosis* (Mtb) infection [5]. A trial of the new TB vaccine candidate M72/AS01$_E$ in adults reported 49.7% efficacy in preventing TB disease at 3 years of follow-up [6]. Given their likely integral role in TB elimination, we review the current state of clinical development of TB vaccines. In the following sections, we provide a general classification of TB vaccines and review the current candidates along the TB vaccine clinical development pathway. We summarize the mathematical modelling literature used to inform vaccine development, focusing on models that address the epidemiologic impact of new TB vaccines. Finally, we describe the future for TB vaccines in the effort towards TB elimination.

Classification of tuberculosis vaccines

Besides conventional characteristics such as the duration of protection and vaccine efficacy, we classify prophylactic TB vaccines along the two major qualitative axes: (a) the host infection status required for efficacy and (b) the mechanism of effect (Figure 1).

The host infection status required for efficacy is defined relative to the tuberculosis natural history state of the vaccine recipient in which the vaccine is effective. Vaccines effective only in individuals who are not infected by Mtb are referred to as 'preinfection' (PRI) vaccines (sometimes referred to as 'pre-exposure' vaccines). In contrast, vaccines effective in individuals who either have current latent infection or have recovered from disease (through treatment or through natural cure) are referred to as 'postinfection' (PSI) vaccines (sometimes referred to as 'postexposure' vaccines). Vaccines effective in uninfected, latent and recovered individuals are known as 'pre- and postinfection' vaccines (P&PI). Therapeutic vaccines, which modify disease in those with active tuberculosis, are not considered in this review.

We classify the mechanism of effect as the point along the progression from infection with Mtb to the development of active tuberculosis disease at which the vaccine exerts its effect. A prevention of infection (POI) vaccine reduces the probability of infection by Mtb. In contrast, the probability of infection is unaffected directly by a prevention of disease (POD) vaccine. POD vaccines act through one or more of (a) reducing the rate of progression to active disease following infection or reinfection with Mtb ('fast progression'); (b) reducing the rate of reactivation from latent infection to active disease; and/or (c) reducing the rate of relapse from recovered to active disease.

Candidates in clinical trials

The need for new TB vaccines and challenges in development

Infant BCG vaccination protects against severe extrapulmonary forms of TB in young children and is an important mainstay of national immunization programmes in TB endemic countries. However, BCG is contraindicated in HIV-positive individuals, an epidemiologically important population, due to an increased risk of disseminated BCGosis. Additionally, estimates of BCG efficacy against adolescent and adult pulmonary TB vary, ranging from an 'absence of clinically important benefit' in Malawi and India, to almost 80% protection in the UK and a North American Indigenous population [7–9]. Vaccines effective against pulmonary TB in adolescents and adults, but also in the elderly, and that are safe and effective in latently infected individuals and HIV-positive individuals are urgently needed.

The major impediment to new TB vaccine development is the lack of a correlate of protection, which necessitates large, long and expensive trials to demonstrate prophylactic efficacy against TB disease. The relatively low incidence of TB implies that adequately powered phase III trials will typically require at least 10 000 participants and cost in the

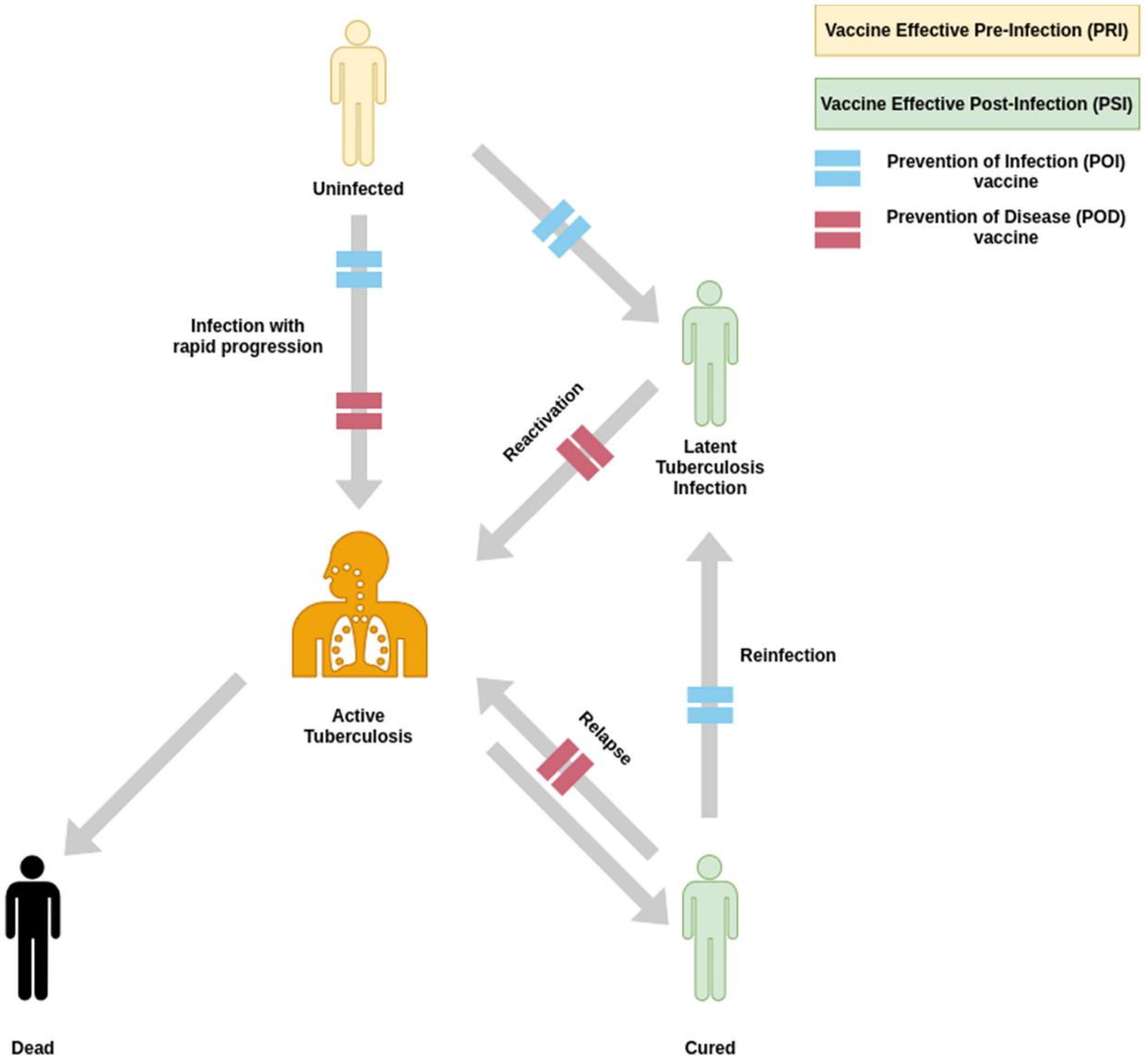

Fig. 1 *Tuberculosis vaccine mechanism of effect and host infection status required for efficacy. Mechanism of effect is indicated by double bars along natural history pathways. Host infection status required for efficacy is indicated by background colour.*

order of USD 100 million or more. Until a correlate of protection exists to allow immunobridging, efficacy trials may be necessary for extending registration to important populations other than those in the initial licensure trial, including HIV-positive populations, other age groups and other geographies. Short, inexpensive challenge studies are not yet an option in TB, as unlike malaria or influenza where quick, safe and effective treatments are available, TB treatment lasts at least 6 months and carries a risk of drug resistance.

Progress and innovation in clinical trials

Despite these challenges, the current TB vaccine candidate development pipeline is the strongest to date. Fourteen vaccine candidates (Figure 2) are in clinical development, including seven entering or

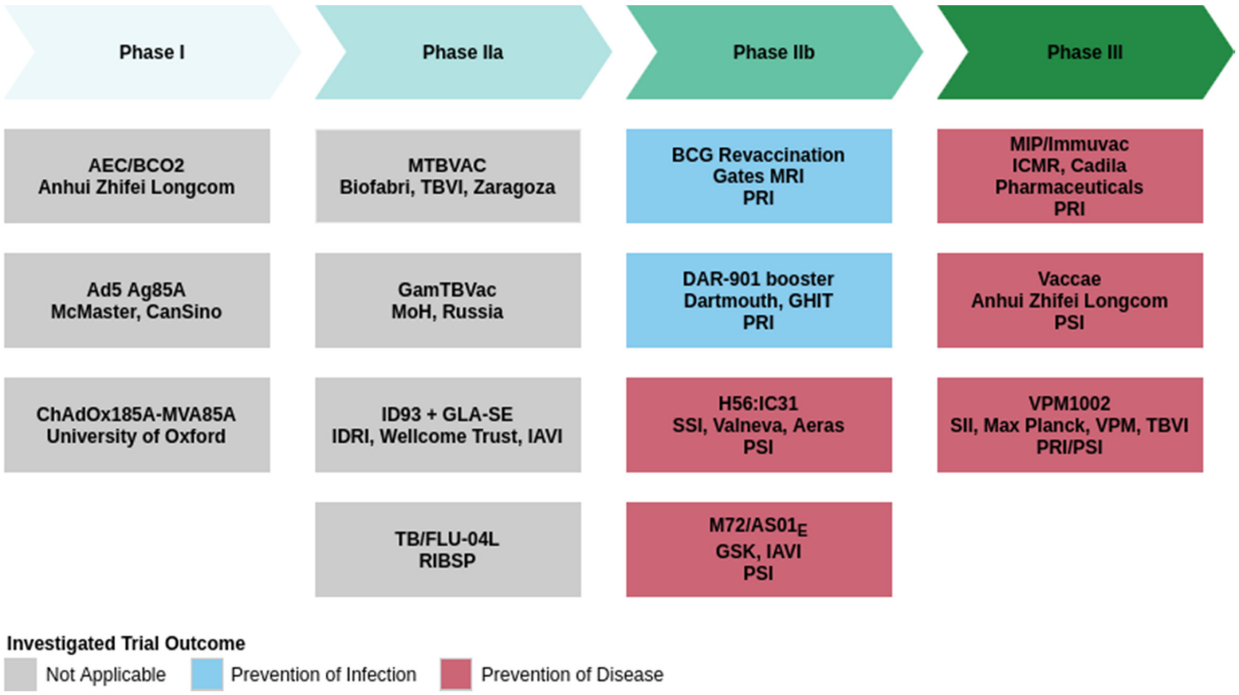

Fig. 2 *Classification of tuberculosis vaccines by trial phase, trial outcome (POI or POD) and population where vaccines were tested for efficacy (PSI, PRI or P&PI). The phase and trial outcome are based on the latest ongoing or completed clinical trials per candidate. POI and POD trial outcomes are only applicable to proof-of-concept or efficacy trials. H56:IC31 is under investigation for prevention of recurrent disease effect. VPM1002 is under investigation for both prevention of primary and recurrent disease effects. The host infection status required for efficacy reflects the various populations the candidate has been or is being trialled in for efficacy.*

already in proof-of-concept or full efficacy trials. The pipeline includes vaccines using viral vectors, live attenuated Mtb, inactivated whole cell and protein/adjuvant technologies.

Alongside the classical phase I/II/III trials, phase IIB (proof-of-concept) trials have been used to provide an initial assessment of efficacy for new TB vaccine candidates. These are valuable in stage-gating and de-risking the TB pipeline before the more substantive investment of a phase III trial. Studies in adults have historically focused on pulmonary disease as their outcome. Now, driven by the need for earlier indications of efficacy and de-risking of phase III investment, proof-of-concept trials may investigate infection or recurrence outcomes. Rates of infection and recurrence are greater than primary disease, so can help minimize trial size, as can recruiting other high-risk populations such as household contacts and healthcare workers. Furthermore, modelling has demonstrated the important contribution of reactivation and relapse to disease burden in many settings, leading to increased recognition of the need to protect postinfection (latently infected or recovered) populations [10–12]. Therefore, increasingly, studies either include or exclusively recruit postinfection populations.

We summarize the status of pipeline candidates in human trials and publicly available plans for upcoming trials.

Vaccine pipeline

Phase I

The early TB vaccine candidate pipeline is currently focused on new approaches to vaccine delivery (e.g. aerosolized, intranasal).

Two adenovirus-vectored candidates based on the mycobacterial antigen 85A are currently in separate phase I trials: Ad5-Ag85A [13] and ChAdOx185A-MVA85A prime-boost [14]. Both trials aim to investigate the safety and immunogenicity of aerosolized compared with intramuscular delivery

in BCG-vaccinated adults. The ongoing phase I trial for Ad5-Ag85A, developed by McMaster University, follows IGRA-negative adults for 24 weeks postadministration. The ongoing phase I trial for ChAdOx185A-MVA85A, developed at Oxford University, is following 39 IGRA-negative participants for 168 days and is expected to complete in late 2020. A phase IB/IIA trial for dose ranging and age de-escalation is ongoing in Uganda, with completion expected in 2022 [15], focusing on intramuscular administration.

AEC/BC02, developed by Anhui Zhifei Longcom, China, is a whole-cell freeze-dried Mtb vaccine delivered in six intramuscular doses. A nonrandomized open-label placebo-controlled phase I trial recruiting 135 adults (18–45 years old) with varying host infection status was completed in 2019, but results are unpublished at the time of writing [16].

Phase IIA

Four candidates have recently completed or are currently in phase IIA trials: TB/FLU-04L, GAMTB-Vac, MTBVAC and ID93 + GLA-SE.

TB/FLU-04L comprises a recombinant replication-deficient influenza virus A expressing mycobacterial antigen ESAT-6, developed by Research Institute of Influenza, St Petersburg [17]. A randomized open-label phase I trial of intranasal or sublingual vaccine administration in 36 IGRA-negative 18- to 50-year-olds has demonstrated safety and tolerability [18]. A phase IIA trial in IGRA-positive individuals is being implemented.

GAMTBVac, a subunit recombinant vaccine containing mycobacterial antigens 85A and ESAT-CFP10, developed by the Gamaleya Research Institute of Epidemiology and Microbiology, Russia, demonstrated safety and underwent dose selection in phase I. An ongoing phase IIA trial to assess safety and immunogenicity (measured as interferon-gamma response) in BCG-vaccinated IGRA-negative adults is expected to be completed in 2020 [19].

In a randomized, double-blind controlled phase IIA trial, MTBVAC (live attenuated *Mycobacterium tuberculosis*) was found to have a similar safety and reactogenicity profile to BCG in infants, and a specific and durable immune response up to one year [20,21]. Two further phase IB/IIA safety and immunogenicity and dose-finding trials are currently recruiting in South Africa, in infants [22] and in adults [23].

Ongoing or upcoming trials of ID93 + GLA-SE (a recombinant protein comprising four Mtb antigens, combined with adjuvant GLA-SE) span phases I to IIA. Safety and age de-escalation has been demonstrated in a South Korean BCG-vaccinated IGRA-negative adolescent phase I trial [24]. Phase IIA demonstrated safety and immunogenicity in 60 adults (aged 18–60 years) with a history of previous treatment for drug-sensitive tuberculosis [25]. A phase IIA trial of 107 BCG-vaccinated IGRA-negative South Korean healthcare workers is ongoing, with expected completion in 2020 [26]. A phase IIB study of 1000 BCG-vaccinated adolescents and adults in South Korea, China, Indonesia, the Philippines and Thailand is planned [4].

Phase IIB

There are four candidates that have recently completed or are currently undergoing phase IIB proof-of-concept efficacy trials: H56:IC31, DAR-901, BCG revaccination and M72/AS01$_E$.

H56:IC31, a fusion protein of mycobacterial antigens 85B, ESAT-6 and Rv2660c with IC31 adjuvant, is currently in a phase IIB trial expected to report in 2022. The study is recruiting 900 HIV-negative adults who have been successfully treated for drug-sensitive tuberculosis [27], with primary end-point of culture-positive recurrent TB disease within 12 months after a second vaccination.

Since the introduction of BCG, only a single new vaccine candidate, SRL-172 (an inactivated whole cell booster derived from non-tuberculous mycobacterium), has demonstrated safety and efficacy in a phase III trial. However, the agar based manufacturing process could not be scaled. A candidate from the same master cell bank, DAR-901, has since been adapted for broth-based production, and recently completed a phase IIb trial [28,29]. This study measured the prevention of Mtb infection in 667 BCG-vaccinated, HIV-negative and IGRA-negative Tanzanian adolescents. A three-dose series of DAR-901 was safe and well-tolerated, but did not show any differences in either primary (IGRA conversion) or secondary (sustained IGRA conversion) end-points [30]. [Correction added on 22 January 2021, after first online publication: this paragraph has been amended.]

Given that the historical literature suggests uncertain BCG efficacy for preventing disease in adults and adolescents, the use of BCG revaccination has been largely discontinued and remains

implemented in only nine countries. However, questions regarding the value of BCG revaccination to protect Mtb-uninfected individuals at high risk of Mtb infection have resurfaced following a three-arm randomized controlled trial recruiting IGRA-negative, neonatally BCG-vaccinated adolescents in South Africa, which compared the efficacy of the new H4:IC31 vaccine candidate or BCG revaccination against a placebo [5]. H4:IC31 did not meet the primary efficacy end-point for the prevention of infection (POI vaccine efficacy: 9.4%, $P = 0.63$), and development was discontinued. However, BCG revaccination did meet the secondary end-point of prevention of sustained infection compared with placebo. Efficacy, measured by sustained IGRA conversion for 6 months, was 45.4% (95% CI; 6.4, 68.1) [5]. As the trial was not primarily designed to study this end-point, a larger trial is required to further investigate this result. A BCG revaccination trial of 1800 BCG-vaccinated IGRA-negative children and adolescents (age 10–18) has been initiated in South Africa, with a primary outcome of prevention of sustained IGRA conversion at 3 and 6 months [31]. Results are anticipated in 2025. Further studies are likely to be needed to investigate whether sustained IGRA conversion translates into prevention of TB disease.

The M72/AS01$_E$ vaccine was the first protein-adjuvant vaccine to demonstrate efficacy against TB disease. The vaccine consists of the M72 antigen (recombinant fusion of Mtb32A and Mtb39A) and the liposome-based AS01$_E$ adjuvant. The phase IIB proof-of-concept randomized, double-blinded, placebo-controlled study enrolled 3575 IGRA-positive HIV-negative adults aged 18–50 years in Kenya, South Africa and Zambia. The primary outcome was bacteriological confirmation of pulmonary tuberculosis, in HIV-negative individuals and sampled before initiation of any treatment. According to this primary case definition, the interim analysis at two years of follow-up demonstrated a vaccine efficacy of 54% (95% CI; 2.9, 78.2). In the final analysis, protection was sustained through to three years of follow-up with overall vaccine efficacy of 49.7% (95% CI; 2.1, 74.2) [6]. Furthermore, a sensitivity analysis on this primary end-point applying a more stringent case definition requiring two bacteriologically positive tests indicated vaccine efficacy of 68.0% (95% CI; 25.1, 86.3). The study also demonstrated a good safety profile and highly persistent humoral and poly-positive cellular responses. The encouraging results of this vaccine and next steps in development were the subject of two World Health Organization consultations in 2019 [32,33]. Consensus was generated around other priority populations requiring further safety and/or efficacy data, including IGRA-negative populations, HIV-positive populations, age escalation (>50 years), age de-escalation, broader geography and pregnant women. Two pathways to registration were considered: a traditional multi-country phase III or single-country accelerated licensure based upon the existing phase IIB data. The accelerated pathway could theoretically achieve first licensure by 2022 but would likely be for a much-restricted indication (e.g. HIV-uninfected, LTBI-positive individuals in South Africa). This would likely lead to subsequent challenges generalizing to other countries, as conducting further placebo-controlled trials once there is no longer equipoise may be deemed unethical. The traditional pathway could ensure broader indication and generalizability but would likely delay initial registration by at least 4–5 years. In January 2020, M72/AS01$_E$ was licensed by GSK to the Gates Medical Research Institute (GMRI). Technology transfer to GMRI and development of a large safety study in people living with HIV and planning of the phase III trial are underway.

Phase III

Three candidates have recently completed or are currently undergoing phase III trials: *M.vaccae*, VPM1002 and Immunovac/MIP.

M.vaccae (a heat-killed preparation of *Mycobacterium vaccae*, developed by Anhui Zhifei Longcom) is already licensed as adjunctive immunotherapy for the treatment of active tuberculosis in China. A phase III efficacy trial of a six-dose regimen investigating prevention of disease in 10,000 individuals with LTBI has been completed [34], and publication of the results is anticipated.

VPM1002 (recombinant BCG modified to improve immunogenicity, developed by the Max Planck Institute of Infection Biology and licensed through Vakzine Projekt Management to Serum Institute of India) has demonstrated safety and immunogenicity in phase I [35]. In an open-label randomized phase IIA trial in Cape Town, VPM1002 has shown safety, tolerability and immunogenicity in 48 HIV-unexposed newborns [36]. A phase IIB in HIV-exposed newborns is ongoing [37]. A phase II/III trial to investigate prevention of recurrence in 2000 participants who have successfully completed treatment for drug-sensitive tuberculosis is underway in India and expected to complete in 2020 [38].

A 12 000-participant three-arm multi-centre randomized placebo-controlled phase III trial to assess the ability of VPM1002 or Immunovac/MIP (below) for preventing disease in household contacts of patients diagnosed with sputum-positive pulmonary TB is underway in India [39].

Immunovac/MIP (heat-killed *Mycobacterium indicus pranii*, a nonpathogenic nontuberculous mycobacterium, produced by Cadila Pharma) has been reported to demonstrate safety and efficacy as an adjunctive therapy for pulmonary TB [40,41], but to our knowledge is being investigated as a prophylactic TB vaccine for the first time.

The potential impact of COVID-19 on TB vaccine trials

The COVID-19 pandemic is likely to have implications for TB vaccine trials. First, trials are likely to be disrupted, halted or delayed, leading to lower recruitment, ability to conduct follow-up visits and altered participant care seeking behaviour. At the time of writing, the phase IIB BCG revaccination confirmatory trial is on hold. Other trials due to start may also be delayed.

Second, COVID-19 may affect TB incidence in study populations through two opposing influences: social distancing and reduced access to care [42,43]. If social distancing reduces Mtb transmission, this may reduce end-point accrual, particularly infection outcomes, and potentially disease outcomes. If access to TB care is reduced, transmission and severity could increase. Preliminary mathematical models suggest that increased social distancing may reduce TB incidence in some settings, with minimal impact on TB deaths, which were found to increase substantially with disruption to TB care [42]. Finally, it is unknown whether COVID-TB coinfection interacts to alter the rate or severity of TB cases.

Conversely, TB vaccine development may benefit from scientific developments due to COVID-19, and vice versa. Importantly, it may be possible to leverage clinical trial sites from COVID-19 site mapping initiatives, and technological developments for remote data collection and digital health monitoring may provide valuable tools to facilitate follow-up in future TB vaccine trials. Public and governmental perception of the value of vaccines has also increased during the pandemic, which may positively affect TB vaccine acceptance and funding.

Summary of pipeline

The current prophylactic TB vaccine pipeline is diverse, with candidates across all phases of trials. Recent positive phase II efficacy results have shifted focus towards adolescent and adult TB vaccines. Several phase III trials are planned, including investigating prevention of disease endpoints. TB vaccine trial design has also evolved, shifting from demonstrating prevention of disease in infants, towards more studies assessing prevention of infection, disease or recurrence in adolescents and adults, including in proof-of-concept studies to de-risk progression to phase III.

Mathematical modelling of tuberculosis vaccines

Other than for BCG, the real-world efficacy of the vaccine candidates discussed above has not yet been established. Questions around their likely population-level impact, targeting, delivery strategy and cost-effectiveness remain, which mathematical modelling aims to address by leveraging empirical data, expert input and scenario analyses.

In 2016, Harris et al [44] published a systematic review of the tuberculosis vaccine modelling literature evaluating the body of knowledge on the epidemiological impact of future TB vaccines. Here, we briefly summarize this systematic review and update the systematic searches to reflect the latest developments in TB vaccine modelling.

Systematically reviewed literature to date

The original systematic review identified 23 studies modelling the epidemiological impact of new TB vaccines [44]. These were summarized based on their proposed vaccine characteristics, implementation setting and epidemiological impacts.

The review found that most studies modelled prevention of disease (POD) or prevention of infection (POI) vaccines in a preinfection (PRI) population, or a POD vaccine in a postinfection (PSI) population. Whilst no clear consensus was achieved regarding the relative impact of vaccine types by host infection status required for efficacy, PSI vaccines appeared to have a generally greater and more rapid impact on the tuberculosis epidemic than PRI vaccines.

The modelling suggested targeting vaccination to all ages, or to adults/adolescents in place of, or in

addition to, neonatal vaccination could substantially increase vaccine impact. Most studies were set in Asia, or modelled Asia-like epidemics. Few studies were set in Africa or included TB-HIV coinfection.

The review highlighted several research gaps, including the lack of studies investigating differential effects of PRI versus PSI efficacy, age targeting of vaccines, impact of vaccines on drug-resistant tuberculosis, nonrandom mixing of individuals or impact of changing mixing patterns on vaccine impact.

Updated systematic literature review

Search methods

We systematically searched PubMed, Embase and the WHO Global Health Library for mathematical modelling studies reporting the epidemiologic impact of new human tuberculosis vaccines since 1 January 2016 using the same search terms as Harris et al [44]. Three-stage sifting was conducted independently by two reviewers (CKW and RAC). We included mathematical modelling studies estimating epidemiologic outcomes of TB vaccination. We excluded studies that modelled BCG vaccines with a single efficacy, studies that modelled the *in vitro* or immunological effects of vaccination, and reviews or commentaries that did not add new results or analysis. The full inclusion and exclusion criteria, search terms and flow diagram are presented in the supporting information.

Experts were also consulted to identify research aims and methods of unpublished work to identify where research gaps may be met by upcoming research.

We first describe the characteristics of the included studies by summarizing the principal modelling methods, vaccine characteristics and subgroups (including risk groups) included in the models. We then discuss and narratively synthesize the findings of these models, grouping the studies by comparison type. We employed the modelling study quality and risk-of-bias appraisal tool developed by Harris et al [44], assessing study design and reporting against 14 criteria, for a maximum score of 28 points.

Results

From 380 records identified through database searches, we identified seven published studies for inclusion. Through expert input, we also identified two unpublished studies and one study published after the search date. The modelled vaccine profiles and outcomes in the eight published papers are summarized in Table 1, and the research aims of the unpublished studies are briefly summarized.

Modelling methods. Seven of the eight included studies used compartmental difference or differential equation models [10,11,45–49], whilst one study implemented an individual-based model [50].

Vaccine characteristics. Vaccine efficacy of 40–80% was most frequently modelled [10,11,45–47,49,50]. Three studies modelled efficacy up to 100% [11,45,48]. Most studies varied vaccine efficacy in discrete intervals to undertake sensitivity analyses around assumptions of vaccine impact [10,11,45,49,50].

Vaccines were modelled as 'leaky' (also known as 'degree') vaccines, where all vaccine recipients receive protection proportional to the vaccine efficacy, in five studies [10,11,45,46,50]; two studies modelled vaccines assuming 'all-or-nothing' (also known as 'take') efficacy, where all successfully vaccinated individuals are completely protected [48,49]. We could not determine whether the vaccine was degree or take in one study [46].

Vaccines providing 10 years of protection were modelled in six studies [10,11,45,46,49,50]. Of these, three modelled durability of greater than 10 years, including up to 40 years [46] and lifelong [48]. One study modelled durations ranging from 2 years to lifelong [11]. One study [48] modelled only lifelong protection, and one study modelled an average vaccine half-life of five years [47]. Vaccine waning was modelled as exponential decay [47] or as 'exact' where all vaccine recipients lost protection at the end of the duration of protection [11].

The eight studies modelled a spectrum of host infection status required for efficacy and prevention of disease and/or infection effect. Two studies, one modelling a POI vaccine [48] and one modelling a POD [49] vaccine, did not specify the host infection status required for efficacy. In contrast, POD and POI effects were modelled in four [10,11,45,46] that assumed PRI efficacy, four studies that assumed PSI efficacy [10,11,45,50] and three that assumed P&PI efficacy [10,11,45]. Two studies modelled PSI efficacy with both POD

Table 1. *Summary of the new literature modelling the epidemiological impact of new TB vaccine impact* (n = 7)

				Vaccine Characteristics											
Author and Year	Summary of Aims	Methods	Setting	Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized[+]	Duration of protection	Age targeting	Other targeting	Infection Status Targeting	Schedule	Time horizon	Outcomes
Shrestha et al. 2016 [49]	Epidemiological impact of spatially targeted vaccination	DE	Gujarat, India	P&PI	POD	60% (degree)	Routine: 80% Mass: 8%	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Untargeted	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 24%
						60% (degree)	Routine: 80% Mass: 80%	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: Similar to UTV
						60% (degree)	Routine: 80% Mass: 80% 1% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 25%
						60% (degree)	Routine: 80% Mass: 80% 3% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 28%
						60% (degree)	Routine: 80% Mass: 80% 5% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 31%
Liu et al. 2017 [48]	Epidemiological impact of 'pulsed' mass vaccination strategy compared with neonatal vaccination	DE	China	PRI	POI	100% (take)	95%	95%[+]	L/L	Neo	-	Uninfected	Routine	18 years	Cannot achieve 2035 End TB goals
						100% (take)	Routine: 70–80% Mass: 10-40%	Routine: 70–80%[+] Mass: 10-40%[+]	L/L	Routine: Neo Mass: All	-	Uninfected	Routine: annual Mass: 3–6 yearly	18 years	Can achieve 2035 End TB goals with 70% neo and 25% 5-yearly mass coverage. Could be achieved sooner with more frequent campaigns or higher coverage.
Shrestha et al. 2017 [50]	Epidemiologic impact of targeting a mining community in South Africa	IBM	South Africa	P&PI	POD	60% (degree)	100% miners	60%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	ICA: 8090 (3750–13300) CAPVD: 0.374
						40% (degree)	100% miners	40%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	CAPVD: 0.276
						80% (degree)	100% miners	80%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	CAPVD: 0.457
						60% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	ICA: 5,510 (2360–10000) CAPVD: 0.254
						40% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	CAPVD: 0.168
						80% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	CAPVD: 0.346
Fu et al. 2018 [46]	Effects of discontinuing BCG in an intermediate burden setting	DE	Taiwan	PRI	POI & POD	29% POD for EP (degree)	100% (assumed)	29%[+]	10 years	Neo	-	Uninfected	Annual (routine)	2018–2027	Discontinuing BCG results in 2.8 (2.3–3.2) additional TB cases
						22% POI; 54% POD for pulmonary TB; 54% POD for EP (degree)	n/s	n/e	10 years	Neo	-	Uninfected	Annual (routine)	2018–2027	Discontinuing BCG results in 82.9 (72.6-91.6) additional TB cases
Renardy and Kirschner 2019 [47]	Assessing the impact of age targeting a PRI vaccine and a PSI vaccine in endemic and nonendemic settings with a continuous age structure	PDE	Cambodia	PRI, PSI-L&R	POI (PRI vaccine) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI: 12–15 yo PSI: 50–70 yo	-	PRI vaccine: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized in 2075
				PRI, PRI (neo), PSI-L&R	POI (PRI vaccines) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI vaccines: Neo, 18–30 yo PSI-L&R Vaccine: 50–70 yo	-	PRI vaccines: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized in 2075, the second PRI vaccine acts as a booster to the neonatal BCG vaccination
			USA	PRI, PSI-L&R	POI (PRI vaccine) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI: 22–30 yo PSI: 50–70 yo	-	PRI vaccine: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized at all years evaluated (2035, 2050, 2075) if the PRI vaccine is targeted to ages 22–30 and the PSI-L&R vaccine is targeted to ages 50–70

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics								Infection Status Targeting	Schedule	Time horizon	Outcomes
				Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized*	Duration of protection	Age targeting	Other targeting				
Harris et al. 2019 [10]	Evaluating age targeting of TB vaccines in China	DE	China	PRI	POD	60% (take)	70%	42%+	10 years	Ado	-	Uninfected	Annual (routine) for 15yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 1.7% (1.4, 2.3), ICA (1000s): 248 (214, 292), NNVc: 1278 (1087, 1481)
					POD	60% (take)	70%	42%+	10 years	Older Adult	-	Uninfected	Annual (routine) for 60yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 3.3% (2.3, 5.3), ICA (1000s): 370 (287, 504), NNVc: 1022 (752, 1318)
				PSI - L	POD	60% (take)	70%	42%+	10 years	Ado	-	Latent	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 0.05% (0.04, 0.07), ICA (1000s): 8 (6, 11), NNVc: 40 065 (29 505, 52 492)
					POD	60% (take)	70%	42%+	10 years	Older Adult	-	Latent	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 6.1% (1.3, 8.7), ICA (1000s): 658 (131, 1081), NNVc: 574 (350, 2886)
				PSI - L&R	POD	60% (take)	70%	42%+	10 years	Ado	-	Latent, recovered	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 0.07% (0.05, 0.09), ICA (1000s): 12 (9, 16), NNVc: 26,831 (20 437, 34 840)
					POD	60% (take)	70%	42%+	10 years	Older Adult	-	Latent, recovered	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 10.8% (10.2, 11.2), ICA (1000s): 1295 (1037, 1469), NNVc: 292 (257, 365)
				P&PI	POD	60% (take)	70%	42%+	10 years	Ado	-	Uninfected, latent, recovered	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 1.8% (1.5, 2.4), ICA (1000s): 259 (224, 304), NNVc: 1223 (1043, 1414)
					POD	60% (take)	70%	42%+	10 years	Older Adult	-	Uninfected, latent, recovered	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 13.8% (12.9, 15.2), ICA (1000s): 1643 (1403, 1893), NNVc: 230 (199, 269)
Awad et al. 2020 [45]	Impact of targeting diabetic individuals with TB vaccines in India	DE	India	PRI	POD	60% reduction in fast progression (degree)	50%	30%+	10 years	n/s	All DM	Uninfected	Annual (routine)	30 years	2050 NNVc 38
				PSI	POD	60% reduction in fast progression; + 50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	Uninfected	Annual (routine)	30 years	2050 NNVc 14
					POD	50% reduction in reactivation (degree)	50%	25%+	10 years	n/s	All DM	Latently Infected	Annual (routine)	30 years	2050 IRR 4.8% 2050 NNVc 105
					POD	50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	Latently Infected	Annual (routine)	30 years	2050 NNVc 25
				P&PI	POD	60% reduction in fast progression; 50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	All	Annual (routine)	30 years	2050 IRR 20.8% 2050 NNVc 17
Harrois et al. 2020 [11]	Impact of vaccine characteristics focusing on POI/POD and duration in China, India,	DE	China	P&PI	POI&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 79% (77–81) ICA: 11.6 million (10.2–12.6), IDA: 0.3 million (0.1–0.5) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 51% (50–51)
				PRI	POD	70% (degree)	Routine: 80%	Routine: 80%	10 years	Routine: 9 yo	-		Routine: annual	26 years	2050 IRR: 19% (14–24)

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics: Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized*	Duration of protection	Age targeting	Other targeting	Infection Status Targeting	Schedule	Time horizon	Outcomes
	and South Africa						Mass: 70%	Mass: 70%		Mass: ≥10 yo		Uninfected, latent, recovered	Mass: 10 yearly		
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 1% (1–2)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 21% (17–26)
				PRI	POI or POI&D	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	BCG-like vaccine. 2050 IRR POI: 16% (13–20) 2050 IRR POI&D: 21% (17–27)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine. 2050 IRR 3-year duration: 4% (3–6) 2050 IRR 10-year duration: 37% (36–37)
			South Africa	P&PI	POI&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 84% (81–87) ICA: 4.3 million (2.5–7.0), IDA: 0.9 million (0.5–1.6) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 52% (44–58)
				PRI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 36% (24–47)
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 12% (4–24)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 37% (28–47)
				PRI	POI or POI&D	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	BCG-like, contraindicated in HIV-positive populations. 2050 IRR POI: 16% (13–20) 2050 IRR POI&D: 21% (17–27)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine. 2050 IRR 3-year duration: 7% (1–11) 2050 IRR 10-year duration: 34% (25–42)
			India	P&PI	POI&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 90% (87–94) ICA: 51.4 million (32.6–76.6), IDA: 4.3 million (2.5–8.4) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 54% (44–61)
				PRI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 51% (42–65)
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 17% (8–31)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 50% (42–64)
				PRI		50% (degree)	Routine: 80%	Routine: 16%	10 years	Routine: 9 yo	-		Routine: annual	26 years	BCG-like vaccine.

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics									Time horizon	Outcomes
				Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized[+]	Duration of protection	Age targeting	Other targeting	Infection Status Targeting	Schedule	
					POI or POI&D		Mass: 70%	Mass: 14%		Mass: ≥10 yo		Uninfected, latent, recovered	Mass: 10 yearly		2050 IRR POI: 39% (32–53) 2050 IRR POI&D: 52% (44–67)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine. 2050 IRR 3-year duration: 11% (8–15) 2050 IRR 10-year duration: 41% (32–46)

Ado, adolescent; BCG, bacillus Calmette–Guérin; CAPVD, Cases Averted Per Vaccine Dose; DE, deterministic/ dynamic/ difference/ differential equation; DM, diabetes mellitus; EP, extrapulmonary tuberculosis; IBM, individual-based model; ICA, incident cases averted; IDA, incident deaths averted; intro, introduced; IRR, incidence rate ratio; L/L, lifelong; n/e, not estimated; n/s, not stated; neo, neonatal; NNVc, number needed to vaccinate to prevent one TB case; P&PI, pre- and postinfection; PDE; partial differential equation; POI, prevention of infection; POI&D, prevention of infection and disease; PRI, preinfection; PSI, postinfection; PSI-L, postinfection: effective in latent infection; PSI-L&R, postinfection: effective in latent and resolved infection; STV, spatially targeted vaccination; TB, tuberculosis; UR, uncertainty range; UTV, untargeted vaccination; yo, year olds; yr, year. [+]Calculated as (coverage × efficacy) where possible.

and POI effects [11,47] and three studies modelled PRI efficacy with both POD and POI effects [11,46,47].

Vaccine deployment, setting, population and risk groups. Eight studies implemented country-level models, two of which were set in multiple countries [11,47]. Three modelled Mtb transmission in China [10,11,48], three in India [11,45,49] and two in South Africa [11,50]. One study compared a high-income country with low Mtb transmission (the United States) against a lower-middle-income country with high levels of Mtb transmission (Cambodia) [47]. Only one study, which investigated spatial targeting, modelled at a subnational level (in the Indian state of Gujarat) [49].

All models were age-structured. Two models stratified their populations by HIV status [11,50]. Both studies modelled an increased risk of TB disease progression and reactivation in people living with HIV, represented antiretroviral therapy (which reduced the impact of HIV on TB progression) and included HIV-specific mortality rates. Shrestha et al. also included age- and sex-specific risk of HIV acquisition and increased risk of TB incidence with decreasing CD4 + cell count. Both studies assumed that new TB vaccines were effective in HIV-positive populations, but one [11] further varied vaccine safety and efficacy in HIV-positive populations. In this study, vaccine protection in HIV-positive individuals was modelled at three levels: equal to HIV negative, 20% relative reduction in protection than HIV negative and contraindicated (not administered).

A single study, set in India, included a diabetes mellitus (DM) stratum [45]. DM was modelled as influencing TB natural history and treatment outcomes, and the DM burden was calibrated to age- and time-specific trends. Vaccination was targeted solely to individuals with DM to assess the population impact of targeting interventions to this risk group. This study did not investigate differential vaccine efficacy by DM status.

Heterogeneous mixing was implemented in four studies [10,11,49,50]. Two studies implemented age-specific contact matrices based on empirical data for China [10,11], and one for South Africa [11]. One study [49] investigated targeting new TB vaccines to high incidence spatial 'hotspots', compared with random untargeted community vaccination. This population-based model implemented

homogeneous mixing within hotspot and non-hotspot populations, but differential mixing between them. Differential inter-population mixing was modelled by varying the fraction of the per capita hazard of Mtb infection generated in each population, which results in Mtb transmission to members of the alternate population. One further study [50] developed an individual-based model of Mtb transmission in miners and their original labour sending communities. This model investigated the impact of targeted vaccination amongst miners in comparison with random vaccination of their originating communities. Miners were assumed to travel to and stay at the mine whilst employed, where they only mix with other miners; on returning to their original communities, they mix with nonminers.

Epidemiologic impact of future new TB vaccines. Seven studies modelled new, hypothetical vaccines [10,11,45,47–50], one of which also included modelling of the potential impact of adolescent BCG revaccination [11]. One study [46] modelled the impact of discontinuing BCG vaccination, with BCG vaccine efficacy varied during scenario analysis. These eight studies, along with their respective modelled vaccine profiles, are summarized in Table 1.

Age-based vaccine targeting—Three studies compared the impact of targeting vaccine delivery by age [10,47,48].

Harris et al [10] investigated the relative impact of targeting adolescents for vaccination compared with older adults in China. Delivery to adolescents was modelled as routine annual vaccination, with 70% coverage of 15-year-olds, beginning in 2025 with an initial catch-up campaign to 16- to 19-year-olds. For older adults, routine vaccination was delivered to 60-year-olds with a catch-up campaign delivered to 61- to 64-year-olds. Due to the low-transmission, high-relapse and reactivation-driven TB epidemic in China, the study found that older adult targeting of vaccination resulted in greater TB incidence rate reduction and lower number needed to vaccinate per case averted than adolescent targeting across all modelled vaccine characteristics.

Liu et al [48] found that routine neonatal vaccination with a high efficacy (100%) vaccine delivered with 95% coverage from 2018 to onwards in China failed to achieve the 'End TB' incidence rate reduction goal by 2035. In contrast, End TB goals were achieved with a mixed targeting strategy, with routine annual neonatal vaccination with 70% coverage, combined with 5-yearly pulsed mass vaccine campaigns applied to all ages with 25% coverage. Decreased inter-pulse intervals and increased mass campaign coverage were predicted to achieve the End TB goals sooner, with 80% neonatal coverage combined with 30% 3-yearly mass campaign coverage from 2018 accomplishing the goals by 2030.

Renardy and Kirschner [47] compared the effect of delivering PRI-POI and PSI-POD vaccines, simultaneously, with two distinct age groups in a high transmission (Cambodia) and low transmission (the United States) setting. They found that TB incidence in 2075 was minimized in the United States through PRI-POI vaccination of adolescents (aged 12–15) and PSI-POD vaccination of adults (aged 50–70). In contrast, in Cambodia, the optimal age group for PRI-POI vaccination increased to age 22–30. Further, in the low transmission setting, the age group targeted for PSI-POD vaccination was a greater determinant of vaccine impact than the age group targeted for PRI-POI vaccination. The latter effect was attributed to a lower rate of primary Mtb infection in the low transmission setting. The study also found that including high coverage routine PRI-POI neonatal vaccination in a high transmission setting potentially reduced TB incidence in 2075 further and shifted the optimal age for adolescent PRI-POI vaccination upwards (to 18- to 30-year-olds).

Host infection status required for efficacy and mechanism of effect—Three studies directly compared vaccines profiles with varying host infection status required for efficacy. One of these studies also compared the relative impact of POI versus POD vaccines.

In the Awad et al [45] model, PRI-POD, PSI-POD and P&PI-POD vaccines were administered to individuals with diabetes mellitus (DM) in India with 50% coverage. The outcome of interest was the number of individuals who needed to receive vaccination to avert a single TB case (NNVc). This study assumed that a PRI vaccine was only administered to DM individuals without TB, whereas a PSI vaccine was only delivered to DM individuals with latent TB. PRI-POD vaccination of populations with DM (conferring lifelong duration of protection, with 60% protection against fast progression following infection, 50% reduction in reactivation

from latent TB and a 50% reduction in infectiousness) was found to result in an NNVc of 14 by 2050. In contrast, PSI-POD vaccination of populations with DM (conferring lifelong duration of protection, 50% reduction in reactivation from latent TB and 60% reduction in infectiousness) was predicted to achieve an NNVc of 25. Finally, simultaneous PRI-POD and PSI-POD vaccination of populations with DM was predicted to achieve an NNVc of 17. Despite lower overall impact, PSI vaccination had a faster epidemiologic impact.

The study of age-targeted vaccination in China by Harris et al [10] modelled POD vaccines and directly compared PRI-POD, PSI-POD, P&PI-POD and a further subtype of PSI vaccination only effective in reducing reactivation from latent TB infection (PSI-L-POD). The study found P&PI-POD, PSI-POD, PSI-L-POD and PRI-POD vaccination of older adults achieved TB incidence rate reductions in 2050 of 13.8% (uncertainty range: 12.915.2), 10.8% (UR: 10.2–11.2), 6.1% (UR: 1.3–8.7%) and 3.3% (UR: 2.3–5.3), respectively. For adolescent vaccination, P&PI-POD and PRI-POD vaccination led to incidence rate reductions in 2050 of 1.8% (UR: 1.5–2.4) and 1.7% (UR: 1.4–2.3), respectively. Adolescent PSI-POD and PSI-L-POD vaccination had a comparatively small impact, leading to incidence rate reductions of 0.07% (UR: 0.05–0.09) and 0.05% (UR: 0.04–0.07), respectively. As above, these findings likely represent a TB epidemic dominated by relapse-driven disease in the elderly population, with a smaller contribution by primary Mtb infection of younger age groups.

In a separate study, Harris et al [11] directly compared the effect of all combinations of P&PI, PSI and PRI against POI, POD and prevention of infection and disease (POI&D) across China, South Africa and India, with the latter reflecting epidemics with greater levels of transmission. Vaccines with a POD effect were found to have the greatest impact overall. A 10-year, 70% efficacy PSI-POD vaccine delivered routinely to 9-year-olds, with 10-yearly campaigns to those aged 10 and above, was predicted to achieve incidence rate reductions of 51% (UR: 50–51), 52% (44–58) and 54% (44–61) in China, South Africa and India, respectively. In contrast, PSI-POI vaccination (vaccines which protect against reinfection) achieved the smallest incidence rate reduction, leading to 1% (1–2), 12% (4–24) and 17% (8–31) in China, South Africa and India, respectively. The impact of PRI-POI and PSI-POI vaccines was intermediate and comparable to one another. In South Africa, a 100% efficacy, 10-year P&PI-POI&D vaccine with equal efficacy between HIV-positive and HIV-negative populations was predicted to achieve incidence rate reductions of 84% (81–87%), falling to 79% (72–84%) and 62% (44–74%) with a relative efficacy reduction of 20% compared with HIV-negative populations or contraindicated in HIV-positive individuals, respectively.

Non-age risk group targeting—Two studies compared targeting subpopulations (not based on age) against untargeted mass vaccination.

Shrestha et al [50] compared the impact of targeting members of a mining population with untargeted vaccination of the originating labour sending community. Mine-targeted vaccination averted 1.46 (95% range: 1.13–1.91) times more TB cases than community vaccination. The greater impact of mine targeting was correlated with the proportion of incident TB occurring amongst adult men (all miners were adult men in this model). Similarly, the study found that the proportion of adult men in the original labour sending community was inversely related to the impact of mine targeting. The study concluded that occupational targeting may be most effective where a substantial demographic gradient of TB incidence with a concurrent demographic gradient by occupation exists.

In a separate study, Shrestha et al [49] compared vaccinating high incidence spatial 'hotspots' of TB with spatially untargeted vaccination in Gujarat, India. With no mixing of individuals between hotspots and the general population, targeting either population led to comparable incidence rate reductions (approximately 24% compared with no vaccine). Vaccination of hotspots with increasing levels of inter-population mixing was predicted to lead to progressively higher vaccine impact. Spatially targeted vaccination was predicted to be more impactful as the relative size of TB incidence in hotspots relative to the general population was increased.

Health economic analyses—Fu et al [46] modelled the cost implications of discontinuing the national BCG programme in an intermediate burden setting (Taiwan), varying BCG efficacy against pulmonary and extrapulmonary TB and accounting for decreased BCG-related side effects and increased

TB incidence. This study found BCG discontinuation to be cost-saving over all scenarios of vaccine efficacy; the incremental cost of TB treatment because of increased burden was small compared with reduced costs of BCG vaccination.

Modelled time frame—The WHO/Stop TB global targets aim to reduce TB incidence rates to 10 cases per 100 000 population per year by 2035, and 'eliminate' TB by 2050 (<1 case per million population). Liu et al [48] presented results suggesting 2035 goals could be met, but assumed vaccine introduction in 2018 and required relatively frequent mass campaigns in addition to neonatal vaccination. Five studies modelled time horizons until at least 2050 [10,11,45–47]. Four of these studies [10,11,45,47] projected that the scenarios of novel vaccines and implementation modelled may not achieve 2035 nor 2050 goals in the countries modelled (Cambodia, South Africa, India and China), but would likely provide an important contribution towards reduction in incidence and cases averted. One study [46] presented outcomes not aligned with 'End TB goals'. Two studies specified their models in relative time, rather than calendar time, so could not be compared with WHO goals [49,50].

Modelling studies in relation to the vaccine pipeline. Only one study [46] modelled a currently in-use vaccine (BCG). As the remaining published studies modelled hypothetical vaccines, their results cannot be directly mapped to the possible epidemiologic impact of late-stage vaccine pipeline candidates. Moreover, not all candidates in the late-stage pipeline have been assessed across comparable populations and implementation scenarios to those in the modelling studies. However, there are broad overlaps between the known (or under-investigation) host infection status required for efficacy and mechanism of effect pipeline vaccine candidates and vaccines investigated in the modelling studies (Table 2), with one study explicitly modelling vaccines with M72/AS01$_E$ and BCG revaccination-like characteristics [11]

M72/AS01$_E$, VPM1002, Vaccae, MIP/Immunovac and H56:IC31 have been investigated or are under investigation for POD effect in PSI populations (Fig 2). Correspondingly, studies by Harris et al [10,11], Awad et al [45], Shrestha et al [49,50] and Renardy and Kirschner [47] have modelled the possible impact of vaccines with PSI-POD effect. VPM1002 is planned to be investigated for PRI-POD efficacy, modelled by Fu et al [46], Harris et al [11] and Awad et al [45]. Finally, PRI-POI effect has been investigated for BCG revaccination and DAR-901 and modelled most closely by Fu et al [46], Renardy and Kirschner [47], Harris et al [11] and Liu et al [48]. Finally, two unpublished studies (below) are expected to directly model epidemiologic impact and cost-effectiveness of M72/AS01$_E$ or M72/AS01$_E$-like vaccination [51,52].

Quality appraisal. We found study quality scores ranging from 11 to 26 out of 28, with a median score of 23 points (Table S4). The major quality gap was in model validation: only 1 of 8 studies [45] was validated.

Unpublished studies. We describe two unpublished studies presented as conference abstracts, identified through expert consultation. The first study was an age-structured dynamic transmission model, which investigates the impact and cost-effectiveness of routine adolescent M72/AS01$_E$ vaccination in India and South Africa [51]. This study includes stratification by HIV status in South Africa. The second study was an age-, drug resistance- and treatment history-stratified dynamic transmission model, which models PRI, PSI and P&PI vaccines with POD effect in India and China, reporting vaccine impact on drug-resistant tuberculosis and cost-effectiveness [52]. Both studies explore outcomes over the 2050 time frame.

Discussion

Since the last systematic review of the epidemiologic impact of TB vaccine modelling literature in 2016 [44], new studies have investigated the differential impact of PRI versus PSI vaccines, combinations of POI and POD effect, and age and risk group targeting of vaccination. Whereas in the previous review, the reason for the polarization of outcomes for PRI versus PSI vaccines was unclear, the new studies reviewed here suggested that PSI versus PRI impact may be driven by the level of Mtb transmission in the modelled epidemiologic setting. Where disease incidence is driven more by reactivation or relapse rather than new infections with fast progression to disease, PSI vaccines were predicted to have greater impact. This differential impact for PRI versus PSI vaccines in recurrence-driven settings like China becomes greater when vaccines are age-targeted: PSI vaccines were most impactful when delivered to older populations.

Similarly, when both PRI and PSI vaccines were deployed simultaneously, to adolescents and older adults, respectively, the age group to which PSI vaccines were targeted was the major determinant of overall vaccine impact in a low transmission environment (the United States). In contrast, in a high transmission environment (Cambodia), the major determinant was the age group to which PRI vaccine was targeted. In the previous review, no models had explicitly explored targeting of vaccination of older adults or the elderly, an evidence gap that has now begun to be addressed in the literature. Finally, evidence for the value of all-age mass campaigns as a supplement to continuous routine neonatal vaccination has also been strengthened.

Seven of eight studies modelled vaccines that included POD effect [10,11,45–47,49,50], whereas only two studies modelled a vaccine with only POI effect [11,48]. One study [11] directly compared POI versus POD vaccination. This study found that PSI-POD vaccination would be likely to have a substantially larger epidemiologic impact than PRI-POD vaccination over the 2050 time frame, but that PRI-POI and PSI-POI vaccination would likely lead to intermediate impact, so POD vaccines would provide greatest impact over the 2050 time frame if effective in PSI populations. Finally, modelling studies have begun to reflect the latest developments in the vaccine development pipeline, now explicitly representing M72/AS01$_E$- and BCG revaccination-like characteristics.

New developments include studies that investigated vaccine targeting to individuals with diabetes mellitus [45], targeting by occupation [50] and targeting to spatial hotspots [49]. These results suggested that targeting of risk groups may contribute to efficiently reducing overall burden, through a lower number of people needed to vaccinate per TB case averted. It is noted that risk group targeting has been studied only in narrow contexts and the generalizability of these findings across epidemiologic settings is unknown. Moreover, other epidemiologically important risk groups, for example malnourished populations [53], may need evaluation depending on context.

Significant research gaps persist. The only study to investigate the impact of vaccination on drug-resistant TB [52] remains unpublished. No new studies investigated how vaccine impact might interact with nonvaccine interventions such as preventive therapy for latent Mtb infection, novel diagnostic technologies or changes to national TB policy, including active case finding strategies. Few studies implemented heterogeneous mixing other than between age groups (e.g. between miners and nonminers, between a hotspot population and nonhotspot populations). No studies assessed how changing patterns of social contact in the general population over time might affect TB vaccine impact. Whilst we identified three new model settings (Taiwan, Cambodia and the United States), the remaining studies remained focused on China, India and South Africa. Studies in other high-burden countries, including Indonesia, the Philippines, Pakistan, Nigeria or Bangladesh that collectively account for 28% of global TB burden, were lacking [1]. Moreover, only one study investigated a subnational setting. As implementation-related questions arise, subnational models will be needed for large, heterogeneous countries. In the previous review, HIV stratification was only present in four studies and was identified as an important research gap for exploring vaccine impact. Of two new studies that included people living with HIV, one investigated differential vaccine safety and efficacy by HIV status. In South Africa, where HIV prevalence is high, contraindication in HIV-positive populations was found to substantially reduce the overall epidemiologic impact of TB vaccination. However, neither study investigated HIV-related targeting. Whilst incremental progress has been made, the impact of TB vaccines on TB-HIV coinfection remains underexplored. One unpublished study including HIV stratification investigating vaccine cost-effectiveness in a high-HIV-burden setting may contribute towards addressing this research need [51].

Previous modelling literature found new TB vaccines to be an overwhelmingly cost-effective intervention. New economic analyses were limited to questions around BCG, and gaps remain for assessing the full potential value of new TB vaccines and for estimating the value of reducing uncertainties around estimates of vaccine impact. Studies have not explored differential costs of differential routes of administration or dose regimens. Finally, the range of vaccine implementation strategies was limited, with no exploration of country-specific delivery strategies grounded in local capacity, strategic objectives or costs. However, cost-effectiveness analyses of new TB vaccines are underway with publication anticipated.

The key strength of this review is the conduct of independent search, filtration, data extraction and quality appraisal by two authors. Analysis of study results was limited by lack of access to underlying data, leading to crude estimates of outcomes such as proportion immunized (if these data were not reported). We found that the median quality of new TB modelling studies was slightly higher than in the previous review, possibly reflecting continuing maturation of TB vaccine modelling as a field.

Our findings, taken together with the results from the systematic review by Harris et al [44] in 2016, suggest a growing consensus amongst TB vaccine models. Overall, Mtb transmission is driven by pulmonary disease amongst adults, with a relatively larger contribution from younger adults in high transmission settings, for example Cambodia, or the elderly in high reactivation settings, for example China. Effective vaccines targeted towards these higher burden populations are likely to achieve a greater and more rapid epidemiologic impact than vaccines targeted towards neonates. As such, routine or period mass campaigns of adolescents and/or adults may be required if End TB targets are to be met. However, the specific characteristics of any new vaccine, and epidemiology within the population to which it is being introduced, must be factored into targeting and deployment strategies. If multiple vaccine candidates with differing characteristics (e.g. PRI vs PSI efficacy) are successfully developed, mixed vaccination strategies targeting differing groups may be appropriate depending on the specific epidemiology of the target setting. Previous work has found adult and adolescent tuberculosis vaccination to likely be overwhelmingly cost-effective. Whilst no further cost-effectiveness analyses have been published, the epidemiological evidence now suggests that targeting to (context-specific) risk groups may be more efficient in terms of number needed to vaccinate per case averted. The cost-effectiveness of such targeting strategies must be explored to inform optimal implementation strategies. Evidence for the impact of vaccines on other cost drivers, such as drug-resistant tuberculosis, needs further exploration and is upcoming. Overall, the implementation aspects of TB vaccine delivery remain underexplored. As there is little precedent for large-scale adolescent and adult vaccination in the order likely required for TB control, and as

Table 2. *Overlap between known or under-investigation host status required for efficacy and mechanism of effect in late-stage vaccines and vaccines in modelling studies*

Investigated for efficacy in:	BCG revaccination PRI-POI	DAR-901 PRI-POI	H56:IC31 PSI-POD	M72/AS01E PSI-POD	MIP/ mmunovac PSI-POD	Vaccae PSI-POD	VPM1002 PRI-POD PSI-POD
Shrestha et al. [49]			a	a	a	a	a
Liu et al. [46]	a	a					
Shrestha et al. [50]			a	a	a	a	a
Fu et al. [46]	a	a					a
Renardy and Kirschner [47]	a	a	a	a	a	a	a
Harris et al. [10]			a	a	a	a	a
Awad et al. [45]			a	a	a	a	a
Harris et al. [11]	a	a	a	a	a	a	a
Harris et al. (unpublished) [51]			a	a	a	a	a
Weerasuriya et al. (unpublished) [52]			a	a	a	a	a

[a]Indicates that a vaccine candidate (column) had characteristics overlapping with a vaccine profile investigated in a modelling study (row). Overlap in vaccine efficacy and duration of protection are not shown.

candidates progress towards licensure, such studies will become increasingly important to inform decision-making.

Concluding remarks and future directions

We have identified critical priorities for M72/AS01$_E$ and BCG revaccination, for other late-stage candidates, for modelling and for the field as a whole.

A larger confirmatory M72/AS01$_E$ trial, currently in-design, should be powered to improve the precision of efficacy estimates, include uninfected populations and further assess safety and immunogenicity in HIV-infected people. Further investigations will need to explore protection in other high-risk groups and the duration of vaccine protection. Results from multiple geographical settings may be required to generalize findings. Investments are needed not only for the next phase of clinical trials, but also to ensure sustainable and affordable supply of vaccine antigens and adjuvant. Preparatory work on licensure and policy pathways, equitable access and delivery should be initiated early to allow rapid implementation, should phase III trial results be positive.

For BCG revaccination, the priority is completing the ongoing confirmation of efficacy trial to estimate vaccine efficacy with more precision, as the original confidence intervals were wide [5]. Further trials are likely to be needed to explore efficacy against disease. Even if confirmed, obstacles to BCG delivery would include its current contraindication for people living with HIV. Support for other candidates should continue in case BCG revaccination or M72/AS01$_E$ do not succeed, and to ensure a pipeline of next-generation vaccines.

Samples from the two recent efficacy trials [5,6] are being examined to identify mechanisms and correlates of protection, which should lead to a better understanding of protective immunity against TB. This, in turn, should guide future vaccine discovery and accelerate the clinical testing of candidates. Trials incorporating other important risk groups, such as the elderly, patients with diabetes or pregnant women, will become important as candidates advance towards the end of the development pipeline.

Tuberculosis vaccine modelling has produced useful new insights over the past four years, by exploring the differential impact of vaccine characteristics, age targeting, spatial or risk group targeting and accounting for drug-resistant TB. Future models should generate evidence on the full value proposition of TB vaccines including comparison with other interventions, more realistic implementation strategies including vaccine targeting, and estimating the value of information to reduce uncertainties about BCG revaccination and M72/AS01$_E$ impact.

The TB vaccine field needs to progress strategically. An increase and diversification of resources is required because currently available funding for TB vaccines [54] is insufficient. Allocation of these resources should include the discovery and development of early pipeline candidates and increasing clinical trial capacity.

Finally, we must prepare now for the prompt and equitable implementation of a successful new vaccine, so that the benefits are felt quickly by people most in need.

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Conflict of interests

RCH reports employment by Sanofi Pasteur, unrelated to TB and outside the submitted work. All other authors have nothing to disclose.

Author contributions

CKW, RGW and RCH conceived the review. CKW and RAC undertook the modelling literature search, review and data extraction. CKW analysed

the results of the literature review. RAC and RCH identified and extracted clinical pipeline data. CKW led writing of the first draft of the article, with contributions from all authors. All authors approved the final draft.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Research question PICOS framework.

Table S2. Search terms used in literature review.

Table S3. Risk of bias tool for assessment of epidemiological modelling studies.

Table S4.PRISMA 2009 Checklist.

Table S5. Results of Quality Appraisal.

Box S1. Inclusion and Exclusion Criteria for Literature Search.

Figure S1.A flowchart of the literature screening for the updated search.

2.5.2 Health Economic Evaluation of TB Vaccines

In this section, I provide context for health economic analyses in this thesis by briefly summarising published dynamic model-based economic evaluations of TB.

In their seminal review, Harris et al.[95] identified seven static[96–99] and dynamic[100–102] modelling studies that evaluated the cost-effectiveness of either new TB vaccines or novel bacillus Calmette-Guérin (BCG) reuse (e.g. with varying efficacy or new targeting). The review in section 2.5.1 identified one additional dynamic model[103]. Published studies included a mix of healthcare and societal perspectives and the overall methodological mix was similar to that found in the economic evaluation of vaccines in general[104].

The static models included three Markov decision-analytic models[96–98] and one cohort-based cost-effectiveness analysis of universal BCG vaccination[99]. Two dynamic models estimated incremental cost-effectiveness ratios (ICERs) of new TB vaccines or novel BCG use[101,102] and one estimated the incremental disability adjusted life years (DALYs) and cost-savings incurred by discontinuation of routine BCG vaccination in Taiwan[103]. The final study overlaid a constrained-optimisation analysis on a dynamic transmission model to mix variable efficacy vaccination with first-line therapy under a fixed healthcare budget[105].

I briefly review the conclusions of the two studies that evaluated a new TB vaccine or novel BCG reuse through dynamic transmission models: Dye[101] and Knight et al.[102]

Dye modelled the impact of revaccinating all *Mtb* uninfected HIV-negative 15-year olds in Cape Town, South Africa, with BCG. This study assumed 10–80% vaccine efficacy and 10 years duration of protection. Vaccination priced at $1–10 had an ICER of $116–9237 per DALY averted when accounting for DALYs averted among vaccine recipients (i.e. the direct effect of vaccination). Including indirect (i.e. transmission) vaccine impact reduced the ICER to $52–4540, rendering vaccination cost-effect at a 1×gross domestic product (GDP) per capita threshold ($8000 in 2011).

Knight et al. estimated the cost-effectiveness of vaccines in 91 low- and middle-income countries assuming tiered vaccine prices by country income group ($1.50–10 per dose) and a 1× Gross National Income per capita cost-effectiveness threshold. This study used a fixed econometric cost model that included vaccine delivery and TB treatment costs (including TB treatment costs to the health system and a fixed productivity loss from the patient perspective).

Due to the fixed cost model, cost-effectiveness estimates in this study derived their uncertainty solely from epidemiologic sources. The cost model did not include country-specific variation in vaccine delivery costs nor differing standards of care.

Knight et al. assumed that MDR/RR-TB accounted for a proportion of all TB, specific for each country and informed by data, for which a proportionate top-up was added to

DSTB costs. However, since MDR/RR-TB was not modelled dynamically, this proportion remained invariant over time.

Knight et al. reported that vaccines targeted at adolescents and adults would be cost-effective or cost-saving over 2024–2050 if vaccine durability was 10 years or more, or efficacy was 20% or greater. In contrast, neonatal vaccination was not cost-effective, unless it had high efficacy and conferred lifelong protection.

Whereas both Knight et al. and Dye investigate adult and adolescent vaccination, the remaining economic evaluations focused on neonatal vaccination—either a novel BCG strategy[97,99,103,105] or adding hypothetical booster vaccines[96,98]. Unlike Knight et al. and Dye, these studies have heterogeneous conclusions, finding neonatal vaccination to be variably cost-effective or ineffective depending on the study context.

2.6 Summary

This chapter had two main components: (i) brief overviews of the natural history and epidemiology of TB and MDR/RR-TB , focusing on India and China and aspects most relevant to vaccines; and (ii) a review of recent developments in mathematical modelling of TB vaccines. These sections identify and provide context for the research gaps first described in chapter 1.

In sections §2.2, 2.3, and 2.4 I described the outsized challenge that MDR/RR-TB poses to TB control. Absolute MDR/RR-TB burden is greatest in India and China, where it also imposes a substantial financial burden to both patients and health systems. Both settings have made substantial recent progress in (MDR/RR-)TB control. India, in particular, has a published short-medium term strategy to scale up programmatic TB control further, which may interact with any new vaccine. It is thus important to quantify the impact of a new TB vaccine in these settings, incorporating MDR/RR-TB and changes to programmatic control. In section 2.5.1, I demonstrated that no studies yet address these questions and confirmed research gap 1.

In section §2.5, I also described the current state of dynamic transmission model-based economic evaluations of new and repurposed TB vaccines. Only one cost-effectiveness analysis included the costs of MDR/RR-TB , which was represented as a (non-dynamic) fixed top-up to DSTB costs. Despite the emergent consensus that adult and adolescent vaccination might be the more cost-effective delivery strategy, no studies appeared to examine the total cost and affordability of large scale adult vaccination. These findings confirm research gap 2 (cost-effectiveness of vaccines when accounting for MDR/RR-TB) and research gap 3 (total cost and affordability of vaccines).

Finally, the systematic review in section 2.5.1 identified age-targeting—of neonates[102,106,107], adults and adolescents[102,107–110] or the elderly[111]—as the most frequently investigated deployment strategy in TB vaccine models. Age-targeting results may be especially

sensitive to structural choices in models that aim to improve age-specific burden and transmission patterns. To this end, only two studies[108,111] implemented age-specific contact (mixing) matrices, neither of which varied these structures over time with evolving demography. Thus, to date, there is no investigation whether vaccine impact estimates are affected by the secular evolution of contact patterns as demography changes (research gap 4).

In the subsequent chapters, I present studies that address these research gaps in turn.

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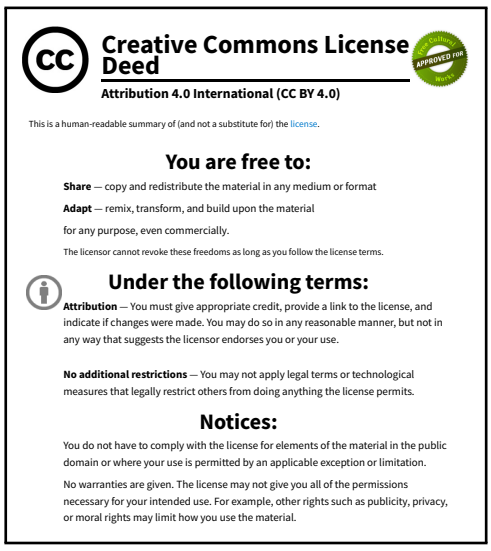
3 Vaccine Impact on Drug Resistant Tuberculosis and Cost-effectiveness

This chapter includes Research Paper 2, which investigates the epidemiologic impact of new vaccines on multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) and their cost-effectiveness. I then briefly review new studies and trial results that have emerged since this study was conceived and their implications for the results of this work.

3.1 Research Paper 2

This research paper is cited as:

> Weerasuriya, C.K., Harris, R.C., McQuaid, C.F. , Bozzani, F., Ruan, Y., Li, R., Li, T., Rade, K., Rao, R., Ginsberg, A.M., Gomez, G. B., White, R. G. The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China. *BMC Med* **19**, 60 (2021). https://doi.org/10.1186/s12916-021-01932-7



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First Name(s)	CHATHIKA KRISHAN		
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Thesis Title	ADVANCING MATHEMATICAL MODELS OF MYCOBACTERIUM TRANSMISSION TO SUPPORT VACCINE INTRODUCTION		
Primary Supervisor	PROFESSOR RICHARD G WHITE		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

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RESEARCH ARTICLE Open Access

The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China

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Abstract

Background: Despite recent advances through the development pipeline, how novel tuberculosis (TB) vaccines might affect rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) is unknown. We investigated the epidemiologic impact, cost-effectiveness, and budget impact of hypothetical novel prophylactic prevention of disease TB vaccines on RR/MDR-TB in China and India.

Methods: We constructed a deterministic, compartmental, age-, drug-resistance- and treatment history-stratified dynamic transmission model of tuberculosis. We introduced novel vaccines from 2027, with post- (PSI) or both pre- and post-infection (P&PI) efficacy, conferring 10 years of protection, with 50% efficacy. We measured vaccine cost-effectiveness over 2027–2050 as USD/DALY averted-against 1-times GDP/capita, and two healthcare opportunity cost-based (HCOC), thresholds. We carried out scenario analyses.

Results: By 2050, the P&PI vaccine reduced RR/MDR-TB incidence rate by 73% (UI:66–76) and 72% (UI:65–77), and the PSI vaccine by 29% (UI: 27–31) and 47% (UI: 37–58) in China and India, respectively.
In India, we found both USD 10 P&PI and PSI vaccines cost-effective at the 1-times GDP and upper HCOC thresholds and P&PI vaccines cost-effective at the lower HCOC threshold. In China, both vaccines were cost-effective at the 1-times GDP threshold. P&PI vaccine remained cost-effective at the lower HCOC threshold with 49% probability and PSI vaccines at the upper HCOC threshold with 21% probability. The P&PI vaccine was predicted to avert 1.0 million (UI: 0.6–1.3) and 0.8 million (UI: 0.5–1.4) second-line therapy regimens in China and India between 2027 and 2050, respectively.

Conclusions: Novel TB vaccination is likely to substantially reduce the future burden of RR/MDR-TB, while averting the need for second-line therapy. Vaccination may be cost-effective depending on vaccine characteristics and setting.

Keywords: Tuberculosis, Drug resistance, Vaccine, Mathematical model

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Background

Rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) threatens to impede global tuberculosis (TB) control efforts and progress towards the World Health Organization End TB targets [1], with approximately half a million incident cases in 2018 [2]. RR/MDR-TB has worse treatment outcomes than drug-susceptible TB (DS-TB) and imposes a disproportionate cost on health systems and patients [3, 4]. Further, prolonged multi-agent treatment for RR/MDR-TB may contribute to wider antimicrobial resistance [5]. As such, there is an urgent need for novel interventions to control and prevent RR/MDR-TB.

Prophylactic TB vaccine candidates progressed considerably through the development pipeline in 2018–2019. Results from the $M72/AS01_E$ [6] and BCG revaccination [7] trials suggest possible vaccine efficacy of 50% and 46% in Interferon-γ release assay (IFNγ) + and IFNγ-negative patients, respectively. These trials did not include RR/MDR-TB endpoints due to its relative rarity.

Mathematical modelling techniques could investigate the potential effect of vaccination on RR/MDR-TB. However, to date, no modelling studies have assessed the epidemiologic impact of novel TB vaccines on RR/MDR-TB. Furthermore, studies of TB vaccine cost-effectiveness have omitted RR/MDR-TB or not modelled RR/MDR-TB dynamically [8, 9].

The global distribution of RR/MDR-TB is heterogenous, with India and China accounting for 27% and 14% of all global cases, respectively [2]. High-quality national RR/MDR-TB burden estimates are derived through large and infrequent drug-resistance surveys; consequently, data to inform drug resistance trends are sparse. In 2017, globally, 3.5% (95% CI 2.5–4.7%) of new and 18% (95% CI 6.3–34%) of previously treated TB cases were estimated to have RR/MDR-TB [10]. Data from China indicate slightly higher rates, with estimates of 7.1% (95% CI 5.6–8.7) and 24% (95% CI 20–24) RR/MDR-TB among new and previously treated cases. Data from India indicate slightly lower-than-global rates. Estimates from the first national drug-resistance survey, reporting in 2018, place RR/MDR-TB among new and previously treated cases at 2.8% (CI 2.3–3.5) and 11.6% (10.2–13.2), respectively. Approximately 69% and 74% of RR-TB cases are estimated to be MDR-TB (defined as resistance to isoniazid in addition to rifampicin) in India and China, respectively, consistent with the global average of 78%. Despite these similarities, China and India have substantially differing demographics, TB epidemiology and health systems [2, 11, 12]. As such, in this study, we modelled the epidemiologic impact, cost-effectiveness and budget impact of prophylactic vaccination against TB, while dynamically modelling epidemics of DS- and RR/MDR-TB in China and India.

Methods

Model structure and calibration

We programmed an age-, treatment history- and drug resistance-stratified compartmental transmission model of TB in R [13], extending previously developed methods [8, 14, 15]. Details of model structure, diagram, equations, calibration, vaccine implementation, demography and health economic analysis are described in Additional file 1 [2, 7, 8, 11–14, 16–101]. The model time horizon was 1950–2050.

The model allowed for five states of TB disease: (1) susceptible; (2) latently infected; (3) active disease (both infectious, i.e., bacteriologically sputum-positive, and non-infectious, i.e., bacteriologically sputum-negative, and extra-pulmonary); (4) on-treatment; and (5) recovered from disease, stratified by drug-susceptible/drug-resistant, and treatment history (Fig. S1 in Additional file 1). All states were stratified by vaccination status. Transitions between states represented acquisition of infection, progression to latency or active disease, conversion of non-infectious to infectious active disease, detection of active disease and initiation of treatment, treatment success or failure, reactivation from latency and relapse from recovered states. Misdiagnosis of RR/MDR-TB was assumed to lead to inappropriate initiation of DS-TB treatment and treatment failure. Consistent with empirical data, progression to active disease following re-infection of latent and recovered populations was assumed to occur at a lower rate than naive populations [42]. We assumed that RR/MDR-TB could develop following drug resistance acquisition in situ while on treatment for DS-TB or following transmission of drug-resistant *M. tuberculosis*. Transmission could occur between drug-resistance strata. We assumed resistance acquisition and RR/MDR-TB treatment began in 1970.

Neonates entered the model uninfected. We modelled 0–100 years in 1-year age groups and applied all-cause mortality to all states, with TB-specific mortality applied to active-disease and on-treatment states. We applied age-assortative contact patterns using empirical data for China [39] and by adapting POLYMOD contact matrices [40] for India.

We obtained prior ranges for natural history parameters from the literature (Additional file 1, section 2.4), including age-stratified ranges where available. We assumed RR/MDR-TB was less than or equally transmissible to DS-TB [28, 29]. We constrained rates of fast progression to active disease, reactivation from latent infection, relapse from recovered state and TB mortality to be greater or equal in children (age < 15 years) than adults [21, 47]; in China, we also constrained these rates to be greater or equal in the elderly (age > 64 years) than in adults (age 15–64). We applied the opposite constraint to natural cure rate [21, 47].

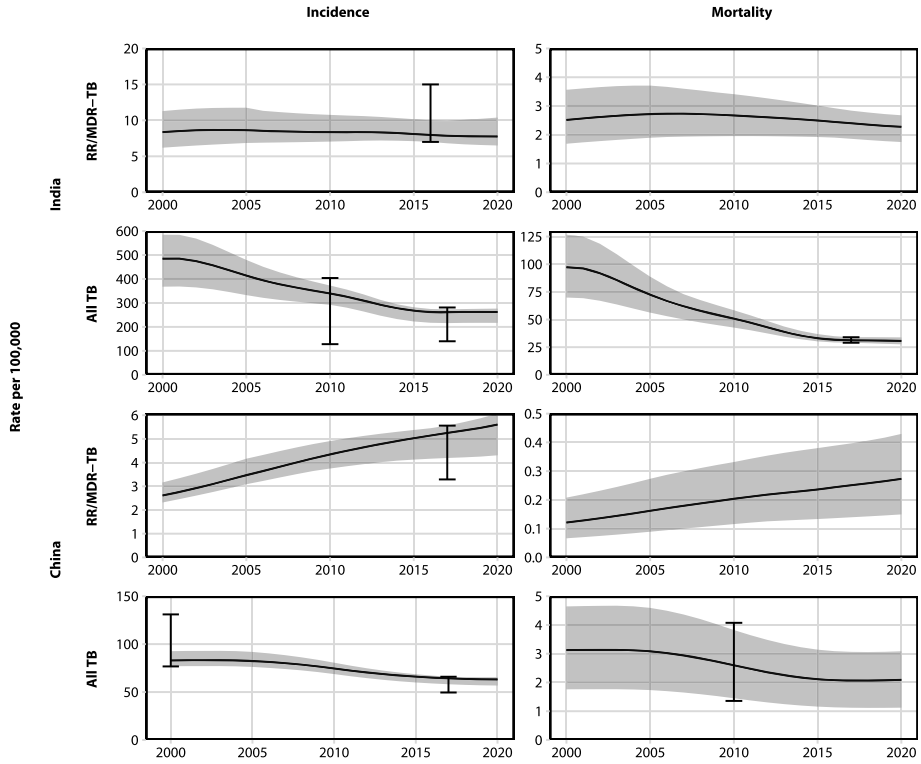

Fig. 1 Model calibration: TB incidence and mortality of RR/MDR-TB and All TB in India and China. Lines represent median model trajectory. RR/MDR-TB mortality presented for comparison–no calibration targets available. Ribbons represent model uncertainty. Error bars represent calibration targets and uncertainty. Note: *y*-axis scales on subplots differ

We used country-specific case-detection rates to inform diagnosis and treatment initiation [31] (Additional file 1, section 2.5). RR/MDR-TB was diagnosed through a combined probability of drug-susceptibility testing (determined by country-specific drug-susceptibility testing coverage) and empirical diagnosis (Additional file 1, section 2.5). We based treatment success for DS-TB and RR/MDR-TB treatment on historical data [31, 58]. In India, we adjusted case-detection and DS-TB treatment success rates for a large private healthcare sector [2, 11, 32], where we assumed a lower treatment success rate for DS-TB and unsuccessful treatment of RR/MDR-TB [Rao, R., *personal communication*]. Beyond 2018, we maintained constant rates of treatment initiation, drug-susceptibility testing coverage and treatment success.

We calibrated the model to historical rates of all TB prevalence, incidence, notification and mortality [2, 34, 35, 69], RR/MDR-TB incidence rate and percentage RR/MDR-TB among notifications (stratified by treatment history) in each country. In India, we fitted to total RR/MDR-TB treatment initiations in the public sector. In China, we constrained the number of RR/MDR-TB treatments contributing to cost-effectiveness calculations to the number of laboratory-confirmed RR/MDR-TB treatment initiations reported by China Centres for Disease Control [31]. Where data allowed, we stratified calibration targets by age group (< 15, 15–64 and ≥ 65 years in China, and < 15 and ≥ 15 years in India).

Model calibration used Approximate Bayesian Computation (ABC) rejection-sampling process and ABC Markov chain Monte Carlo sampling. We randomly subsampled 1000 fully calibrated parameter sets to generate model runs, whose median trajectory we used as an estimate of central tendency and whose maximum and minimum trajectories represent uncertainty intervals.

Vaccine implementation

We simulated vaccine introduction in 2027 for each country and estimated vaccine impact for 2027–2050 by comparison to the corresponding unvaccinated baseline model runs.

We modelled two simultaneous vaccination strategies: routine annual vaccination and mass vaccination campaigns. We assumed routine annual vaccine administration to 9-year-olds, co-delivered with human papillomavirus (HPV) vaccine, with coverage of 80%, based on HPV vaccine coverage in South Africa and secondary school enrolment ratios in China and India. Mass campaigns were delivered 10-yearly to ages ≥ 10 at 70% coverage based on

existing data for Menafrivac mass campaigns delivered to 1–29-year-olds. We delivered vaccination to populations in the model who had neither active disease or nor were receiving treatment, assuming no pre-immunisation testing for latent TB [73]. No other targeting or eligibility criteria were applied. We assumed a prevention of disease vaccine, priced at US$10, conferring 50% efficacy for 10 years, with vaccine efficacy in individuals with a previous history of M. tb infection ("post-infection"; PSI) or irrespective of infection ("pre- and post-infection"; P&PI). Vaccine was modelled as a reduction in the rates of progression to disease following infection, reactivation from latency and relapse from the recovered state. The reduction was proportional to vaccine efficacy. A lower burden of active disease further depressed the force of infection, leading to lower rates of M. tb transmission. We modelled vaccination as equally protective against DS-TB and RR/MDR-TB and in those with or without previous treatment history for either. In addition to the direct prevention of disease mechanism (above), vaccine reduced RR/MDR-TB burden indirectly by reducing DS-TB burden. Reduced DS-TB burden translated to reduced total patient-time on treatment for DS-TB, leading to lower drug-resistance acquisition. Vaccine waning was implemented as instantaneous at the end of duration of protection. We did not explicitly represent existing Bacillus Calmette–Guérin (BCG) immunisation programmes as we assumed protection conferred by BCG to be reflected in calibration targets.

As measures of vaccine impact, we calculated percentage reduction in incidence rate and mortality rate, in vaccine scenarios in 2030 and 2050, compared to baseline and corresponding number of cumulative averted TB cases and deaths.

Cost, cost-effectiveness and budget impact

We estimated costs from a public sector perspective using an ingredients approach. Unit cost assumptions, estimates and full references are provided in Additional file 1, section 5. Briefly, we calculated costs incurred by the vaccine and TB programmes.

We estimated three categories of intervention (vaccine programme) costs: vaccine, delivery and programme costs. We modelled vaccines priced at US$10 as the base case. We estimated US$1.13–2.40 (routine) or US$1.20–2.47 (mass campaign) delivery cost per person vaccinated in India, and US$1.60–2.80 for both routine and mass campaign delivery cost in China. Programme costs included mass campaign organisation and management, which we estimated from the literature at US$25,374,949 per campaign in India, and US$16,133.10 per 10,000 persons vaccinated per campaign in China.

TB programme costs represented service costs for TB diagnosis (including drug-susceptibility testing) and treatment (Additional file 1, section 5.1). For India, we added costs representing nutritional support payments to patients and government incentives to improve TB case notification in the private healthcare sector. We inflated historic cost-data to 2018 values where appropriate.

We calculated incremental costs of vaccination as the difference in total costs predicted between vaccine and corresponding baseline scenario.

Using standardised outputs from the model (deaths due to DS and RR/MDR-TB by age and year and time spent with active DS and RR/MDR-TB disease), we calculated total (DS-TB and RR/MDR-TB) disability-adjusted life years (DALYs) averted by vaccination. We applied disability weights per the Global Burden of Disease study [95] and life expectancy from the UN World Population Prospects [38]. Future costs and DALYs averted were discounted at 3%.

We calculated incremental cost-effectiveness ratios (ICERs) for the 1000 vaccine runs and constructed cost-effectiveness acceptability curves for each vaccine profile through a probabilistic sensitivity analysis. Input costs were sampled from their corresponding uncertainty ranges and attached to each vaccine run. We report the proportion of ICERs which fall below three illustrative thresholds per country: 1-times 2018 World Bank gross domestic product (GDP) per capita and the lowest and highest healthcare opportunity cost (HCOC) thresholds estimated by Ochalek et al. [101].

We present budget impact for immunisation and TB programmes separately. For the immunisation programme, we present total costs incurred by instantaneous deployment of vaccine. For the TB programme, we present annual total costs for programmatic management of TB. Health economic analysis was undertaken in line with the Consolidated Health Economic Evaluation Reporting Standards [102] (Additional file 2).

Scenario analysis

We conducted scenario analyses in two areas: product related, pertaining to vaccine characteristics and cost, and baseline related, pertaining to uncertainty in programmatic (non-vaccine) TB management and associated future health system investments.

Under product-related scenario analysis, we modelled vaccines with 30%, 70% and 90% efficacy, 5-years duration of protection, 30% mass campaign coverage and a vaccine price of US$30. There are no vaccine candidates in advanced development that prevent disease solely in uninfected (i.e., pre-infection) populations. Therefore, we present vaccines effective pre-infection (PRI) vaccines as a scenario analysis.

For baseline-related uncertainty, to capture the impact of vaccination in the context of uncertainty in future

health system investments, and in contrast to the baseline scenario with no programmatic change after 2018, we defined an alternative "Policy" scenario, representing a scaled-up programmatic TB management for each country (Additional file 1, section 2.6).

For China, the Policy scenario was informed by country expert opinion. It included linearly scaling up drug-susceptibility testing coverage to 90% by 2036 and introduction of a standard 9-month RR/MDR-TB treatment regimen (with the same treatment success rate), linearly increasing this to 40% of all second-line therapy by 2036 [*Li, R., personal communication*].

For India, the National Strategic Plan of the Indian Revised National Tuberculosis Control Programme [36] informed the Policy scenario, defined as (1) increased case detection rate (combined across private and public sectors) to 85%, (2) increased drug-susceptibility testing coverage among public sector notifications to 100% and (3) increased proportion of notifications originating from the private sector to 35%, all by 2025.

Model uncertainty

The final estimates of uncertainty in the results reflect a combination of epidemiologic input parameter uncertainty (delineated through sampling during calibration) and cost input uncertainty (incorporated through sampling during the probabilistic sensitivity analysis for cost-effectiveness analysis).

Role of the funder

The study funder was involved in developing the research question and commented on the draft manuscript, but had no role in study design, data collection, analysis, interpretation, nor writing the initial draft. The corresponding author had full access to all study data and materials and had final responsibility for the decision to submit for publication.

Results

Calibration

We calibrated to all TB prevalence, incidence, notification and mortality, and to RR/MDR-TB specific rates of incidence, proportion among all TB notifications (stratified by treatment history) and number of treatment initiations (Fig. 1; further details in Additional file 1, section 6). The model predicted a RR/MDR-TB incidence and mortality rate per 100,000 in 2018 of 7.8 (UI: 6.7–10.1) and 2.4 (UI: 1.8–2.8) in India, respectively, and 5.4 (UI: 4.2–5.7) and 0.3 (UI: 0.1–0.4) in China, respectively (Fig. 1, rows 1 and 3). Baseline epidemiologic projections (without vaccine) are provided in Additional file 1, section 6. The model predicted that RR/MDR-TB incidence in China was predominantly driven by infection of susceptible (naive) individuals. In contrast, RR/MDR-TB incidence in India was driven by equal proportions of new infection of susceptible and re-infection of latently infected individuals (Additional file 1, section 7.2).

Epidemiologic impact

A summary of the epidemiologic impact of both P&PI and PSI vaccines is presented in Figs. 2 and 3 and Tables 1 and 2.

In India, we found the P&PI vaccine reduced the RR/MDR-TB incidence rate in 2050 by 72% (UI: 65–77), corresponding to 2.0 (UI: 1.4–4.1) million cases averted (Table 1, Fig. 2). The PSI vaccine reduced the RR/MDR-TB incidence rate in 2050 by 47% (UI: 37–58), corresponding to 1.3 (UI: 0.9–2.6) million cases averted (Table 1, Fig. 2). The P&PI and PSI vaccines reduced all TB incidence rate in 2050 by 67% (UI: 59–71) and 44% (UI: 39–49), respectively (Table 1, Fig. 3).

In China, we found the P&PI vaccine reduced the RR/MDR-TB incidence rate in 2050 by 73% (UI: 66–76), corresponding to 2.1 (UI: 1.1–2.7) million cases averted (Table 2, Fig. 2). The PSI vaccine reduced the RR/MDR-TB incidence rate in 2050 by 29% (UI: 27–31), corresponding to 0.7 (UI: 0.5–0.9) million cases averted (Table 2, Fig. 2). The P&PI and PSI vaccines reduced all TB incidence rate in 2050 by 56% (UI: 53–59) and 37% (UI: 35–38), respectively (Table 2, Fig. 3).

We found a similar relative effect of P&PI vaccines compared to PSI vaccines on RR/MDR-TB mortality rate and deaths averted, and on all TB mortality rate, and cases and deaths averted (Tables 1 and 2).

Averted treatment

In India, P&PI and PSI vaccines were predicted to avert 0.8 (UI: 0.5–1.4) million and 0.5 (UI: 0.3–1.1) million RR/MDR-TB treatment regimens (not shown). In China, the model predicted the P&PI and PSI vaccines would avert 1.0 (UI: 0.6–1.3) million and 0.3 (UI: 0.2–0.4) million RR/MDR-TB treatment regimens, respectively (not shown).

Cost-effectiveness

In India, in a discounted analysis, we estimated ICERs of $151 (UI: 82–210) and $284 (UI: 189–389) for P&PI and PSI vaccines priced at USD 10, respectively (Fig. 4), over 2027–2050. The P&PI vaccine was predicted to be cost-effective in 100% of model runs at the 1-times GDP, and upper and lower HCOC thresholds. The PSI vaccine was predicted to be cost-effective in 100%, 99% and 27% of runs at the 1-times GDP, upper HCOC and lower HCOC thresholds, respectively.

In China, in a discounted analysis, we estimated ICERs of $3663 (UI: 2763–4754) and $6059 (UI: 4591–7749) for P&PI and PSI vaccines priced at USD 10, respectively (Fig. 4), over 2027–2050. The P&PI vaccine was

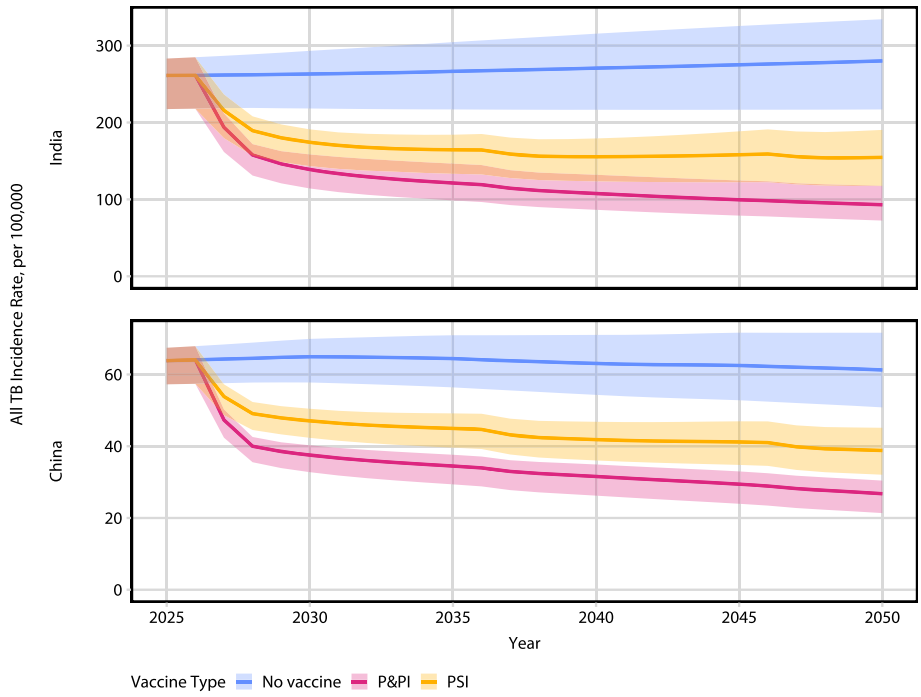

Fig. 2 Incidence rate reduction of all TB by 50% efficacy, 10-year duration of protection pre- and post-infection efficacy (P&PI) and post-infection efficacy (PSI) vaccines in India (top) and China (bottom). Lines represent median model incidence rate; ribbons represent model uncertainty. Vaccine is introduced in 2027. Note: *y*-axis scales on subplots differ

predicted to be cost-effective in 100% of runs at the 1-times GDP threshold and upper HCOC threshold, and 49% of runs at the lower HCOC threshold. The PSI vaccine was cost-effective at 100% and 21% of runs at the 1-times GDP and upper HCOC threshold, but not cost-effective at the lower HCOC threshold.

Budget impact

The total undiscounted costs for instantly deployed mass campaigns and routine annual vaccination for a 50% efficacy P&PI vaccine providing 10 years of protection and total savings in the TB programme over 2027–2050 are presented in Table 3. Immunisation programme costs were similar for a PSI vaccine priced at US$10 in India and China (Additional file 1, section 9) but with lower TB programme savings. The total annual expenditure by the National Tuberculosis Programmes for India and China over 2027–2050 is shown in Fig. 5.

Scenario analyses

We found increasing vaccine efficacy increased percent incidence rate reduction, cases averted, percent mortality rate reduction, deaths averted in both RR/MDR-TB and all TB, and averted DS-TB and RR/MRD-TB treatment regimens. Reduced duration of protection to 5 years or reduced vaccine efficacy (Additional file 1, sections 7.3 and 7.4) had the opposite effect. PRI vaccines had a comparable or lower impact than PSI vaccines in all cases except for RR/MDR-TB in China, where PRI effect was greater than PSI (Additional file 1, sections 7.2 and 7.3).

We found vaccines (of all types, efficacies and durations of protection) affected a similar per cent incidence rate reduction and per cent mortality rate reduction in both all TB and RR/MDR-TB, in both India and China, in the Policy scenario as compared to the unchanged baseline. Fewer cases and deaths were averted in the Policy scenario, leading to a lower absolute impact of vaccination. ICERs for vaccination were higher in undiscounted analyses, with a vaccine priced at US$30, and in the Policy scenario for each country (Additional file 1, section 8).

Discussion

We estimate that the introduction of new TB vaccines in India and China in 2027 might substantially reduce RR/MDR-TB burden by 2050. A pre- and post-infection vaccine (effective in all individuals, irrespective of their infection status by M. tb) was projected to reduce RR/MDR-TB incidence rate by approximately 70% in both India and China if delivered annually to 9-year-olds and every 10 years to ages 10 and above. A post-infection vaccine (effective only in individuals with latent M. tb infection or who have recovered from TB) was projected

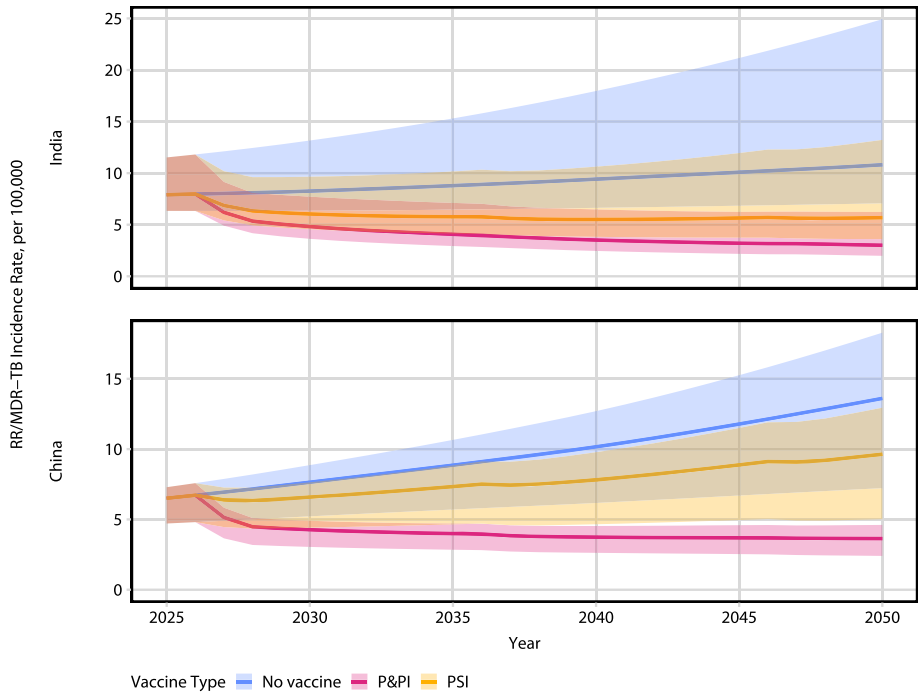

Fig. 3 Incidence rate reduction of RR/MDR-TB by 50% efficacy, 10-year duration of protection pre- and post-infection efficacy (P&PI) and post-infection efficacy (PSI) vaccines in India (top) and China (bottom). Lines represent median model incidence rate; ribbons represent model uncertainty. Vaccine is introduced in 2027

to impart lower but still substantial reductions of approximately 50% and 30% RR/MDR-TB incidence rate reduction in India and China, respectively.

P&PI vaccines priced at US$10 were highly likely to be cost-effective in India and China at the 1-times GDP and upper HCOC thresholds. In India, P&PI vaccines were also likely to be cost-effective at the lower HCOC threshold. While we found PSI vaccines to be less cost-effective than P&PI vaccines in general, a PSI vaccine priced at US$10 remained highly likely to be cost-effective at the 1-times GDP threshold in both India and China and at the upper HCOC threshold in India. In both countries, vaccination was projected to avert approximately 1 million RR/MDR-TB regimens by 2050.

We attributed the greater PSI vaccine impact on RR/MDR-TB in India than China, to the proportionally greater rate of re-infection and fast progression of latent RR/MDR-TB (which is avertible through post-infection vaccine efficacy) at baseline (Additional file 1, section 7.2). Moreover, in China, the RR/MDR-TB epidemic—driven by new infections among susceptible (naive)

Table 1 India–Epidemiologic impact for 50% efficacy, 10-year duration of protection vaccines. Estimates are median (uncertainty interval) values. Incidence and mortality rate reductions compare annual values of vaccine vs baseline in 2030 and 2050. Cases and deaths averted are cumulative over 2027–2030 and 2027–2050

		Pre- and post-infection vaccine		Post-infection vaccine	
Resistance status	**Outcome**	**2030**	**2050**	**2030**	**2050**
RR/MDR-TB	% Incidence rate reduction in year	42% (37–45)	72% (65–77)	27% (20–34)	47% (37–58)
	% Mortality rate reduction in year	20% (15–24)	69% (60–75)	13% (8–19)	45% (33–55)
	Cumulative cases averted, millions	0.2 (0.1–0.3)	2.0 (1.4–4.1)	0.1 (0.1–0.2)	1.3 (0.9–2.6)
	Cumulative deaths averted, millions	0.015 (0.008–0.02)	0.4 (0.3–0.7)	0.009 (0.004–0.015)	0.3 (0.2–0.4)
All TB	% Incidence rate reduction in year	47% (41–51)	67% (59–71)	34% (28–39)	44% (39–49)
	% Mortality rate reduction in year	36% (28–41)	66% (59–71)	25% (18–31)	44% (38–49)
	Cumulative cases averted, millions	6.1 (5.0–7.0)	57.1 (45.9–70.0)	4.3 (3.3–5.2)	39.6 (31.4–48.2)
	Cumulative deaths averted, millions	0.4 (0.3–0.5)	5.9 (4.7–7.9)	0.3 (0.2–0.3)	4.1 (3.0–5.3)

Table 2 China–Epidemiologic impact for 50% efficacy, 10-year duration of protection vaccines. Estimates are median (uncertainty interval) values. Incidence and mortality rate reductions compare annual values of vaccine vs baseline in 2030 and 2050. Cases and deaths averted are cumulative over 2027–2030 and 2027–2050

		Pre- and post-infection vaccine		Post-infection vaccine	
Resistance status	**Outcome**	**2030**	**2050**	**2030**	**2050**
RR/MDR-TB	% Incidence rate reduction in year	44% (42–46)	73% (66–76)	14% (13–16)	29% (27–31)
	% Mortality rate reduction in year	22% (18–24)	67% (59–72)	8% (6–10)	28% (25–30)
	Cumulative cases averted, millions	0.2 (0.1–0.2)	2.1 (1.1–2.7)	0.05 (0.04–0.06)	0.7 (0.5–0.9)
	Cumulative deaths averted, millions	0.003 (0.001–0.005)	0.1 (0.0–0.2)	0.001 (0.001–0.002)	0.04 (0.02–0.06)
All TB	% Incidence rate reduction in year	42% (40–44)	56% (53–59)	28% (26–29)	37% (35–38)
	% Mortality rate reduction in year	29% (26–32)	53% (48–58)	21% (18–24)	35% (33–36)
	Cumulative cases averted, millions	1.4 (1.2–1.5)	10.5 (8.9–12.0)	0.9 (0.8–1.0)	6.9 (5.9–7.8)
	Cumulative deaths averted, millions	0.02 (0.01–0.04)	0.4 (0.2–0.5)	0.02 (0.01–0.03)	0.3 (0.1–0.4)

individuals—was more impacted by PRI than PSI vaccine efficacy (Additional file 1, section 7.2).

We found that vaccination averted a substantially higher absolute number of all TB cases and deaths in India than China. This reflected higher TB incidence and substantially higher TB mortality at baseline in India than China. The greater averted burden translated to greater averted life-years otherwise lost to TB; thus, despite lower TB management costs, for all vaccine profiles, ICERs in India were lower than in China. Correspondingly, savings in the TB programme were greater in India than China and reflect an underestimate for both countries, as vaccine-mediated protection and the dynamic impact of vaccination on the TB epidemic would continue to suppress TB burden beyond the model time horizon.

This study had several limitations pertaining to (1) model parameterisation and structure, (2) baseline scenarios and (3) vaccine implementation, which we consider in turn.

Data to substantiate natural history parameters for RR/MDR-TB were sparse and heterogeneous [28, 103, 104]. We assumed RR/MDR-TB transmissibility was equal to or lower than DS-TB [28, 29] and sampled from wide parameter priors. In the absence of evidence or a priori reasoning for differing values, we assumed other RR/MDR-TB and DS-TB parameters had the same values. As new empirical evidence arises, our predictions and estimates can be updated, but it is currently difficult to identify their direction of bias. Further, we maintained constant country-specific contact patterns over the model time horizon between DS and RR/MDR-TB. If individuals with RR/MDR-TB were to mix with one another preferentially, our results may overestimate vaccine impact.

To test our baseline assumptions of post-2018 constant case detection rates and drug-sensitivity testing coverage, we implemented a contrasting scaled up programmatic management scenario based on country-specific national policy. Our conclusions regarding relative vaccine impact remained robust to programmatic scale-up. However, we did not change RR/MDR-TB treatment success rate nor introduce a theoretical future highly effective diagnostic

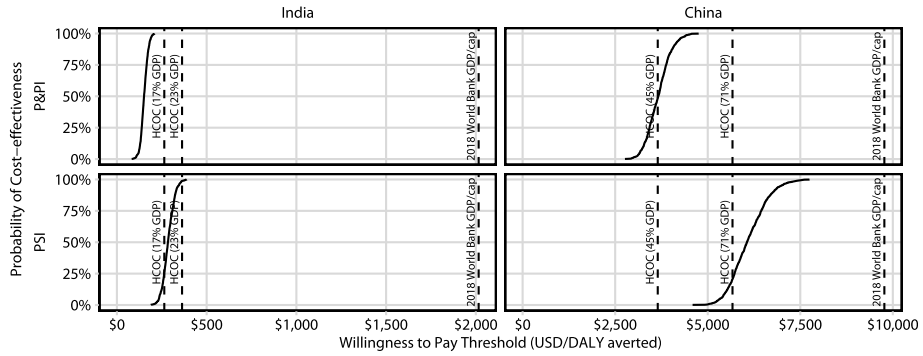

Fig. 4 Cost-effectiveness acceptability curves. Vertical axis shows the probability that 50% efficacy, 10-year duration of protection pre-and post-infection (P&PI; top) and post-infection (PSI; bottom) vaccines are cost-effective at or below a given willingness to pay value (horizontal axis), in India (left) and China (right). Reference lines are 2018 World Bank GDP and upper and lower health-care opportunity-cost thresholds. Note: *x*-axis scales differ between subplots

Table 3 Estimated cumulative total cost of vaccine programmes and cumulative TB programme savings over 2027–2050. Costs are presented for a 50% efficacy P&PI vaccine providing 10-years of protection. All costs are undiscounted and in billions USD

	Type	Amount
India	Routine vaccination costs	$5.2 (4.9–5.4)
	Mass vaccination costs	$33.4 (31.9–34.6)
	All vaccination programme costs	$38.6 (37.1–39.9)
	TB Programme savings	$19.4 (13.0–27.2)
China	Routine vaccination costs	$3.4 (3.2–3.5)
	Mass vaccination costs	$38.1 (36.4–39.2)
	All vaccination programme costs	$41.5 (39.8–42.6)
	TB programme savings	$5.2 (3.9–6.8)

technology, either of which may reduce vaccine impact estimates. In India, we assumed the private health sector did not treat RR/MDR-TB successfully, based on in-country expert opinion. Should overall treatment success improve because of a larger private sector engagement effort, relative vaccine impact might remain stable, but absolute impacts may be reduced. We cannot speculate on the impact on cost-effectiveness, as this would depend on the specific mechanism of increased private sector engagement. Should the strategic focus of the Indian National Tuberculosis Programme change to include improved RR/MDR-TB treatment in the private healthcare sector, a new baseline scenario could be modelled to estimate the potential effect on vaccine impact. In China, we assumed the number of RR/MDR-TB treatment initiations contributing to programme costs was equal to the number starting treatment as reported by the Chinese Centre for Disease Control and Prevention (CDC). However, the averted number of treatments estimate applies to *all* RR/MDR-TB treatment—both CDC and non-CDC. As the total RR/MDR-TB treatment volume is unconstrained, our result of averted treatment may be an overestimate. We confined our health-economic analysis to a public sector healthcare perspective. TB-related costs to patients, including indirect costs from seeking healthcare and productivity losses, can be substantial [3]; these costs are not factored into our cost-effectiveness analysis. However, our analysis does include TB programme costs related to patient and private sector support: in India, we included nutritional support payments to TB patients and payments to incentivise private sector healthcare providers.

We implemented vaccine waning as an instantaneous loss of efficacy. If empirical data suggested a different waning shape, our estimates may over or underestimate the impact. We did not investigate vaccine targeting (e.g. by age, or by RR/MDR-TB risk group); targeting could improve cost-effectiveness estimates but reduce overall impact. We assumed population-wide mass campaigns were deployed instantaneously, with simultaneously applied costs, instead of through phased multi-year

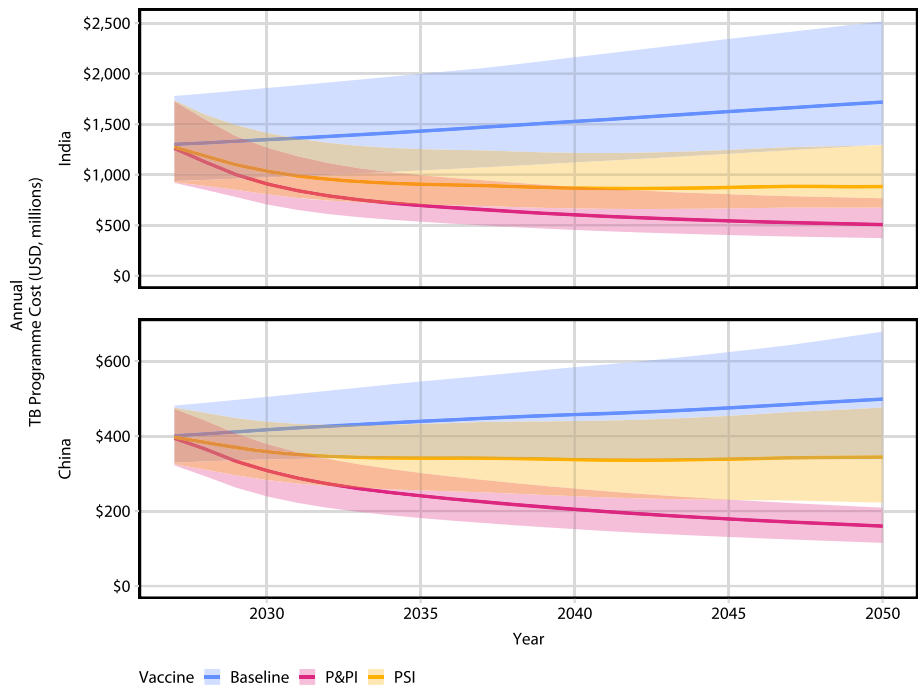

Fig. 5 Budget impact analysis. Annual expenditure by the national TB programmes TB-related costs. Vertical axis represents annual expenditure, in millions USD, by the national TB programme, with and without vaccine, in India (top) and China (bottom). Lines represent median modelled expenditure; ribbons represent model uncertainty

campaigns. These assumptions have one main consequence: vaccine-associated costs, which were calculated assuming that countries do not need additional capacity to deliver these campaigns, are an underestimate. However, as the benefits of such campaigns were also realised from the start, the ICERs may not be an underestimate. Finally, while we capture the cost-savings due to averted RR/MDR-TB treatment, the positive externalities this affords through a reduced contribution to antimicrobial resistance are not included in the cost-effectiveness analysis. We assumed a US$10 price per vaccine course and vaccine introduction in 2027. Should vaccine price decline over time, this might increase the probability of cost-effectiveness at the low HCOC threshold in either country or of PSI vaccines in China at the upper HCOC threshold. We speculate that delayed vaccine introduction by a few years would affect vaccine costs and benefits to similar extents and so is unlikely to substantially alter our findings.

Any evaluation of new TB vaccines must be compared to BCG. Neonatal BCG is still offered routinely in India and China [105]. Epidemiologic evidence suggests that BCG prevents severe disease—particularly miliary tuberculosis and tuberculous meningitis—in young children [106]. The effect of neonatal BCG vaccination on pulmonary tuberculosis risk in adults with estimates ranging from none to substantial [107–109]. Current evidence indicates that neonatal BCG vaccination will be inadequate to end transmission of M. tb among adults, which is a prerequisite for global TB elimination. In contrast, we suggest that adolescent and adult vaccination—with efficacy similar to late-stage vaccine candidate M72/AS01$_E$—which prevents pulmonary TB disease may be a useful contributor towards this goal.

Previous estimates of TB vaccine cost-effectiveness either omit MDR-TB or do not model MDR-TB dynamically [8, 9]. This is the first study to dynamically model the impact of potential novel vaccines on MDR-TB. We modelled both the de novo acquisition of drug-resistance and transmission of drug-resistant *M. tuberculosis*. We also developed a country-specific cost model and estimated the cost-effectiveness of these vaccines. Consequently, our ICER estimates incorporated both the direct impact of vaccination on RR/MDR-TB and indirect effects due to reduced transmission. In India, we also adjusted for differential treatment by the private sector.

Conclusions

Novel TB vaccination is likely to substantially reduce the future burden of RR/MDR-TB, while averting the need for RR/MDR-TB treatment. Vaccination may be cost-effective, but this depends on the local context and specific characteristics of the vaccine. There is an urgent need for new TB vaccines to prevent disease and for further investment in and acceleration of development of such vaccines to progress towards global TB elimination goals. As development of such vaccines continues, decision-makers should consider their potential role in national tuberculosis programmes and in wider antimicrobial resistance control efforts.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-01932-7.

Additional file 1: Technical Appendix. **Figure S1** Model diagram. **S2** Case Detection and Treatment Success Rates. **S3** Demographic Model–India and China. **S4** Posterior distributions of sampled parameters—India. **S5** Posterior distributions of sampled parameters—India (contd). **S6** Posterior distributions of sampled parameters—China. **S7** Posterior distributions of sampled parameters—China (contd). **S8** Calibration Results—All Tuberculosis in India. **S9** Calibration Results—RR/MDR-TB in India. **S10** Baseline (no vaccine) projections–India. **S11** Calibration Results—Prevalence and Incidence of All TB in China. **S12** Calibration Results—Notifications and Mortality of All TB in China. **S13** Calibration Results—RR/MDR-TB in China. **S14** Baseline (no vaccine) projections–China. **S15** Latent tuberculosis infection. **S16** Incident tuberculosis, disaggregated by incidence source. **S17** Incidence Rate Reduction in India. **S18** Mortality Rate Reduction in India. **S19** Incidence Rate Reduction in China. **S20** Mortality Rate Reduction in China. **S21** RR/MDR-TB Cases Averted in India by 2030 and 2050. **S22** RR/MDR-TB Deaths Averted in India by 2030 and 2050. **S23** All TB Cases Averted in India by 2030 and 2050. **S24** All TB Deaths Averted in India by 2030 and 2050. **S25** RR/MDR-TB Cases Averted in China by 2030 and 2050. **S26** RR/MDR-TB Deaths Averted in China by 2030 and 2050. **S27** All TB Cases Averted in China by 2030 and 2050, **S28** All TB Deaths Averted in China by 2030 and 2050. **S29** RR/MDR-TB Treatment Regimens Averted by 2030 & 2050 in India. **S30** DS-TB Treatment Regimens Averted by 2030 & 2050 in India. **S31** RR/MDR-TB Treatment Regimens Averted by 2030 & 2050 in China. **S32** DS-TB Treatment Regimens Averted by 2030 & 2050 in China. **S33** ICER for vaccination in India at USD 10 per vaccine. **S34** ICER for vaccination in India at USD 30 per vaccine. **S35** ICER for vaccination in China at USD 10 per vaccine. **S36** ICER for vaccination in China at USD 30 per vaccine. **S37** ICER for vaccination in China at USD 10 per vaccine. **S38** ICER for vaccination in China at USD 30 per vaccine. **S39** ICER for vaccination in India at USD 10 per vaccine and 30% mass campaign coverage. **S40** ICER for vaccination in China at USD 10 per vaccine and 30% mass campaign coverage. **Tables S1** Model equations—symbols. **S2** Parameters for births and deaths. **S3** Parameters determining transmission and drug-resistance. **S4** Parameters determining disease progression. **S5** Parameters determining disease relapse and natural cure. **S6** Parameters related to treatment initiation and treatment success. **S7** Scale up of drug sensitivity testing coverage in the "Policy" scenario in China. **S8** RR/MDR-TB treatment regimens in the China "Policy" scenario. **S9** Calibration targets—India Rates are expressed per 100,000 population. **S10** Calibration targets—China. **S11** China Incidence Target Data. **S12** Modelled vaccine types and impact on disease states. **S13** TB-related Unit Costs. **S14** Vaccine-related Costs. **S15** Willingness to Pay Thresholds. **S16** Vaccine Impact by 50% efficacy, 10-year P&PI and PSI vaccines. **S17** Incidence of TB disaggregated by origin.

Additional file 2. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

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Authors' contributions
CKW undertook conceptualization, study design, data collection, programming, analysis and manuscript writing. RCH, GG and RGW undertook conceptualization, study design and manuscript writing. RCH contributed to data validation. CFM and FB contributed to manuscript writing. FB contributed to data collection and validation. YR, RL, LT, KR and RR contributed to country-level data validation and manuscript writing. AG contributed to conceptualization and manuscript writing. GBG and RGW contributed equally to this manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
GBG reports currently being employed at Sanofi Pasteur. RCH reports currently being employed at Sanofi Pasteur. RCH reports grants from IAVI, during the conduct of the study; personal fees from Sanofi Pasteur, unrelated to TB and outside the submitted work. Sanofi Pasteur did not provide funding for this work and had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AG reports grants from Bill and Melinda Gates Foundation, grants from UK DFID, during the conduct of the study; and during this period, Aeras and IAVI (AG's employers during the time period) conducted TB vaccine clinical trials in collaboration with Sanofi and with GSK. However, neither paid any funds directly to AG or to Aeras or IAVI. All other authors declare no competing interests.

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Publisher's Note

3.2 Technical Appendix

Reprint Notes This technical appendix was originally published online in *BMC Medicine* with Research Paper 2. It is reprinted in this chapter and has been reformatted to fit with the remainder of the thesis. The reprint differs from the original only in **pagination** and **typography**. The **cross-references** and **citations** in the reprint are internal and do not refer to the remainder of the thesis. The original published version is available online at:
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The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug resistant tuberculosis in China and India

Technical Appendix

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Model Description

1 Summary

We took the following overarching steps during our analysis:

1. Constructed a dynamic transmission model of tuberculosis stratified by age, prior treatment history, drug resistance status and vaccina status. We only enabled the vaccine stratum during vaccine simulation.
2. Calibrated the model to nationally representative epidemiologic data from China and India.
3. Constructed future baseline scenarios of programmatic MDR-TB and TB management (i.e. without novel TB vaccines).
4. Implemented a country-specific cost-model for programmatic management of TB and RR/MDR-TB within the future baseline scenarios.
5. Implemented vaccines into the future baseline scenarios and estimate epidemiologic impact, vaccine cost-effectiveness, budget impact and treatment regimens averted by vaccination in comparison to baseline.

2 Model Structure and Parameterisation

We represented the following states of tuberculosis within the model:

1. Susceptible (never infected by Mycobacterium tuberculosis);
2. Latent infection (infected with Mycobacterium tuberculosis, but without active disease);
3. Infectious active disease (symptomatic bacteriologically positive disease capable of transmission);
4. Non-infectious active disease (symptomatic TB, but bacteriologically negative and incapable of transmission);
5. On-treatment for tuberculosis and;
6. Resolved (asymptomatic, having recovered from active tuberculosis, either via treatment or through natural cure).

A diagram of the model is presented in Figure S1.

Where appropriate, the natural history states were orthogonally stratified into three layers:

1. by treatment history, into never-treated and previously-treated status;
2. by drug-sensitive or drug-resistance status; and
3. by new TB vaccine vaccination status (the vaccinated stratum was only enabled when modelling vaccine scenarios).

Susceptible populations infected by either drug sensitive or drug resistant Mycobacterium tuberculosis could become latently infected or rapidly and directly to active disease. Populations in the active disease state had three possible exit routes: (1) detection and treatment; (2) natural cure; or

(3) death from tuberculosis or other causes. Those who naturally cured moved to the resolved state. Those starting treatment entered the treatment state where they could either succeed treatment (and move to the resolved state) or fail (and move back to active disease). Treatment failures were redirected back to active TB disease. Latently infected and resolved populations could reactivate and relapse, respectively, back into the active disease state. These populations could also be reinfected and experience rapid progression to active disease but their rate of rapid progression to disease was lower than a naive individual—presumed due to pre-existing immunity—due to existing infection (latent) or previous experience of infection (resolved) .

We introduced an additional vaccine stratum, duplicating the drug resistance- and treatment history- strata within it, when simulating vaccine.

We modelled age in single years, over the range 0–99 years, and simulated over 1900–2050 in calendar time with a 3-month model timestep. Within this period, 1900–1999 represented "burn in" where the model equilibrated between various states. We calibrated to data select time points between 2000–2017, and projected from the model from 2018 to 2050. The full demographic model is described in section 2.7. We programmed the model in the R language for Statistical Computing [1] and implemented it as a series of difference equations.

2.1 Drug Sensitive Stratum

We modelled infection of the susceptible population at rate λ^S. Following infection, a proportion (p–"fast progressors") progressed directly to active disease, whereas the remainder (1-p) became latently infected. Those who progressed to active disease developed either *infectious* or *non-infectious* active disease through a partitioning parameter f. Latently infected populations could (1) remain latent; (2) reactivate to active disease at rate v or; (3) be reinfected at a reduced rate compared to the susceptible population (reduction specified by parameter x).

From the active disease compartments, populations could:

1. be detected and initiated on treatment, moving to a treatment compartment or;
2. undergo natural cure, moving to the resolved compartment or;
3. die due to tuberculosis.

Those initiated on treatment could:

1. be successfully treated and transition to the resolved compartment or;
2. experience treatment failure and transition back to the active disease compartment or
3. die on treatment

We used the WHO definition of prior treatment for tuberculosis ($\geq$ 2 months of previous anti-tuberculosis therapy). Consequently, populations in the *never-treated* drug-sensitive on-treatment compartment exited to destinations in the *previously-treated* stratum. Entry into the resolved state in the "never treated" stratum was only possible through natural cure. As was in latent infection, the resolved state conferred protection against reinfection compared to the susceptible population (through parameter x). Resolved populations could relapse back to active disease, but *could not* transition to the latently infected state.

Similarly, we only represented susceptible and latent states in the never-treated stratum. By definition, any populations with any previous experience of tuberculosis disease or treatment could

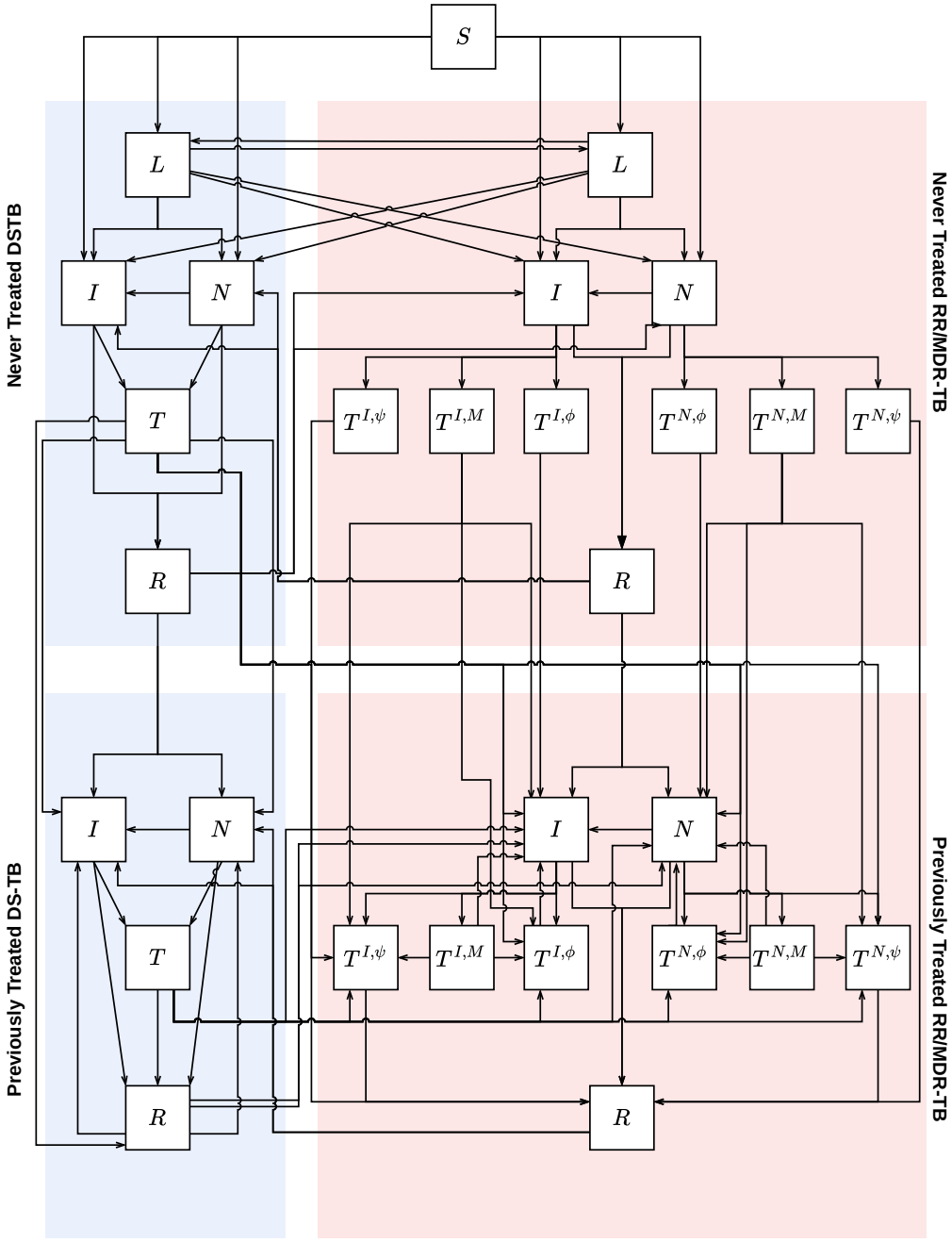

Figure S1: Model diagram. Compartments on blue background represent DS-TB. Compartments on red background represent RR/MDR-TB. Compartment symbols as follows: **S:** susceptible; **L:** latent; **I**: active infectious disease; **N:** active non-infectious disease; **T**: on-treatment, with ψ, ϕ, and M representing RR/MDR-TB treatments which succeed, fail and are misdiagnosed and treated with DS-TB treatment regimen, respectively; **R:** resolved.

not re-enter the susceptible state. Similarly, entry into the latent infection state was only possible from the susceptible state, or through re-infection while in the latent infection state itself. Relapse from the resolved state to latent infection was not possible in this model. Drug resistant populations in their respective susceptible, latent infection and resolved states could also be infected with drug sensitive tuberculosis as described above. Extant drug resistant latently infected and resolved states conferred also protection against drug sensitive reinfection. Populations experiencing treatment failure would transition back into active infectious disease, or active non-infectious disease in proportion to the relative prevalence of infectious vs non-infectious active disease in the preceding time step.

2.2 Drug Resistant Stratum

The drug resistant stratum differed from the drug sensitive in two key areas:

1. Acquisition of resistance
2. Treatment (stratification of outcomes and misdiagnosis)

A proportion of the population on treatment for drug-sensitive tuberculosis developed drug-resistance. We began the acquisition of drug resistance in 1970—timed to co-incide with the discovery of rifampicin [2–4]. We implemented this as a flow of a fixed proportion [5, 6] of the drug-sensitive on-treatment for tuberculosis population (in both treatment history strata) to the previously-treated drug-resistant stratum.

The population moving from the drug-sensitive to drug-resistant stratum in this way comprised multiple sub-populations. Firstly, a proportion was converted to a drug-resistant tuberculosis treatment regimen and moved into the previously-treated drug-resistant on-treatment compartments, through the *proportion correctly treated* parameter ($P_c(t)$—section 2.5). The remainder moved to previously-treated drug-resistant active disease (both infectious and non-infectious, determined by parameter f). Acquisition of resistance and transition to latent infection was impossible; latent infection is not represented in the previously treated stratum. Moreover, such a transition would represent a move from active disease on treatment to asymptomatic latent infection.

Treatment in the drug resistant stratum differed from drug sensitive stratum as follows. In the drug sensitive stratum, all treatment was aggregated into a single state from which treatment success, failure or death were possible outcomes. In comparison, in the drug resistant stratum, transition from active disease into treatment was disaggregated. Those with active disease could be empirically misdiagnosed and transition into a "misdiagnosed and treatment state", where they received inappropriate treatment for drug-sensitive tuberculosis. Alternatively, they could be correctly diagnosed and transition to treatment for drug resistant tuberculosis, either into treatment which is predestined to succeed, or into treatment which is predestined to fail. Correct identification and diagnosis of drug-resistant tuberculosis was governed by parameters determining the *proportion receiving drug sensitivity testing* (for infectious active drug-resistant disease) and *proportion empirically diagnosed* (for both infectious and non-infectious drug-resistant disease), described in section 2.5. Treatment successes moved to the resolved compartment. Treatment failures returned to the previously-treated active disease state (infectious or non-infectious) from which they originated. In contrast to drug sensitive tuberculosis, transitions from drug-resistant infectious active disease remained separate to those with non-infectious active disease. The on-treatment predestined-to-fail state originating from active infectious disease continued to be

infectious on treatment. This structure of treatment allowed for independent counting of time spent on treatment by both treatment failures and successes.

2.3 Equations

Model equations are described in sections 2.3.1, 2.3.22.3.3 and 2.3.4. A key to symbols in the equations is provided in Table S1.

2.3.1 Susceptible Compartment

Births in year k are added in the first timestep of each year to the susceptible compartment.

$$S_{t,0} = S_{t,0} + b_k$$

Mortality and new infections were then applied to the susceptible compartment.

$$S_{t,j} = (1 - \mu_{t-1,j} - \lambda^S_{t-1,j} - \lambda^R_{t-1,j})S_{t-1,j}$$

2.3.2 Drug-Sensitive Tuberculosis

Never-Treated Drug-Sensitive Tuberculosis

$$L^S_{t,j} = (1-\mu_{t-1,j})L^S_{t-1,j}+(1-p_j)\lambda^S_{t-1,j}(S_{t-1,j}+xL^R_{t-1,j})+v_jL^S_{t-1,j}-x\lambda^S_{t-1,j}pL^S_{t-1,j}-x\lambda^R_{t-1,j}L^S_{t-1,j}$$

$$\begin{aligned} I^S_{t,j} = (1 - \mu_{t-1,j})I^S_{t-1,j} + \omega N^S_{t-1,j} + p_j f_j \lambda^S_{t-1,j}(S + xL^R_{t-1,j} + xL^S_{t-1,j}) \\ + v_j f_j L^S_{t-1,j} + (p_j x\lambda^S + {}_j r_j) f_j R^S_{t-1,j} \\ + p_j f_j x\lambda^S_{t-1,j} R^R_{t-1,j} - (n_j + \kappa^I_{t-1,j} + \mu_i)I^S_{t-1,j} \end{aligned}$$

$$\begin{aligned} N^S_{t,j} = \quad & (1 - \mu_{t-1,j})N^S_{t-1,j} + p_j(1 - f_j)\lambda^S_{t-1,j}(S + xL^R + xL^S) \\ & + v_j(1 - f_j)L^S_{t-1,j} + (1 - f_j)(p_j\lambda^S + r_j)R^S_{t-1,j} + (1 - f_j)p_j x\lambda^S_{t-1,j}R^R_{t-1,j} \\ & - (n_j + \kappa^N_{t-1,j} + \mu_n)N^S_{t-1,j} - \omega N^S_{t-1,j} \end{aligned}$$

$$T^S_{t,j} = (1 - \mu_{t-1,j})T^S_{t-1,j} + \kappa^I_{t-1,j}I^S_{t-1,j} + \kappa^N_{t-1,j}N^S_{t-1,j} - (\xi + \psi^S + \phi^S + \mu_T)T^S_{t-1,j}$$

$$R^S_{t-1,j} = (1 - \mu_{t-1,j})R^S_t + n_j(I^S_{t-1,j} + N^S_{t-1,j}) - (p_j x\lambda^S_{t-1,j} + r_j + p_j x\lambda^R_{t-1,j})R^S_{t-1,j}$$

Previously-Treated Drug-Sensitive Tuberculosis The equations which follow determine changes in the *previously*-treated drug sensitive compartments. Superscript pR and pS indicate previously-treated drug-resistant and drug-sensitive compartments, respectively.

Table S1: Model equations—symbols.

Type	Symbol	Description
Super/sub-scripts	Subscripts i	Time step
	Subscript j	Age
	Super-scripts R, S, pR, pS	Applied to terms to indicate to resistant- or sensitive- ; p represents previously-treated.
	Super-scripts I, N	Applied to terms relating to active infectious- or non-infectious TB, respectively
	Super-scripts M, C	Applied to κ terms to indicate correct diagnosis and treatment initiation rate onto RR/MDR-TB treatment (C) or misdiagnosis and treatment initiation onto DS-TB treatment (M).
Compart-ments	S	Susceptible (naive to infection)
	L	Latently-infected
	T	On-treatment
	I	Active infectious disease
	N	Active non-infectioius disease
	R	Resolved following active disease, through treatment or natural cure
Coefficients	κ	Treatment initiation risks, derived from case detection ratio (as per section 2.5.2).
	ψ, ϕ	% Treatment failure and success, respectively
	λ	Transmission parameter
	$\mu_{i,j}, \mu_I, \mu_N, \mu_T$	Mortality risks: background, active infectious disease, active non-infectious disease and on-treatment respectively.
	ξ	Risk of acquiring multidrug resistance on first line therapy
	p_j	Proportion of (re-) infected Susceptible, Latents or Recovereds developing active TB, in age group j
	x	Protection from re-infection or developing active TB due to being latently infected or recovered from infection
	v_j	Risk of reactivation in age j of latently infected population
	f_j	Proportion of new active cases directly becom- ing infectious (primary disease), at age j
	ω	Risk of converting from non-infectious to infec- tious active case
	n_j	Risk of natural cure
	r_j	Risk of relapse from recovered to active (RR/MDR-)TB
	b_k	Number of births in year k
	$P_c(t)$	Proportion correctly diagnosed and initiated onto RR/MDR-TB treatment; see section 2.5.2 and eq 5.
	$Y_{t,j}$	Ratio of infectious- to non-infectious drug-sensitive disease in timestep t
	τ^M, τ^C	Exit risk, per time-step from drug-resistant TB treatment compartments, representing 24-months (τ^C) and 6-months (τ^M) of treatment.

$$I_{t,j}^{pS} = (1-\mu_{t-1,j})I_{t-1,j}^{pS} + \omega N_{t-1,j}^{pR} + (p_j x\lambda^S + {}_j r_j) f_j R_{t-1,j}^{pS} + p_j f_j x\lambda_{t-1,j}^S R_{t-1,j}^{pR} + Y_{t-1,j}\phi^S(T_{t-1,j}^S + T_{t-1,j}^{pS}) - (n_j + \kappa_{t-1,j}^I + \mu_i)I_{t-1,j}^{pS}$$

$$N_{t,j}^{pS} = (1-\mu_{t-1,j})N_{t-1,j}^{pS} + (1-f_j)(p_j\lambda^S + r_j)R_{t-1,j}^{pS} + (1-f_j)p_j x\lambda_{t-1,j}^S R_{t-1,j}^{pR} - (n_j + \kappa_{t-1,j}^N + \mu_n)N_{t-1,j}^{pS}$$

$$T_{t,j}^{pS} = (1-\mu_{t-1,j})T_{t-1,j}^{pS} + \kappa_{t-1,j}^I I_{t-1,j}^{pS} + \kappa_{t-1,j}^N N_{t-1,j}^{pS} - (\xi + \psi^S + \phi^S + \mu_T)T_{t-1,j}^S$$

$$R_{t-1,j}^{pS} = (1-\mu_{t-1,j})R_t^{pS} + n_j(I_{t-1,j}^{pS} + N_{t-1,j}^{pS}) + \psi^S(T_{t-1,j}^S + T_{t-1,j}^{pS}) - (p_j x\lambda_{t-1,j}^S + r_j + x\lambda_{t-1,j}^R)R_{t-1,j}^{pS}$$

2.3.3 Drug-Resistant Tuberculosis

Never-Treated Drug-Resistant Tuberculosis The equations which follow determine changes in the never treated drug resistant compartments.

Here, superscript R and S indicates never-treated drug-resistant and drug-sensitive compartments respectively.

$$L_{t-1,j}^R = (1-\mu_{t-1,j})L_{t,j}^R + (1-p_j)\lambda_{t-1,j}^R(S_{t-1,j} + xL_{t-1,j}^S) + v_j L_{t-1,j}^R - x\lambda_{t-1,j}^R pL_{t-1,j}^R - x\lambda_{t-1,j}^S L_{t-1,j}^R$$

$$I_{t,j}^R = (1-\mu_{t-1,j})I_{t-1,j}^R + \omega N_{t-1,j}^R + p_j f_j \lambda_{t-1,j}^R(S + xL_{t-1,j}^R + xL_{t-1,j}^S) + v_j f_j L_{t-1,j}^R + (p_j x\lambda^R + r_j)f_j R_{t-1,j}^R + p_j f_j x\lambda_{t-1,j}^R R_{t-1,j}^S - (n_j + \kappa_{t-1,j} + \mu_i)I_{t-1,j}^S$$

$$N_{t,j}^R = (1-\mu_{t-1,j})N_{t-1,j}^R + p_j(1-f_j)\lambda_{t-1,j}^R(S + xL^R + xL^S) + v_j(1-f_j)L_{t-1,j}^R + (1-f_j)(p_j x\lambda_{t-1,j}^R + r_j)R_{t-1,j}^R + (1-f_j)p_j x\lambda_{t-1,j}^R R_{t-1,j}^S - (n_j + \kappa_{t-1,j}^N + \mu_n)N_{t-1,j}^R - \omega N_{t-1,j}^R$$

$$T_{t,j}^{I\psi} = (1-\mu_{t-1,j})T_{t-1,j}^{I\psi} + \kappa^{C,I}\psi^R I_{t-1,j}^R - (\tau^C + \mu)T_{t-1,j}^{I\psi}$$

$$T_{t,j}^{I\phi} = (1-\mu_{t-i,j})T_{t-1,j}^{I\phi} + \kappa^{C,I}\phi^R I_{t-1,j}^R - (\tau^C + \mu)T_{t-1,j}^{I\psi}$$

$$T_{t,j}^{N\psi} = (1-\mu_{t-1,j})T_{t-1,j}^{N\psi} + \kappa^{C,N}\psi^R I_{t-1,j}^R - (\tau^C+\mu)T_{t-1,j}^{N\psi}$$

$$T_{t,j}^{N\phi} = (1-\mu_{t-i,j})T_{t-1,j}^{N\phi} + \kappa^{C,N}\phi^R I_{t-1,j}^R - (\tau^C+\mu)T_{t-1,j}^{N\psi}$$

$$T_{t,j}^{M,I} = (1-\mu_{t-i,j})T_{t-1,j}^{M,I} + \kappa^{M,I} I_{t-1,j}^R - (\tau^M+\mu_m)T_{t-1,j}^{M,I}$$

$$T_{t,j}^{N,I} = (1-\mu_{t-i,j})T_{t-1,j}^{N,I} + \kappa^{M,N} I_{t-1,j}^R - (\tau^M+\mu_m)T_{t-1,j}^{N,I}$$

$$R_{t,j}^R = (1-\mu_{t-1,j})R_{t-1,j}^R + n_j(I_{t-1,j}^R + N_{t-1,j}^R) - (\lambda_{t-1,j}^R p_j x + r_j + \lambda_{t-1,j}^S p_j x)R_{t-1,j}^R$$

Previously-Treated Drug-Resistant Tuberculosis The equations which follow determine changes in the *previously*-treated drug sensitive compartments. Superscript pR and pS indicate previously-treated drug-resistant and drug-sensitive compartments, respectively.

$$\begin{aligned} I_{t,j}^{pR} = (1-\mu_{t-1,j})I_{t-1,j}^{pR} + \omega N_{t-1,j}^{pR} + (x\lambda^R + r_j)f_j R_{t-1,j}^{pR} + f_j x\lambda_{t-1,j}^R R_{t-1,j}^{pS} \\ + \xi f_j(1-P_c(t))(T_{t-1,j}^S + T_{t-1,j}^{pS}) + \tau^C(T_{t-1,j}^{I\phi} + T_{t-1,j}^{pI\phi}) \\ + \tau^M(1-P_c(t))(T_{t-1,j}^{M,I} + T_{t-1,j}^{pM,I}) - (n_j + \kappa_{t-1,j}^I + \mu_T)I_{t-1,j}^S \end{aligned}$$

$$\begin{aligned} N_{t-1,j}^{pR} = (1-\mu_{t-1,j})N_{t-1,j}^{pR} + (1-f_j)(x\lambda_{t-1,j}^R + r_j)R_{t-1,j}^{pR} + (1-f_j)x\lambda_{t-1,j}^R R_{t-1,j}^{pS} \\ + \xi(1-f_j)(1-P_c(t))(T_{t-1,j}^S + T_{t-1,j}^{pS}) + \tau^C(T_{t-1,j}^{N\phi} + T_{t-1,j}^{pN\phi}) \\ + \tau^M(1-P_c(t))(T_{t-1,j}^{M,N} + T_{t-1,j}^{pM,N}) - \omega N_{t-1,j}^{pR} - (n_j + \kappa_{t-1,j}^N + \mu_n)N_{t-1,j}^R \end{aligned}$$

$$\begin{aligned} T_{t,j}^{pI\psi} = (1-\mu_{t-1,j})T_{t-1,j}^{I\psi} + \kappa^{C,I}\psi^R I_{t-1,j}^{pR} + \psi^R P_c(t)\tau^M(T_{t-1,j}^{M,I} + T_{t-1,j}^{pM,I}) \\ + f_j P_c(t)\psi^R\xi(T_{t-1,j}^S + T_{t-1,j}^{pS}) - (\tau^C + \mu_T)T_{t-1,j}^{I\psi} \end{aligned}$$

$$\begin{aligned} T_{t,j}^{pI\phi} = (1-\mu_{t-1,j})T_{t-1,j}^{I\phi} + \kappa^{C,I\,R}\phi^R I_{t-1,j}^{pR} + \phi^R P_c(t)\tau^M(T_{t-1,j}^{M,I} + T_{t-1,j}^{pM,I}) \\ + f_j P_c(t)\phi^R\xi(T_{t-1,j}^S + T_{t-1,j}^{pS}) - (\tau^C + \mu_I)T_{t-1,j}^{I\psi} \end{aligned}$$

$$T_{t,j}^{pN\psi} = (1-\mu_{t-1,j})T_{t-1,j}^{N\psi} + \kappa^{C,N}\psi^R N_{t-1,j}^{pR} + \psi^R P_c(t)\tau^M(T_{t-1,j}^{M,N} + T_{t-1,j}^{pM,N}) + (1-f_j)P_c(t)\psi^R\xi(T_{t-1,j}^{S} + T_{t-1,j}^{pS}) - (\tau^C + \mu_T)T_{t-1,j}^{N\psi}$$

$$T_{t,j}^{pN\phi} = (1-\mu_{t-1,j})T_{t-1,j}^{N\phi} + \kappa^{C,N}\phi^R N_{t-1,j}^{pR} + \phi^R P_c(t)\tau^M(T_{t-1,j}^{M,N} + T_{t-1,j}^{pM,N}) + (1-f_j)P_c(t)\phi^R\xi(T_{t-1,j}^{S} + T_{t-1,j}^{pS}) - (\tau^C + \mu_N)T_{t-1,j}^{N\phi}$$

$$T_{t,j}^{M,I} = (1-\mu_{t-1,j})T_{t,j}^{M,I} + \kappa_{t-1,j}^{M,I} I_{t-1,j}^{pR} - (\tau^M + \mu_I)T_{t-1,j}^{M,I}$$

$$T_{t,j}^{M,N} = (1-\mu_{t-1,j})T_{t,j}^{M,N} + \kappa_{t-1,j}^{M,N} I_{t-1,j}^{pR} - (\tau^M + \mu_N)T_{t-1,j}^{M,N}$$

$$R_{t,j}^{pR} = (1-\mu_{t-1,j})R_{t-1,j}^{pR} + n_j(I_{t-1,j}^{pR} + N_{t-1,j}^{pR}) + \tau^C(T_{t-1,j}^{pI\psi} + T_{t-1,j}^{pN\psi} + T_{t-1,j}^{I\psi} + T_{t-1,j}^{N\psi}) - (p_j x\lambda_{t-1,j}^{S} + r_j + \lambda_{t-1,j}^{R}x)R_{t-1,j}^{pR}$$

Treatment Initiation Rate Terms Per section 2.5.2 and equation 5, we (1) partitioned overall treatment initiation, κ for RR/MDR-TB into initiation of correct vs incorrect (misdiagnosis) therapy; (2) included probabilities of empirical detection vs drug-sensitivity testing; into four sub-components (equation 1). These were the specific treatmment initiation rates onto correct treatment for active infectious RR/MDR-TB; correct treatment for active non-infectious RR/MDR-TB; incorrect (misdiagnosed) treatment for active infectious RR/MDR-TB; and incorrect (misdiagnosed) treatment for active non-infectious RR/MDR/TB. Treatment inititiation onto correct treatment was then partitioned into those predestinated to succeed and fail treatment, as described above.

$$\begin{aligned}
\kappa_{t,j}^{C,I} &= \kappa_{t,j}^{I} P_c(t) \\
\kappa_{t,j}^{C,N} &= \kappa_{t,j}^{N} P_c(t) \\
\kappa_{t,j}^{M,I} &= \kappa_{t,j}^{I}(1-P_c(t)) \\
\kappa_{t,j}^{M,N} &= \kappa_{t,j}^{N}(1-P_c(t))
\end{aligned} \tag{1}$$

2.3.4 Vaccine Stratum

We duplicated all compartments, where for a given compartment C, we created a corresponding compartment C_V. The equations determining flow between the C_V compartments were identical to those for C, with coefficients for v, r and p modified by vaccine efficacy, as described in section

4. Within the time step of immunisation, vaccination and waning of protection were implemented as flow from $C \rightarrow C_V$ and $C_V \rightarrow C$ respectively, per equation 2,

$$\begin{aligned} C_V &= C_V + qC - (1-q)wC_V \\ C &= C - qC + (1-q)wC_V \end{aligned} \tag{2}$$

where q represents the coverage of vaccination and w represents the proportion experiencing waning of protection in that time step.

2.4 Natural History Parameters

Natural history parameters with prior ranges and references are presented in Tables S2–S5.

The natural history of tuberculosis varies with age, which manifests as differences in presentation (including extra-pulmonary, pulmonary or disseminated disease), rates of progression following infection, reactivation from latency, relapse following natural cure or treatment and tuberculosis related mortality [7–10]. Therefore, we modelled the corresponding natural history parameters p (progression to active disease), f (progression to infectious disease), v (reactivation from latency), r (relapse from cure or after treatment), μ_I and μ_N(infectious and non-infectious TB mortality) as age-variant. We independently sampled age-specific values for children (age<15), and adults (age $\geq$ 15) for these parameters in the India model. We also sampled additional age-specific values for elderly (age $\geq$ 65) in the China model, including an elderly-specific risk of natural cure (n), as data were available to calibrate this model to additional targets for elderly age groups.

Age-specific parameter ranges were based on data where available (Tables S2–S5). No direct data was found to inform the upper bound of the parameter p (progression to active disease) in the elderly age-group. Therefore, we assumed that immunocompromise served as a reasonable approximation of age-related decline in immunity and used data from HIV+ populations to inform this value, consistent with historical literature [11, 12]. Point estimates of overall, all-age TB mortality risk were informed by systematic reviews of data from the pre-chemotherapeutic era [13, 14]. Based on empirical data [7], we applied age-specific TB mortality calibration factors ($uiscale$ terms) to these point estimates (represented by TB mortality parameters μ_I and μ_T), to generate age-specific TB mortality risks used within the model (Table S2). To allow for higher rates of progression, infectiousness and reactivation from latency in the elderly, and higher TB mortality in children and elderly, than adults, we constrained the sampling process (section 3.1) to retain parameter values only if the elderly/child values were greater than adult values [7–10].

Values for z (risk of transmission per infectious contact), x (protection against reinfection conferred by latent infection or resolved disease), ω (risk of converting from non-infectious to infectious disease), ξ (risk of developing drug-resistance on first line therapy) were fixed across ages.

We calibrated force of infection by multiplying *Mycobacterium tuberculosis* transmission parameters ($\lambda^S_{i,j}$ and $\lambda^R_{i,j}$) by calibration factors q^S and q^R for DS-TB and RR/MDR-TB, respectively. Estimates of the fitness cost of multidrug resistance and its consequent impact on relative transmissibility are heterogeneous [15–17]. In the absence of a precise estimate, we assumed (1) that drug-resistance was unlikely to confer a transmissibility benefit; and (2) a wide prior range of fitness, constrained to be lower than or equal to DS-TB and derived q^R by multiplying q^S with sampled fitness parameter DR_TS (Table S3). We derived an estimate of the risk of acquiring

drug-resistance on DS-TB treatment from systematic reviews of the impact of rifampicin duration on TB treatment outcomes [5, 6, 18].

2.5 Diagnosis and Treatment Parameters

We used case detection ratios (CDR) from WHO [19] to inform treatment initiation from active infectious disease (compartments I and N). We fitted a generalised logistic function to CDR data from China and India [19] to remove artefactual noise in the data and derive a smoothed curve over 2000–2017 (Figure S2A). We then converted CDR to a risk of treatment initiation from prevalent active disease (section 2.5.2). We applied the same case detection ratio to both DS-TB and RR/MDR-TB tuberculosis, as we modelled the identification of drug-resistance as an event subsequent to diagnosis (section 2.5.2). To fit the model to case-notification and incidence data, we applied a scaling factor ($cdrscale$—Table S6) prior to converting to a treatment initiation risk. Bacteriologically negative (non-infectious) tuberculosis was assumed to be detected at a lower rate relative to bacteriologically positive TB [11], using a sampled parameter e.

We independently sampled values of natural cure, mortality and case detection scaling factors during the calibration process (section 3.1) and discarded sample sets where the resulting scaled sum of treatment initiation, mortality and natural cure (the total outflow from active disease) exceeded 1. When simulating increased future case detection (and therefore treatment initiation) in the India "Policy" scenario (section 2.6), we scaled this total outflow to equal 1 as necessary, while maintaining the relative proportions of treatment initiation, natural cure and mortality.

Parameter prior ranges, constraints and details are summarised in Table S6.

2.5.1 Private-Public Health Sector Treatment Proportions in India

In India, the CDR accounted for differential detection the public and private sectors. We adjusted the case detection ratio for the presence the private sector, which manages approximately 40–66% of all tuberculosis treatment [20, 21]. Despite this only 20% of tuberculosis case notifications were estimated to originate from private sector providers in 2017 [22, 23]. Moreover, the quality of care and treatment outcomes in the private sector differ to that of the public sector [22].

We accounted for the presence of the private sector in India by incorporating (1) the proportion TB treatment in the private sector, ppm; and (2) the proportion of all case notifications originating from the private sector. We increased the proportion of case notifications arising from the private sector from 0% in 2012 to 20% in 2017 per WHO data [22] and adjusted the overall case detection ratio as per,

$$\begin{aligned} R &= \frac{T_{\text{Pu}} + T_{\text{Pr}}}{I} \\ T_{\text{Pr}} &= ppm(T_{\text{Pu}} + T_{\text{Pr}}) \\ T_{\text{Pu}} &= \frac{C \cdot I \cdot N_{\text{Pu}}}{P_{\text{Pu}}} \\ R &= C \cdot \frac{N_{\text{Pu}}}{P_{\text{Pu}}} \left(1 + \frac{ppm}{1 - ppm}\right) \end{aligned} \tag{3}$$

where R is adjusted case detection ratio, assuming each notification reflects a treatment initiation, I is incidence, C is case detection ratio, N_{Pu} is the the proportion, among notifications, which

originate in the public sector, P_{Pu} is the proportion of treatment initiations in the public sector which are notified[1], ppm is the proportion of all treatment which occurs in the *private sector,* T_{Pr} is the total treatment volume in the private sector and T_{Pu} is the total treatment volume in the public sector.

The upper bound for the ppm prior range was informed by literature, which suggests up to 66% of treatment might occur in the private sector [21]. We derived the lower bound compatible with WHO notification data through back-calculation [22]. WHO estimates that percentage of *notifications* that originate from the private sector climbs from 0% 2012 to 20% in 2017, which in the "Policy" baseline scenario we further increase to 35% by 2025. We combined this range 0–35% with reported case detection ratio data for India until 2018 [19] (and an assumed increase in case detection ratio to 85% by 2025 in the "Policy" scenario—section 2.6) to estimate a minimum bound of 37% using equation 3. Here, we assumed (1) that 100% of public sector treatment initiations are notified; (2) the proportion of private sector treatment initiations *which are* notified cannot exceed 100% of all private sector treatment initiations; and (3) overall risk of treatment initiation cannot exceed 100%.

2.5.2 Treatment Initiation

WHO defines case detection as the ratio of case notifications among estimated *incident* cases. Assuming that each case notification corresponded to an initiation of anti-tuberculosis treatment, we modelled the outflow from prevalent, active, disease as the sum of treatment, natural cure and mortality. Based on this assumption, we derived a risk of treatment initiation per equation 4.

$$\begin{aligned} \text{CDR} &\approx \frac{\kappa}{\kappa + \mu + n} \\ \kappa &\approx \frac{\text{CDR}(\mu + n)}{1 - \text{CDR}} \end{aligned} \tag{4}$$

Here, κ is risk of treatment initiation; CDR is case detection ratio; μ is mortality risk; and n is risk of natural cure.

In the drug sensitive stratum, following treatment initiation we moved populations from the active disease compartments into the on-treatment compartment, assuming that all such cases receive correct anti-tuberculosis therapy.

In contrast, although we *initiated* drug-resistant active disease cases onto treatment at the same rate as drug-sensitive active disease, they subsequently moved to one of three on-treatment destinations: successful RR/MDR-TB treatment, failing RR/MDR-TB treatment and failing (inappropriate) DS-TB treatment. We first partitioned the treatment initiation outflow into two streams—correct treatment (onto RR/MDR-TB treatment, irrespective of treatment outcome) or incorrect treatment (onto DS-TB treatment)—using the *proportion correctly treated*:

$$P_c(t) = P_{dst}(t) + P_e(t)(1 - P_{dst}(t)) \tag{5}$$

where $P_c(t)$ is proportion correctly treated at time t; $P_{dst}(t)$ is proportion receiving drug sensitivity testing at time t; and $P_e(t)$ is proportion empirically identified as drug-resistant at time

[1] P_{Pu} was assumed to equal 100% when calculating the adjusted case detection ratio, but uncertainty was introduced by adding uncertainty intervals to notification rate calibration targets (section 3.2)

t.

To construct functions $P_{dst}(t)$ and $P_e(t)$, we linearly interpolated from zero (in 2007 and 1970) to values *dst_p* in 2018 and *emp_tx_p* in 2018, respectively. *dst_p* was the proportion receving a drug sensitivity test in 2018 and *emp_tx_p* was the proportion empirically identified as drug-resistant in 2018. A study on scale up of programmatic MDR-TB management in China [24] and results from the first national tuberculosis anti-tuberculosis drug resistance survey of India [25] indicate that programmatic drug-sensitive testing was initiated in 2006–2007; therefore, we initialised $P_{dst}(t)$ at zero in 2007 for both China and India. DST coverage was set at 35% in 2018 based on data from the national strategic plan for tuberculosis elimination in India [26] and expert opinion from both China and India. Beyond 2018, $P_{dst}(t)$ remained constant ("Status Quo" scenario) or incremented ("Policy" baseline scenario) as described in section 2.6. We assumed that bacteriologically-negative patients did not receive drug-sensitivity testing; therefore for identification of non-infectious (bacteriologically-negative) RR/MDR-TB, we set $P_{dst}(t)$ equal to 0. We sampled *emp_tx_p* during calibration (section 3.1).

Once partioned, we further stratified the "correct treatment" flow using the RR/MDR-TB treatment success rate (see section 2.5.3) into successful and failing RR/MDR-TB treatment respectively.

RR/MDR-TB treatment in China

Based on 2013 drug resistance survey results, WHO estimates approximately 46–69,000 cases of RR-TB among all notified pulmonary TB disease in China [19]. However, between 2014–2017, the global TB database reports only 5,807–13,069 laboratory confirmed cases of RR/MDR-TB diagnosed and treated in China. We modelled this gap as treatment occurring outside the of Chinese Centre for Disease Control and Prevention (CDC) tuberculosis dispensary system [27]. We sampled a parameter chr, which we used to partition the total RR/MDR-TB treatment initiations in the model; the chr treatment subflow was calibrated to total RR/MDR-TB volume in the China CDC system, which used towards cost-effectiveness calculations (sections 3.1 and 5.4).

2.5.3 Treatment Regimens

Per WHO guidelines [46, 47], we assumed a treatment duration of 6 months for DS-TB treatment and 24-months for RR/MDR-TB treatment (the latter up to 2018—section 2.6 for differences between baseline scenarios).

We used DS-TB treatment success rates for India and China per the WHO TB database [19] up to 2018 (Figure S2B), which we held constant when projecting into the future in all scenarios. For India, we assumed WHO values to applied to treatment in the public sector; we assumed treatment success rate in the private sector to be 5% lower at any given time point and calculated an overall treatment success rate using the private-public mix parameter ppm (sections 2.5.1 and 3.1).

For second line therapy we assumed a constant treatment success rate of 46% and 48% in China and India respectively [48, 49] from 1970 over the model time horizon.

2.6 Baseline Scenarios

We assumed a baseline scenario of unchanged future programmatic (i.e. non-vaccine) management of DS-TB and RR/MDR-TB as constant case detection, drug-sensitivity testing and TB treatment after 2018. In this document, this is referred to as the "Status Quo" scenario. To test

Table S2: Parameters for births and deaths

Symbol	Description	Prior Range and Constraints	References
Births			
b_k	Number of births in year k	Source data per UN ESA	[28]
Deaths			
$\mu_{i,j}$	Background (all cause) risk of deaths	Calculated from UN DESA Population Division mortality projections as number of projected deaths in a given age, divided by the total projected population in that age group j, in year i	[28]
μ_I	Death risk for infectious untreated TB, varies by age	0.6	[14]
μ_N	Death risk for non-infectious untreated TB, varies by age	0.21 Both values calibrated by $uiscale$ to TB mortality, as below	
μ_T	Death risk on-treatment for DS-TB, varies by age	0.035 Value calibrated by $uiscale$ to TB mortality, as below The definition of treatment failure in RR/MDR-TB include mortality; therefore, a specific mortality term is not applied while "on-treatment" for RR/MDR-TB. Instead, mortality terms for infectious and non-infectious RR/MDR-TB are applied as appropriate.	[13]
$uiscaleA$ $uiscaleC$ $uiscaleE$ (China only)	Calibration factor for TB mortality	uiscaleC = uiscale[j < 15] = (-)0.99 – (+)0.99 uiscaleA = uiscale[j $\geq$15] = (-)0.99 – (+)0.99 (India) uiscaleA = uiscale[j ≥ 15, <65] = (-)0.99 – (+)0.99 (China) uiscaleE = uiscale[j ≥ 65] = (-)0.99 – (+)0.99 (China) Constraint: Parameter set only retained if child (India and China) and elderly (China only) parameters selected were greater than or equal to adult parameter.	Assumed

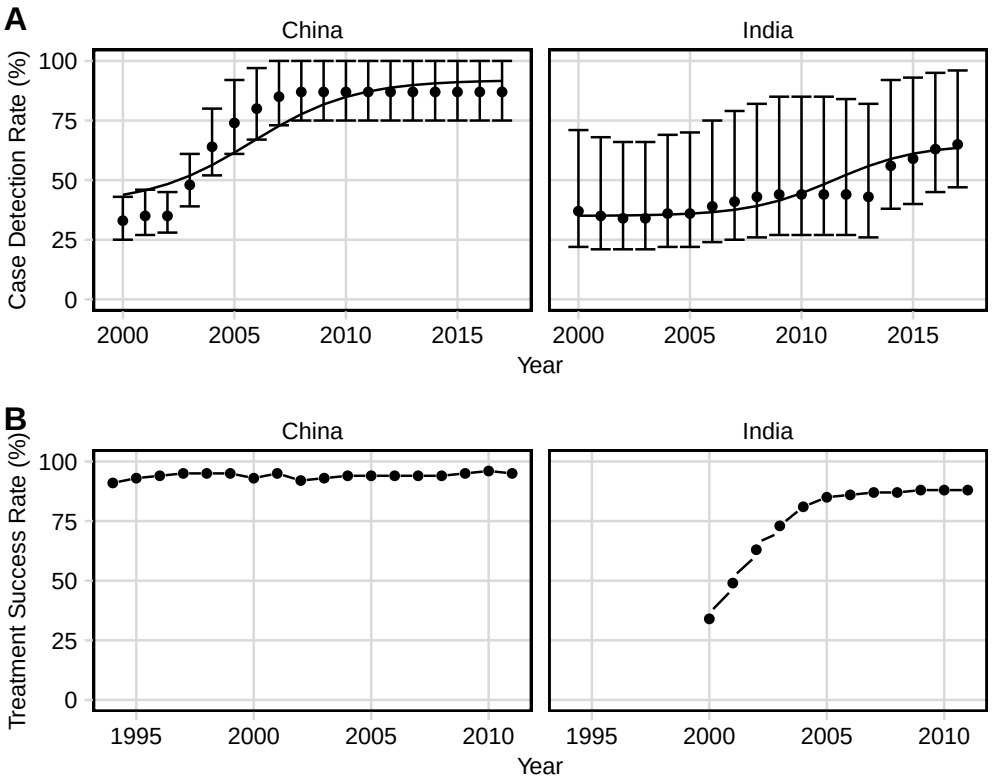

Figure S2: Case Detection and Treatment Success Rates. **A**: case detection ratios for China and India. Dots represent WHO estimates, solid line represents fitted curve. **B:** Treatment Success Rate for first line therapy. Source for A and B: WHO Tuberculosis Database [19].

Table S3: Parameters determining transmission and drug-resistance

Symbol	Description	Prior Range and Constraints	References
Transmission			
$\lambda^S_{i,j}, \lambda^R_{i,j}$	M. tb transmission risk (force of infection) in time step i, for age j for DS-TB and RR/MDR-TB	Calculated in model (equations 6 and 7)	
q^S	Force of infection calibration factor—DS-TB	Scales respiratory contacts to annual number of contacts and calibrates to TB incidence Calibration range: 0–1 (China) and 0–5 (India)	Assumed
q^R	Force of infection calibration factor—RR/MDR-TB	Calculated as: $q^R = q^S \times \text{DR\_TS}$	Assumed
$D_{m,y}$	Daily number of respiratory contacts by age group m and contacts in age group y	Calibrated by q^S to match TB incidence	[29, 30]
z	Probability of transmission per respiratory contact between an Infectious and Susceptible individual	Fixed: 0.1	[12, 31, 32]
Drug Resistance			
ξ	Risk of acquiring multidrug resistance on first line therapy	0.003–0.012	[5, 6, 18]
DR_TS	Relative transmission fitness of RR/MDR-TB	0–1	Assumed

the effect of these assumptions, we performed a scenario analysis by simulating vaccine in an alternative "Policy scenario" which incorporated country-specific changes to programmatic TB management.

India

Per the National Strategic Plan for Tuberculosis Elimination 2017-25 [26] we implemented the following in the India "Policy" scenario:

1. Linearly increase overall case detection ratio (across both private and public sectors) to 85% by 2025;
2. Increase in drug sensitivity testing coverage among public sector notifications from 35% in 2018 [2] to 100% in 2025;
3. Increase in proportion of notifications originating in the private sector to 35% by 2025.

We assumed that all RR/MDR-TB treatment in the private sector was unsuccessful [*Rao, R., National Tuberculosis Elimination Programme, personal communication*].

China

In the "Policy" scenario for the China case study, we implemented the following programmatic management of MDR-TB:

[2] The NSP 2017-2025 reports the proportion of notified pulmonary TB patients receiving a drug-sensitivity test in 2016 as 30% [26].

Table S4: Parameters determining disease progression following infection

Symbol	Description	Prior Range and Constraints	References
p_j	Proportion of (re-) infected Susceptible, Latents or Recovereds developing active TB, in age group j	p[j < 15] = 0.01–0.06 p[j ≥ 15] = 0.08–0.2 (India) p[j ≥ 15, <65] = 0.08–0.2 (China) p[j ≥ 65] = 0.08–0.36 (adult and HIV-positive range) Constraints: In China, the parameter set was retained only if elderly parameter selected was greater than or equal to adult parameter.	[12, 31–33]
x	Protection from re-infection or developing active TB due to being latently infected or recovered from infection	(1-x) = value for the level of protection afforded Range: 0.25–0.41	[31, 32, 34, 35]
v_j	Risk of reactivation in age j of latently infected population	v[j<15] = 0.0001–0.0003 v[j ≥15] = 0.0001–0.0003 (India) v[j ≥15, j<65] = 0.0001–0.0003 (China) v[j ≥ 65] = 0.0001–0.04 (elderly; China) Constraint: In China, parameter set only retained if elderly parameter selected was greater than or equal to adult parameter.	[7, 12, 31, 35, 36]
f_j	Proportion of new active cases directly becom- ing infectious (primary disease), at age j	f[j < 15] = 0-0.15 f[j ≥ 15] = 0.25-0.75 (India) f[j ≥ 15, <65] = 0.25-0.75 (China) f[j ≥ 65] = 0.19-0.75 (elderly; China) Constraint: In China, parameter set only retained if adult parameter selected was greater than or equal to elderly parameter.	[7, 10, 31, 32, 37, 38]
ω	Risk of converting from non-infectious to infec- tious active case	Range: 0.007 - 0.02	[39]

Table S5: Parameters determining disease relapse and natural cure

Symbol	Description	Prior Range and Constraints	References
n_j	Risk of natural cure	Range: 0.1–0.25 (India) Age stratified in China: n[j<55] = 0.1–0.25 n[j 55-64] = (n[j<55] + n[j ≥ 65])/2 n[j ≥ 65] = 0.1–0.25 Constraint: In China, parameter set only retained if adult parameter selected was greater than or equal to elderly parameter.	[31, 32]
r_j	Risk of relapse from recovered to active (RR/MDR-)TB	r[j <15] = 0.01–0.07 r[j ≥ 15] = 0.01–0.07 (India) r[j ≥ 15, <55] = 0.01–0.07 (China) r[j ≥ 55, <65] = (r[j<55] + r[j ≥ 65])/2 (China) r[j ≥ 65] = 0.01–0.07 (China)	[40–45]

Table S6: Parameters related to treatment initiation and treatment success

Parameter Symbol	Description	Prior Range and Constraints	References
κ	Treatment initiation rate, derived from case detection ratio (as per section 2.5.2).	NA	[19]
CDRscale_k	case detection ratio scaling factor in year k (see section	CDRscale[j = all] = (-)0.99 – (+)0.99 (India) CDRscale[j$\leq$ 15] = (-)0.99 – (+)0.99 (China) CDRscale[j$>$ 15, $\leq$ 54] = + (-)0.99 – (+)0.99 (China) CDRscale[j $\geq$65] = + (-)0.99 – (+)0.99 (China) CDRscale[j$>$ 55, $\leq$ 64] = (CDRscale[j$>$65] + CDRscale[j$>$ 15, $\leq$ 55])/2 (China) CDRscale factors were applied to CDR as per scaling function f: $f(\text{CDR}) =$ $\begin{cases} \text{CDR} + (1 - \text{CDR}) \times cdrscale & \text{if } cdrscale \geq 0 \\ \text{CDR} + \text{CDR} \times cdrscale & \text{if } cdrscale < 0 \end{cases}$ In India, a single scaling factor was used across all age groups; in China, scaling factors for children, adults and elderly were used. Constraints: In China, parameter sets only retained if values for elderly (j$\leq$15) were lower than for adults.	[19]
emp_tx_p	Proportion empirically being started on RR/MDR-TB treatment in 2018	0-1	Assumed
e	Relative case-detection of non-infectious cases	0.4–0.8	Assumed
ppm	(India only) Proportion of private sector treatment among all treatment of DS-TB	0.37–0.66	Derived by calculation from sources [20, 21]

Table S7: Scale up of drug sensitivity testing coverage in the "Policy" scenario in China

Year	DST coverage
2018	35
2019	45
2020	50
2021	60
2026	70
2031	80
2036-	90

1. Scale up of DST coverage (Table S7).
2. Change in RR/MDR-TB treatment regimen from a sole 24-month regimen to a mixture of 3 regimens, two of length 24 months and one of length 9 months, with no change in treatment efficacy, but with differing regimen costs (Table S8).

2.7 Demographic Model

We populated the underlying demographic model with new births per year and all-cause, age-wise mortality with data published by the United Nations Department of Economic and Social Affairs (UN ESA), Population Division [28].

We input the absolute number of births per annum into the first time step of the year. Age-wise mortality data was available in 5-year age- and calendar-year blocks; this is converted to annual, single-year age-wise mortality risk and these values were used as all-cause (background) mortality within the model. TB mortality was not removed from all-cause background mortality as its contribution was expected to be small. The median model trajectory for total population by age group as compared to UN ESA estimates are shown in Figure S3 for India and China.

[3] 6LFX(MFX)-BQD-LZD-CFZ-CS/14MFX-CFZ-CS
[4] 6CmLfx(Mfx)PtoCsZ/18LfxPtoCsZ

Table S8: RR/MDR-TB treatment regimens in the China "Policy" scenario.

Length (months)	Regimen	2018	2019–2020	2021–2025	2026–2030	2031–2035	2036–
9	Short Course	0%	10%	30%	40%	40%	40%
24	R1[3]	0%	10%	30%	40%	50%	55%
	R2[4]	100%	80%	40%	20%	10%	5%

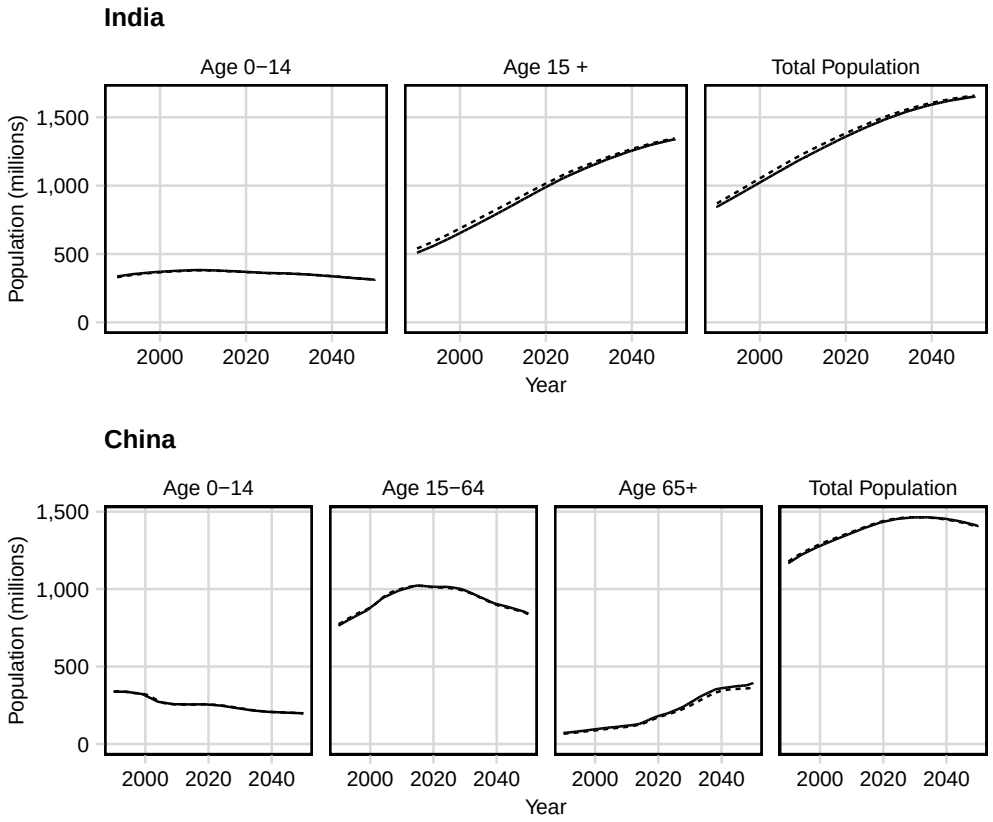

Figure S3: Demographic Model–India and China. Solid line represents median model population projection. Dashed lines represent UN ESA medium-estimate population projections until 2050. The age groups are those by which we stratified model calibration factors and targets.

2.8 Transmission and Contact Mixing

Both TB and MDR-TB have age-specific epidemiologic patterns of incidence and age-dependent natural history parameters. Given this, we incorporated age-specific prevalence of infectious active disease and age-assortativity into the calculation of the age-dependent force-of-infection parameter λ (equations 6 and 7).

$$\lambda_{i,j}^{S} = q^{S}\left(1 - e^{-\sum_{y=1}^{y_{\max}} z \cdot D_{m,y} \cdot \frac{I_y^W}{N_y}}\right) \tag{6}$$

$$\lambda_{i,j}^{R} = q^{R}\left(1 - e^{-\sum_{y=1}^{y_{\max}} z \cdot D_{m,y} \cdot \frac{I_y^M}{N_y}}\right) \tag{7}$$

$$q^{R} = q^{S} \times \text{DR\_TS} \tag{8}$$

Here, i represents the time step; j is the age of interest, which suffers risk of infection; m is the broad ae class, in contact matrices, which contains the age j; y is the broad age class, in contact matrices, which contacta group m. There are $y_{\max}$ age classes; $D_{m,y}$ is the contact matrix, representing the average number of unique contacts by each member of y with members of group m; N_y is the total population in y, across age groups and compartments; I_y is the total number of infectious individuals in y across age all groups; z is the probability of transmission per infectious respiratory contact; and q^S, $q^R$and DR_TS are calibration factors described in section 2.4.

For the China case study we used an social contact matrix for China adapted by Harris, Sumner, Knight, et al. [11] and Harris [50], initially based contact data from a study based in Southwest China [29] of 1821 individuals divided among urban and rural areas. This study found strong assortativity among age-based contacts and similar total contacts between urban and rural residents.

2.8.1 India

For the India case study, we used the socialmixr R package [51] to adapt data from the POLYMOD [30] study to the population structure of India in 2015. We applied population estimates from the UN ESA [28]. The POLYMOD study includes the results of eight nationally representative prospective surveys across European countries, which estimated the daily contact patterns of individuals over the entire population age range. POLYMOD reported found contact patterns to be highly age-assortative, particularly among schoolchildren and young adults.

The social mixing model within the socialmixr package estimates the number of contacts made by an individual of age group i, with members of age group j per unit time (m_{ij}), leading to contact matrix D. The *total* number of contacts, a_i, made by i group individuals is scaled by an assortativity parameter, b_{ij}, reflecting a preference for contact with j group members and the proportion of the total population comprising group j, c_j. This gives

$$m_{ij} = [a_i] \cdot [b_{ij}] \cdot [c_j] \tag{9}$$

We collapsed the population in China into three age groups (age $\leq$ 14 years, age 15–64 years and age $\geq$ 65 years). First, we calculated *total* contact rates (a) for each group by aggregating data published in the original POLYMOD study per equations 11. We then computed the proportion of

each age group j in the total POLYMOD study population, c_j and then back calculated assortativity parameters (b) from equation 9 to derive the assortativity matrix A (equation 9).

$$\mathbf{D} = \begin{matrix} \\ \text{i} \\ \text{j} \\ \text{k} \end{matrix} \begin{matrix} \begin{matrix} \text{i} & \text{j} & \text{k} \end{matrix} \\ \begin{bmatrix} m_{ii} & m_{ji} & m_{ki} \\ m_{ij} & m_{jj} & m_{kj} \\ m_{ik} & m_{jk} & m_{kk} \end{bmatrix} \end{matrix} \tag{10}$$

$$\begin{aligned} a_i &= m_{ii} + m_{ij} + m_{ik} \\ a_i &= m_{ji} + m_{jj} + m_{jk} \\ a_k &= m_{ki} + m_{kj} + m_{kk} \end{aligned} \tag{11}$$

$$\mathbf{A} = \begin{matrix} \\ \text{i} \\ \text{j} \\ \text{k} \end{matrix} \begin{matrix} \begin{matrix} \text{i} & \text{j} & \text{k} \end{matrix} \\ \begin{bmatrix} b_{ii} & b_{ji} & b_{ki} \\ b_{ij} & b_{jj} & b_{kj} \\ b_{ik} & b_{jk} & b_{kk} \end{bmatrix} \end{matrix} \tag{12}$$

We then re-applied each age group total contact rate, a_i, to the assortativity parameter of the contact group of interest, b_j and j group proportion (c_j) *for India* (from UN ESA data) to generate an asymmetric pair-wise contact matrix. Finally, we used our new estimated contact rates (m) and computed the total contacts made by groups i and j (equal in a perfect survey). To ensure that the total reciprocal *number* of contacts between any two groups was equal, we averaged these two values and re-computed new contact *rate* as per equation 13.

$$\begin{aligned} m_{ij} &= m_{av} \cdot N_i \\ m_{ji} &= m_{av} \cdot N_j \\ m_{\text{av}} &= \frac{(m_{ij} \cdot N_i) + (m_{ji} \cdot N_j)}{2} \end{aligned} \tag{13}$$

Here m_{av} is the average total number of contacts; N_i is the population in age group i; and N_j is the population in group j.

3 Model Calibration

3.1 Sampling and Calibration Method

We employed a two-stage calibration process to fit the model to calibration targets (section 3.2).

In the first stage, we utilised Approximate Bayesian Computation Accept-Reject Random sampling (ABC-RS) [52] to identify parameter space corresponding to a partial fit of the full calibration target set (>10 calibration targets). We used these partially fitted parameter sets as seeds to initialise an Approximate Bayesian Computation Markov Chain Monte Carlo (ABC-MCMC) [52, 53] rejection sampling process, to find parameter sets fitting incrementally greater numbers of calibration targets until all targets were satisfied. The parameter space was then further explored using the ABC-MCMC process to generate parameter sets fully compatible with the epidemiologic and health economic data. Within both the ABC-RS and ABC-MCMC sampling processes, we assumed uniform prior distributions for all parameters. We sampled along approximately 200 parallel Markov Chains each generating 40,000 samples. Finally, 1,000 fully fitted parameter sets were randomly selected from approximately 100,000 sets in India and 30,000 sets in China. We used these sets to generate 1,000 runs each for the Status Quo and Policy baseline scenarios. These 1,000 model runs captured uncertainty in TB natural history and costs for each baseline scenario. We then implemented the vaccine scenarios on each of these 1,000 runs for each baseline scenario to model vaccine impact.

3.2 Calibration Targets

We calibrated the model to China and India specific epidemiologic targets detailed in Tables S10 and S9 respectively.

3.2.1 India

We calibrated the India country model to seventeen calibration targets, four of which were specific to RR/MDR-TB (Table S9). These included prevalence, incidence, mortality and notification rates for all TB, and for incidence rate, laboratory confirmed RR/MDR-TB treatment initiations and proportion of RR/MDR-TB cases among notifications for all TB. Where data permitted, we calibrated to age-specific targets. Unless otherwise specified, calibration target quantities represent the same inter-compartmental transitions described in the China case study, above.

India has not reported the results of a nationally representative tuberculosis prevalence survey. Therefore, we used estimates of bacteriologically-positive prevalence rate derived through pooling subnational estimates [54] as a calibration target for all TB prevalence rate. We calibrated all TB incidence to WHO estimates of all-age all TB incidence rate. While age-stratified incidence is not reported by WHO nor by country authorities, model-based estimates of paediatric TB burden suggest that approximately 8% of incident TB in 2010 in India occured in children (age <15). Assuming the relative proportion of burden between children and adults remained the same between 2000 and 2017, we calculated age-specific incidence calibration targets from WHO overall incidence estimates and UN ESA [28] population estimates.

We calibrated to all TB mortality rate and age-specific notification rates per WHO estimates [19]. As discussed in section 2.5.1, we adjusted treatment initiation rates for the presence of the private sector, including private sector contributions towards case notifications, which are estimated to have risen from 0% in 2012 to approximately 20% of in 2017, as reported by WHO [22]. Further,

a systematic review of case detection and patient retention throughout the tuberculosis "case-cascade" in the Indian Revised National Tuberculosis Control Programme has estimated that of 72% of prevalent TB patients who reach diagnostic centres, only 59% are subsequently registered on treatment. To allow for (1) uncertainty in the contribution of the private sector towards case notifications; and (2) losses between diagnosis and treatment initiation, we assumed a 20% uncertainty interval around WHO point-estimates of case notification data when constructing notification rate calibration targets.

The model was calibrated to RR/MDR-TB incidence rates as reported by WHO [22] and proportions of RR/MDR-TB cases among notified cases as reported in the first national anti-tuberculosis drug-resistance survey of India [25]. We calibrated the proportion of RR/MDR-TB treatment diagnosed through drug-sensitivity testing ($P_{dst}(t)$—section 2.5.2) to the reported number of laboratory confirmed RR/MDR-TB treatment initiations in 2017 [19].

3.2.2 China

We calibrated the China country model to twenty six calibration targets, six of which were specific to RR/MDR-TB epidemiology and treatment (Table S9). These included prevalence, incidence, mortality and notification rates for all TB and to RR/MDR-TB incidence rate, volume of RR/MDR-TB treatment in the CDC system, and proportion of RR/MDR-TB among new- and previously-treated case notifications. Where data permitted, we calibrated to age-specific targets.

We calibrated the prevalence rate of bacteriologically-positive tuberculosis (overall—including both drug-sensitive and drug-resistant), by age, to results from nationally representative prevalence surveys in 2000 and 2010 [24]. In this model, this represented the sum of I disease states across treatment history and drug-resistance strata.

Age-specific tuberculosis mortality rates for tuberculosis were provided by CDC [*Tao, L., personal communication*]; in the model, these represent disease specific mortality in the I, N, and T compartments. Although WHO estimates suggest a low case-fatality rate for TB in China [22], evidence suggests that up to 50% of pulmonary TB patients are attributed a non-TB cause of death, suggesting potentially high levels of misclassification [55, 56]. We therefore assumed a 50% uncertainty interval around mid-point estimates of mortality as calibration targets.

Notification rates represented treatment initiations (transitions from I or N compartments into T compartments. To account for overdiagnosis of bacteriologically negative tuberculosis in China, we reduced the contribution of bacteriologically-negative and/or clinically diagnosed case notifications to total case notification targets by 15%, per expert opinion [*Tao, L., CDC, personal communication*]. Case notifications reported by WHO before 2013 are disaggregated by bacteriologic status; for notification rate calibration targets before 2013, we directly reduced the sputum smear-negative notification value and total notifications to adjust for overdiagnosis. For targets including and beyond 2013, we reduced the value of clinically diagnosed new tuberculosis notifications and recalculated total notifications.

Patients in China can access TB care through either the CDC-based tuberculosis dispensary system, or through the parallel hospital-based system [27]. We assumed that case notification data only originated from the CDC system, which accounts for 80% of (all TB) treatment. Furthermore, evidence suggests that the screening algorithm utilised by China NTP may misclassify TB by up to 20% [11, 57]. Taken together, we applied a 20% uncertainty interval to age-stratified point-estimates of adjusted case notifications (as above) reported by WHO for China to derive final notification rate calibration targets.

Incidence (transitions *into* disease states I and N) was calibrated to WHO Global Tuberculosis Report [22] and Global TB database indidence data [19]. Incidence rates for RR/MDR-TB and RR/MDR-TB treatment volume were derived from WHO estimates [19, 22]. WHO estimates of incidence are derived from case notification data; following the case notification adjustment (above) we adjusted the corresponding values of all TB and RR/MDR-TB incidence rate. RR/MDR-TB incidence rate was adjusted using the WHO Global Tuberculosis Report method [22, 58] using equation 14 and data per Table S11.

$$I_{\text{MDR}} = I\left((1-f)p_n((1-r)+r\rho)+fp_r\right) \tag{14}$$

Here f is the cumulative risk for incident cases to receive a non-relapse retreatment (following treatment failure or return after default); I is incidence of tuberculosis; I_{MDR} is incidence of MDR-TB; ρ is risk of RR/MDR-TB in relapses relative to previously untreated cases; p_n is proportion of RR/MDR-TB among new notifications; p_r is proportion of RR/MDR-TB among previously treated notifications; and r is proportion of relapses of the sum of new and relapse cases.

The number of RR/MDR-TB cases treated in the Chinese CDC system was derived from the WHO Global TB database [19] where we assumed 20% uncertainty interval, as for all TB case notifications. The proportion of RR/MDR-TB among case notifications was derived from nationally representative drug-resistance survey data [59, 60] and internal data from CDC [*Tao, L., personal communication*].

Table S9: Calibration targets—India. Rates are expressed per 100,000 population

Calibration target	Year	Subgroup	Target Range	References
All TB				
Prevalence rate	2015	Overall	195–312	[54]
Incidence rate	2000	Overall	149–473	[19, 61]
	2017	Overall	140–281	
	2000	0–14 Years	42–134	
	2017	0–14 Years	45–91	
	2000	15+ Years	192–609	
	2017	15+ Years	176–354	
Mortality rate	2017	Overall	29–34	[19]
Notification rate	2007	15+ Years	118–178	[19]
	2007	Overall	81–122	
	2017	15+ Years	139–209	
	2017	0–14 Years	6–9	
	2017	Overall	107–160	
RR/MDR-TB				
Incidence rate	2016	Overall	7–15	[22]
% Resistant among notified cases	2016	Never Treated	2–3	[25]
	2016	Previously Treated	10–13	
Lab confirmed RR/MDR-TB Treatments	2017	Overall	28,760–43,140	[19]

Table S10: Calibration targets—China. Rates are expressed per 100,000 population. CDC: Chinese Center for Disease Control and Prevention

Calibration target	Year	Subgroup	Target Range	References
All TB				
Prevalence rate	2000	Overall	163–195	[24]
		15–29 years	72–116	
		30–44 years	96–146	
		60+ years	510–609	
	2010	Overall	101–132	
		15–29 years	40–86	
		30–44 years	54–99	
		60+ years	106–168	
Incidence rate	2000	Overall	77–131	[19]
	2017	Overall	50–66	
Mortality rate	2010	Overall	1.36–4.07	
		0–14 years	0.06–0.18	
		15–64 years	0.88–2.65	
		65+ years	8.28–24.84	
Notification rate	2015	Overall	41.19–61.79	[19]
		0–14 years	1.22–1.84	
		15–64 years	43.9–65.85	
		65+ years	93.9–140.85	
RR/MDR-TB				
Incidence rate	2017	Overall	4.6–7	[22]
% Resistant among notified cases	2007	Never Treated	4.59–7.09	[59]
	2007	Previously Treated	21.73–29.98	
	2013	Never Treated	5.6–8.7	
	2013	Previously Treated	20–28	
CDC confirmed treatment initiations	2017	Overall	5,943–7,132	[19]

Table S11: Data values used to substantiate recalculation of adjusted TB incidence targets in China [58] China Incidence Target Data

Parameter	Mean	Standard Deviation
f	0.007745	0.00183
r	0.02983	0.002473
ρ	3.377	0.3759
p_n	0.0713	0.00801
p_r	0.2408	0.01918

4 Vaccine implementation

To model vaccination, we duplicated both drug resistance and treatment history strata and moved immunised populations from their state in the unvaccinated stratum to the corresponding state in the vaccinated stratum. Similarly, when the effect of the vaccine waned (loss of protection), these populations moved in the reverse direction, from a given state in the vaccinated strata to the corresponding state in the unvaccinated strata (equation 2).

We implemented a "Prevention of Disease" (PoD)-type vaccines, conferring protection against the development of active TB disease. We did not model a "Prevention of Infection", PoI, vaccine effect—infection by *M. tb* and transmission was identical vaccinated and unvaccinated strata. To model a PoD vaccine, we multiplied the following model parameters by a factor equal to (1 − vaccine efficacy):

1. Primary ("fast") progression from the susceptible state (p);
2. Reactivation from the latently infected state (v);
3. Relapse from the resolved state (r).

This represented a "*leaky*" type vaccine, wherein disease continues to manifest in vaccine recipients, albeit at a rate reduced in proportion to the efficacy of the vaccine.

We modelled three subtypes of PoD vaccines, whose effect depended on the extant host infection status at the time of vaccination: (1) "pre-infection" (PRI) vaccines were only effective in susceptible individuals; conversely, "post-infection" (PSI) vaccines were effective in those with latent infection and resolved infection; "pre- and post-infection" (P&PI) vaccines were effective in all three types of host infection status (Table S12). Vaccines did not affect treatment related parameters (detection, treatment success or failure rates), natural cure rates nor TB related mortality. Waning (loss of protection) occurred instantly and exactly at the end of the duration of protection.

We did not explicitly represent existing Bacillus Calmette–Guérin (BCG) immunisation programmes as we assumed protection conferred by BCG to be reflected in calibration targets.

4.1 Vaccine Characteristics

There is no currently no licensed adult vaccine to prevent tuberculosis. Two candidates in advanced clinical development—M72/AS01$_{\mathrm{E}}$ and BCG revaccination[5]—have reported efficacies of 49.7% and 45.4% at 3 and 2 years follow up, respectively [62, 63]. BCG revaccination was administered to IFNγ negative populations, whereas M72/AS01$_{\mathrm{E}}$ was administered to IFNγ positive populations. Additionally, WHO preferred product characteristics (PPC) for new tuberculosis vaccines [64] specifies a minimum duration of protection of at least 10 years, with a minimum efficacy of 50%. To encompass the WHO PPC specification, BCG revaccination and M72/AS01E, we modelled vaccines conferring protection for 5- and 10-years, with efficacy between 30–90% in 20% increments, across PRI, PSI and P&PI vaccine types.

4.2 Deployment

Previous modelling studies suggest that age-targeting vaccination—to adults, adolescents or the elderly—is likely to achieve a greater impact on all TB burden than infant or early childhood immunisation [11, 12]. This is reflected in the WHO PPCs for new TB vaccines [64] which

[5] Revaccination administered to adults

Table S12: Modelled vaccine types and impact on disease states

Vaccine type	States which vaccine is applied to (and effective in)			
	Susceptible (S)	Latent (L)	Active Disease (I or NI)	Recovered (R)
Pre-infection (PRI)	Yes	No	No	No
Post-Infection (PSI)	No	Yes	No	Yes
Pre- and Post-infection (P&PI)	Yes	Yes	No	Yes

consider these populations the priority target for TB vaccine development. However, to date, there are no major adult diseases against which large-scale routine vaccination is administered to serve as a direct analogue to model adult TB vaccine programmes.

We assumed vaccine administration through two strategies, routine vaccination and mass campaigns, both beginning in 2027. We generated assumptions around vaccine coverage based on immunisation programmes for other diseases, applied to similar age groups in other settings.

We assumed continuous routine TB vaccination was delivered to children aged 9 with 80% coverage, along with human papillomavirus vaccine (HPV). The routine coverage estimate was based on secondary school enrolment rates in China and India, and HPV vaccine programme coverage among schoolchildren in South Africa [65, 66].

Mass campaigns were delivered to ages 10 and above at a 10-yearly frequency. Menafrivac campaigns delivered to 1–29 year olds in South Africa were reported to achieve coverage of 70–98% [67]. However, routine vaccination for influenza in China [68, 69]and mass adult campaigns for Japanese encaphalitis in India [70]—both of which were delivered to populations including the elderly—have reported coverage estimates of 36–49% and 58%, respectively. As our mass campaign age-group was wide, including the elderly, we based our mass campaign coverage (70%) on the lower bound of the Menafrivac coverage estimate. In addition, we simulated mass vaccination campaigns at 30% coverage as an additional conservative scenario analysis.

5 Cost-effectiveness Analysis

We calculated total cost from a public healthcare sector perspective as comprised of total tuberculosis programme costs (section 5.1) and vaccine programme costs (section 5.2). We then derived Disability Adjusted Life Years (DALYs) incurred due to active tuberculosis disease in the (unvaccinated) baseline scenarios and their corresponding vaccinated scenario and calculated the difference as the health benefit of vaccination (section 5.3). We derived the incremental cost-effectiveness ratio of vaccination (section 5.4) as a measure of cost-effectiveness.

5.1 TB-related Cost Model

The unit costs of TB management are summarised in Table S13 fo India and China. We estimated costs from a health service perspective using an ingredient approach [71]. To inform the cost calculations, we obtained unit costs for DS- and RR/MDR-TB diagnosis, drug-sensitivity testing and DS- and RR/MDR-TB treatment. In addition, for India, we added the estimated cost of incentives provided *to* the private sector to improve case notification and cost of providing nutritional support to patients on treatment for tuberculosis (in both private and public sectors). The annual total service delivery cost was calculated as the sum of unit costs incurred each year. We assumed a top-up of 50% of assumed programme cost, based on the national expenditure report to the WHO TB programme [22].

The annual total cost was calculated as the sum of the unit cost per output multiplied by the quantity of outputs each year. The outputs included:

1. Number of persons with presumptive TB tested, calculated from the number of people diagnosed;
2. Number of person-months of drug sensitive TB treatment;
3. Number of drug sensitivity tests conducted;
4. Number of people started on drug resistant TB treatment; and
5. Number of person-months of drug resistant TB treatment.

To calculate costs of diagnosis, we multiplied the unit costs for diagnosis by the number of people tested. The number of people tested was calculated using a Test-to-Diagnosis Ratio (TDR), to adjust for false-negative and true-negative test results. TDR values of 3.57 and 6.48 were applied to China [72] and India [26] in country-specific starting years 2011 and 2016, respectively. We then adjusted the TDR value in each subsequent year by the prevalence of active tuberculosis.

5.2 Vaccine-related Cost Model

We separated vaccine-related costs into vaccine, delivery and program costs. The unit costs are summarised in Table S14.

In India, we used a national analysis of variation in cost and performance of routine immunisation service delivery[73] to derive uncertainty ranges for routine vaccine delivery cost. We used estimates from the Indian measles-rubella vaccination campaign operational guidelines [74] to add delivery costs in mass campaigns.

In China, delivery costs were sourced from literature [75, 76]. We assumed delivery costs per person immunised to be the same in mass campaign or routine settings. Programme costs

Table S13: TB-related Unit Costs

Country	Cost	Value [range] (USD)		Distribution	Source
India	DSTB diagnosis, per patient	14.82	[11.86–17.79]	Normal	[78–80]
	RR/MDR-TB diagnosis, per patient (assumed to be DSTB diagnosis cost +20%)	17.78	[14.23–21.35]		Assumed
	Drug sensitivity testing, per patient	6.00	[4.80–7.20]	Normal	[80]
	DS-TB treatment, per patient-month	26.43	[21.15–31.71]	Normal	[81–83]
	RR/MDR-TB treatment, per patient-month	216.19	[187.88–244.50]	Normal	[81–83]
	Patient nutritional support	7.46			[26]
	Private sector incentive	3.73			[26]
China[6]	DSTB diagnosis, per patient	27.05	[21.63–32.47]	Normal	[84, 85]
	RR/MDR-TB diagnosis, per patient (assumed to be DSTB diagnosis cost +20%)	32.46	[25.96–38.96]	Normal	Assumed
	Drug sensitivity testing, per patient	13.20	[11.78–14.62]	Normal	[86]
	DS-TB treatment, per patient-month	28.41	[27.14–29.68]	Normal	[48, 84]
	RR/MDR-TB treatment—no injectables, per patient-month	746.84	[377.29–861.73]	β	[48, 84]
	RR/MDR-TB treatment—including bedaquiline, per patient-month	346.29	[276.77–413.84]	β	[48, 84]

Table S14: Vaccine-related Costs

Country	Cost	Value [range] (USD)		Distribution	Source
India	Delivery cost per regimen (routine)	1.88	1.13−2.40	β	[73]
	Delivery cost per regimen (mass)	1.95	1.20−2.47	β	[74]
	Vaccine campaign cost (fixed)	25,374,949.00			[74]
China	Delivery cost per regimen (routine)	2.32	1.60−2.80	β	[75, 76]
	Delivery cost per regimen (mass)	2.32	1.60−2.80	β	[75, 76]
	Vaccine delivery cost (variable cost per 10,000 vaccinated through mass campaigns)	16,133.10			[77]

associated with mass campaigns were estimated from a study of nationwide catch-up vaccination for hepatitis B [77].

In both countries, we modelled a USD 10 and USD 30 price per vaccine based on expert opinion. We calculated the annual total cost as the sum of the unit cost per vaccine multiplied by quantity of vaccines delivered plus programme costs.

5.3 Disability Adjusted Life Years Calculations

To calculate benefits associated with vaccination, we calculated the difference in total Disability Adjusted Life Years (DALYs) associated with tuberculosis infection between each vaccine and each of the two baseline scenarios. We used the disability weight (0.333) for tuberculosis as reported in the Global Burden of Disease 2013 study [87] and calculated total DALYs incurred as per WHO

[6] Additional costs for first- and RR/MDR-TB treatment received from CDC [Tao, L., personal communication]

Table S15: Willingness to Pay Thresholds

	Threshold	Value	% GDP
China	WHO[7]	9771	100
	HCOC (lower)	3650	45
	HCOC (upper)	5669	71
India	WHO	2016	100
	HCOC (lower)	264	17
	HCOC (upper)	363	23

CHOICE [88].

5.4 Cost-effectiveness Analysis and Willingness to Pay Thresholds

We calculated the incremental cost effectiveness ratio as the ratio between the incremental benefit, in DALYs averted, and the incremental cost, in USD, for each run across vaccination and baseline scenario. Both costs and benefits were discounted to 2027 (when vaccination began) at 3%, per the Gates Reference Case for Economic Evaluation [89]. We analysed cost-effectiveness by 2050, reflecting a 23 year timeframe in line with WHO END TB [90] and UN SDG TB control targets [91]. We constructed a cost-effectiveness acceptability curve for each vaccine profile, per country and per baseline scenario and present an estimated probability of vaccine cost-effectiveness against a continuous willingness-to-pay (WTP) threshold. We report probability of cost-effectiveness against three WTP thresholds from the literature (Table S15):

1. WHO threshold—1 times gross domestic product (GDP) per capita [84, 92]
2. Healthcare opportunity cost (HCOC) based threshold [93]

[7] WHO values represent 2018 World Bank GDP per capita estimates.

Furthers Results and Discussion

6 Calibration and Baseline Scenario Projections

6.1 Posterior Distributions of Parameters

Posterior distributions for parameters sampled and described in sections 2.4 and 2.5 are presented here for India (Figures S4 and S5) and China (S6 and S7).

6.2 India

6.2.1 Calibration

Calibration results are summarised in Figures S8 and S9.

We calibrated the model to all prespecified targets.

All TB notification rates were predicted to be 103 [UI 86–122] per 100,000 and 142 [UI 118–169] per 100,000 among all ages and adults (age>14) in 2007, and 119 [UI 107–131] per 100,000, 24 [UI 23–27] per 100,000 and 156 [UI 140–174] per 100,000 among all ages, children (age<15) and adults (age>14) in 2017, respectively (Figure S8A). All TB incidence rates for all ages, children (age<15) and adults (age>14) were predicted to be 339 [UI 292–373] per 100,000, 104 [UI 91–107] per 100,000 and 450 [UI 381–498] per 100,000 in 2010, and 261 [UI 216–273] per 100,000, 65 [UI 60–74] per 100,000 and 339 [UI 278–354] per 100,000 in 2017, respectively (Figure S8B). All TB mortality rate was predicted to be 31 [UI 29–34] per 100,000 in 2017 (Figure S8C). The model predicted all TB prevalence rate to be 218 [UI 195–310] per 100,000 in 2015 (Figure S8D).

The model predicted RR/MDR-TB incidence to be 8 [UI 7–10] per 100,000 in 2017 (Figure S9A). Laboratory confirmed RR/MDR-TB treatments were predicted to be 37,184 [UI 28,841–43,133] in 2017 (Figure S9B). The proportion of RR/MDR-TB cases among all TB notifications in 2016 was predicted to be 2.7% [UI 2.0–3.0] among never-treated cases and 11.0% [UI 10.0–13.0] among previously-treated cases, respectively (Figure S9C).

6.2.2 Baseline Scenario Projections

Model projections for overall and RR/MDR-TB epidemiology for India over 2018–2050 are presented in Figure S10.

At baseline, with no new vaccine and no change to programmatic management of TB after 2018 (the "Status Quo" baseline scenario), the model projected all TB prevalence rate at 216 [UI 191–301] per 100,000 in 2018 and 237 [UI 191–341] per 100,000 in 2050 (Figure S10A). Overall incidence was predicted to be 262 [UI 217–274] per 100,000 in 2018 and 280 [UI 217–334] per 100,000 (Figure S10B) 2050. Overall mortality was predicted to be 31 [UI 29–34] per 100,000 in 2018 and 32 [UI 25–40] per 100,000 in 2050 (Figure S10C). RR/MDR-TB incidence was predicted to be 8 [UI 7–10] per 100,000 in 2018 and 11 [UI 7–25] per 100,000 (Figure S10D). RR/MDR-TB mortality rate was predicted at 2 [UI 2–3] per 100,000 in 2018 and 3 [UI 2–5] per 100,000 in 2050 (Figure S10E). The proportion of RR/MDR-TB cases among never treated TB notifications was predicted to be stable at 3% [UI 2–3] in 2018 and 4% [UI 2–7] in 2050; the corresponding proportion among previously treated TB notifications was predicted to be 10% [UI 9–13] in 2018 and 13% [UI 10–23] in 2050 (Figure S10F).

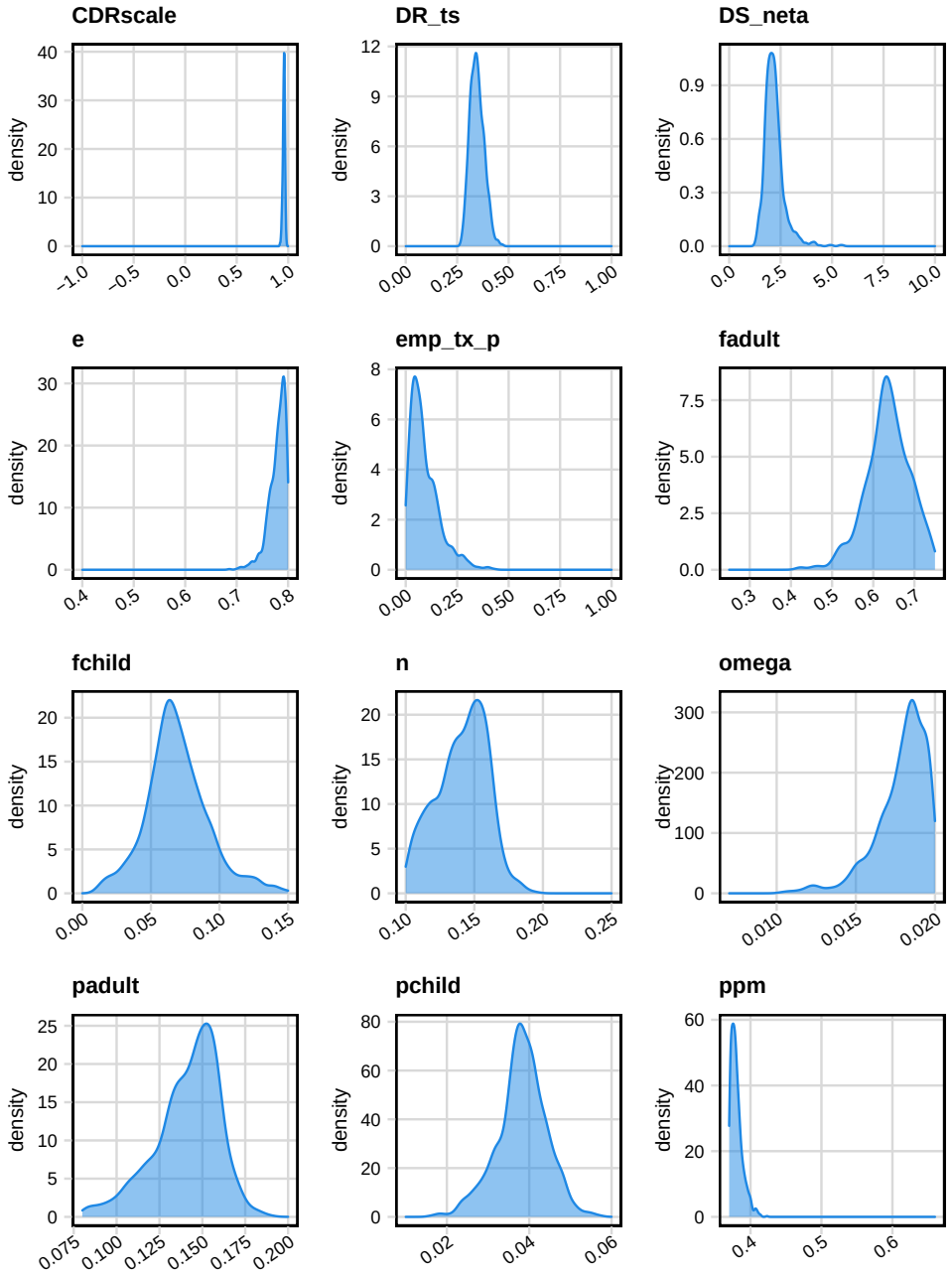

Figure S4: Posterior distributions of sampled parameters—India. Subplots show probability density of parameter values (y-axis) plotted against the prior range (x-axis) of each parameter. Parameter names suffixed with *adult or A* indicate adult specific parameters. Suffixes *child* or *C* indicate children-specific sampled parameters. **CDRscale**: case detection ratio scaling factor ($cdrscale$). **DR_ts**: RR/MDR-TB relative transmission fitness cost. **DS_neta**: transmission scaling factor for all TB. **e**: relative probability of case detection of non-infectious TB. **emp_tx_p**: proportion empirically diagnosed and treated for RR/MDR-TB. **fadult and fchild**: proportion fast progressing to infectious active TB. **n:** natural cure; **omega:** risk of converting from non-infectious to infectious TB. **padult and pchild**: proportion fast progressing to active TB. **ppm**: proportion of all TB treated in private sector.

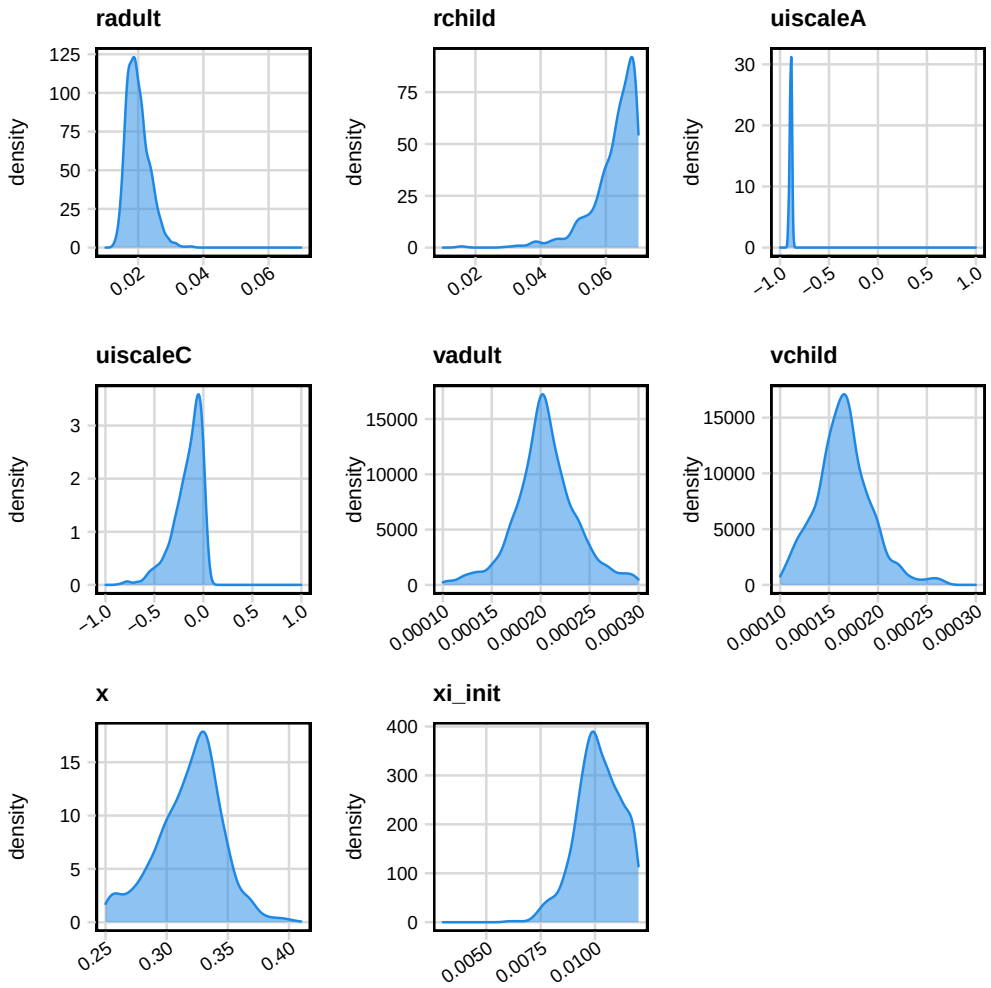

Figure S5: Posterior distributions of sampled parameters—India (contd.). Subplots show probability density of parameter values (y-axis) plotted against the prior range (x-axis) of each parameter. Parameter names suffixed with *adult or A* indicate adult specific parameters. Suffixes *child* or *C* indicate children-specific sampled parameters. **radult and rchild**: r, risk of relapse from resolved disease. **uiscaleA and uiscaleC**: TB mortality scaling factors. **vadult and vchild**: v, risk of relapse from latent disease. **x**: x, relative protection against reinfection in latent and resolved compartments; **xi_init**: ξ, risk of acquiring drug resistance on-treatment for DS-TB.

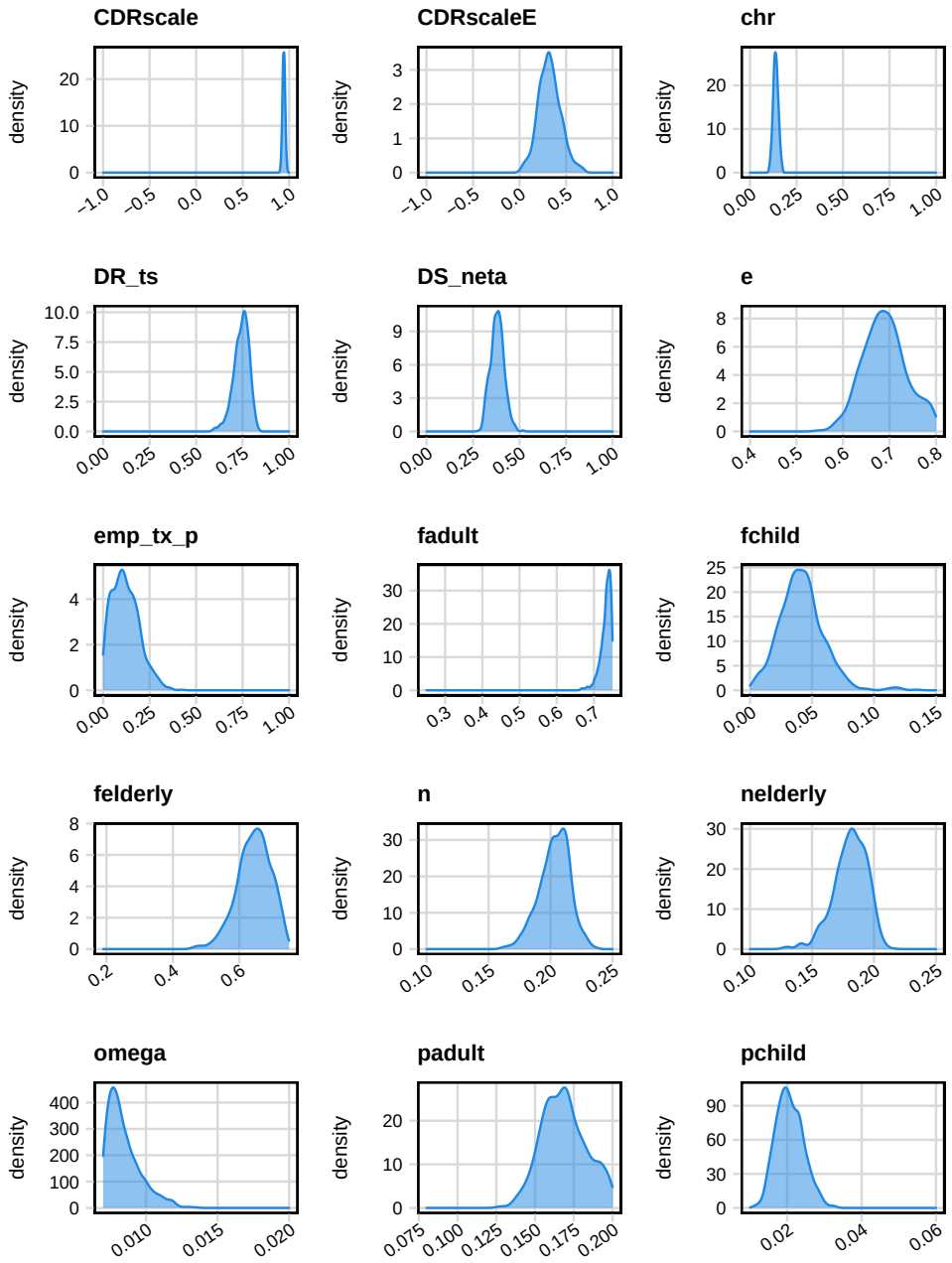

Figure S6: Posterior distributions of sampled parameters—China. Subplots show probability density of parameter values (y-axis) plotted against the prior range (x-axis) of each parameter. Parameter names suffixed with *adult or A* indicate adult specific parameters. Suffixes *child* or *C* indicate children-specific sampled parameters. Suffixes *elderly* or *E* indicate elderly-specific parameters. **CDRscale and CDRscaleE**: case detection ratio scaling factor ($cdrscale$). **chr**: proportion of RR/MDR-TB treatment in CDC system. **DR_ts**: RR/MDR-TB relative transmission fitness cost. **DS_neta**: transmission scaling factor for all TB. **e**: relative probability of case detection of non-infectious TB. **emp_tx_p**: proportion empirically diagnosed and treated for RR/MDR-TB. **fadult, fchild and felderly**: proportion fast progressing to infectious active TB. **n and nelderly:** natural cure; **omega:** risk of converting from non-infectious to infectious TB. **padult and pchild**: proportion fast progressing to active TB.

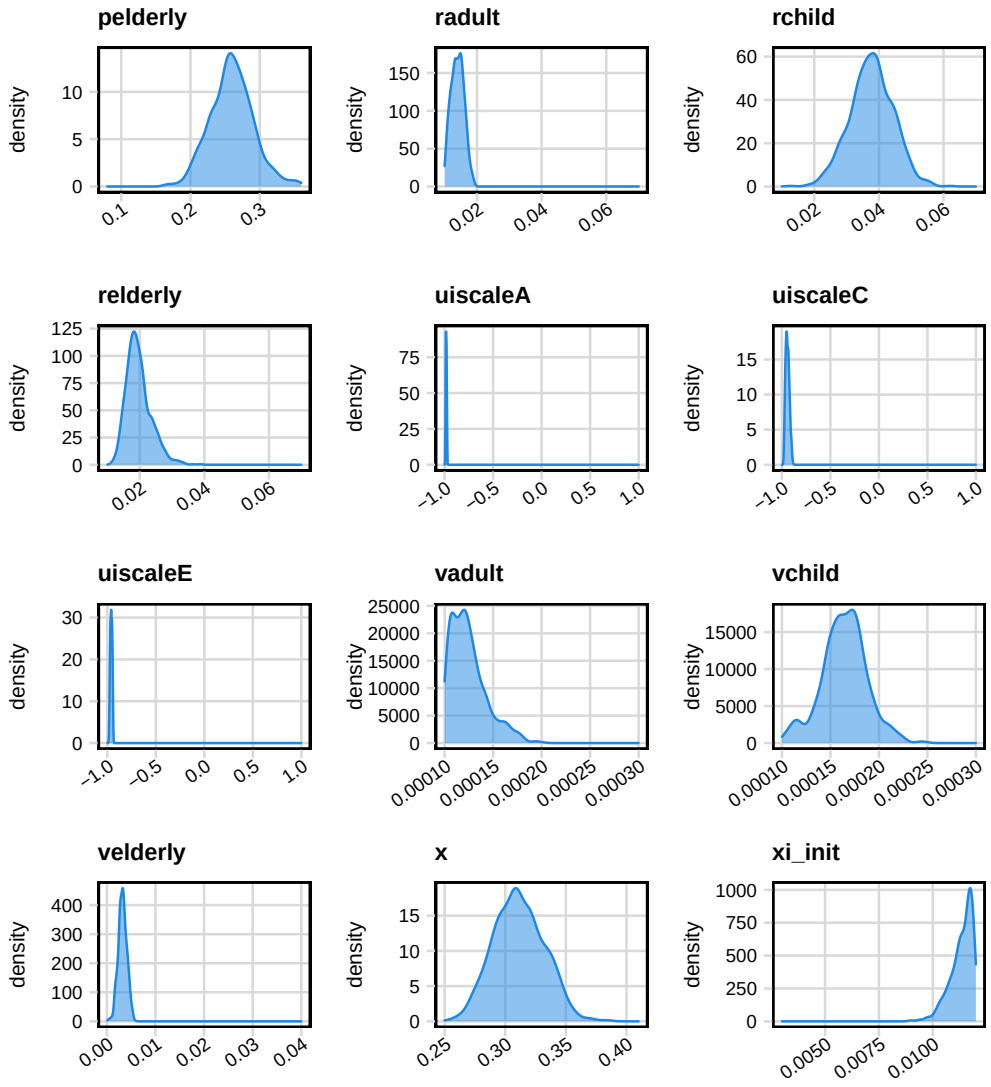

Figure S7: Posterior distributions of sampled parameters—China (contd.). Posterior distributions of sampled parameters—India (contd.). Subplots show probability density of parameter values (y-axis) plotted against the prior range (x-axis) of each parameter. Parameter names suffixed with *adult or A* indicate adult specific parameters. Suffixes *child* or *C* indicate children-specific sampled parameters. **pelderly**: proportion fast progressing to active TB. **radult, rchild relderly**: r, risk of relapse from resolved disease. **uiscaleA, uiscaleC and uiscaleE**: TB mortality scaling factors. **vadult, vchild and velderly**: v, risk of relapse from latent disease. **x**: x, relative protection against reinfection in latent and resolved compartments; **xi_init**: ξ, risk of acquiring drug resistance on-treatment for DS-TB.

In the "Policy" baseline scenario with scaled up programmatic TB management, all TB burden declined and then plateaued compared to 2018. All TB prevalence rate, incidence rate, and mortality in 2050 were predicted to be 180 [UI 136–268] per 100,000 (Figure S10A), 238 [UI 183–292] per 100,000 (Figure S10B) and 24 [UI 19–31] per 100,000 (Figure S10C) respectively. RR/MDR-TB incidence and mortality were predicted to be 7 [UI 5–15] per 100,000 (Figure S10D) and 2 [UI 1–3] per 100,000 (Figure S10E) by 2050 respectively. The proportion of RR/MDR-TB among never treated and previously treated notifications in 2050 was predicted to be 3% [UI 2–5] and 7% [UI 6–14] respectively (Figure S10F).

6.3 China

6.3.1 Calibration

The model predicted prevalence rates of all TB for all adults (age >14), ages 15-29, ages 30-44, ages 45-59 and ages >59 of 178 [UI 168–187] per 100,000, 82 [UI 72–92] per 100,000, 132 [UI 121–146] per 100,000, 179 [UI 174–195] per 100,000 and 531 [UI 510–564] per 100,000 in 2000 and 178 [UI 168–187] per 100,000, 82 [UI 72–92] per 100,000, 132 [UI 121–146] per 100,000, 179 [UI 174–195] per 100,000 and 531 [UI 510–564] per 100,000 in 2010 respectively (Figure S11A). All TB incidence rates were predicted at 83 [UI 77–93] per 100,000 and cninc2017 in 2000 and 2017 respectively (Figure S11B).

All TB notification rates in 2010 were predicted at 47 [UI 43–56] per 100,000, 2 [UI 1–2] per 100,000, 52 [UI 48–65] per 100,000 and 100 [UI 90–134] per 100,000 for across all ages, in children (age < 15), adults (age > 14 & and < 65) and elderly (age > 64), respectively (Figure S12A and C). All TB mortality rates in 2010 were predicted at 3 [UI 1–4] per 100,000, 0.1 [UI 0.1–0.2] per 100,000, 1.6 [UI 0.9–2.6] per 100,000 and 17 [UI 8–25] per 100,000 for across all ages, in children (age < 15), adults (age > 14 & and < 65) and elderly (age > 64), respectively (Figure S12B and D).

The model predicted RR/MDR-TB incidence to be 5 [UI 4–6] per 100,000 in 2017 (Figure S13A). RR/MDR-TB treatment by the Chinese Center for Disease Control and Prevention were predicted to be 6,544 [UI 5,943–7,131] in 2017 (Figure S13B). The proportion of RR/MDR-TB cases among all TB notifications was predicted to be 4.9% [UI 4.6–5.9] among never-treated cases in 2007, 22.6% [UI 21.7–26.0] among previously-treated cases in 2007, 7.6% [UI 6.7–8.6] among never-treated cases in 2013, and 26.5% [UI 23.0–28.0] among previously-treated cases in 2013 respectively (Figure S13C).

6.3.2 Baseline Scenario Projections

Model projections for overall and RR/MDR-TB epidemiology for China over 2018–2050 are presented in Figure S14.

At baseline, with no new vaccine and no change to programmatic management of TB after 2018 (the "Status Quo" baseline scenario), the model projected all TB prevalence rate at 76 [UI 74–79] per 100,000 in 2018 and 86 [UI 77–94] per 100,000 in 2050 (Figure S14A). All TB incidence rate was predicted to be 64 [UI 63–65] per 100,000 in 2018 and 62 [UI 59–66] per 100,000 in 2050 (Figure S14B). All TB mortality rate was predicted to be 2.1 [UI 1.4–2.8] per 100,000 in 2018 and 2.8 [UI 1.8–4.0] per 100,000 in 2050 (Figure S14C). RR/MDR-TB incidence rate was predicted to be 5 [UI 5–6] per 100,000 in 2018 and 15 [UI 12–17] per 100,000 in 2050 (Figure S14D). RR/MDR-TB mortality rate was predicted to be 0.2 [UI 0.2–0.4] per 100,000 in 2018 and 0.8 [UI 0.5–1.2] per 100,000 in 2050 (Figure S14E). The proportion of RR/MDR-TB cases among never treated TB notifications was predicted to be 10% [UI 9–11] in 2018 and 28% [UI 23–30] in

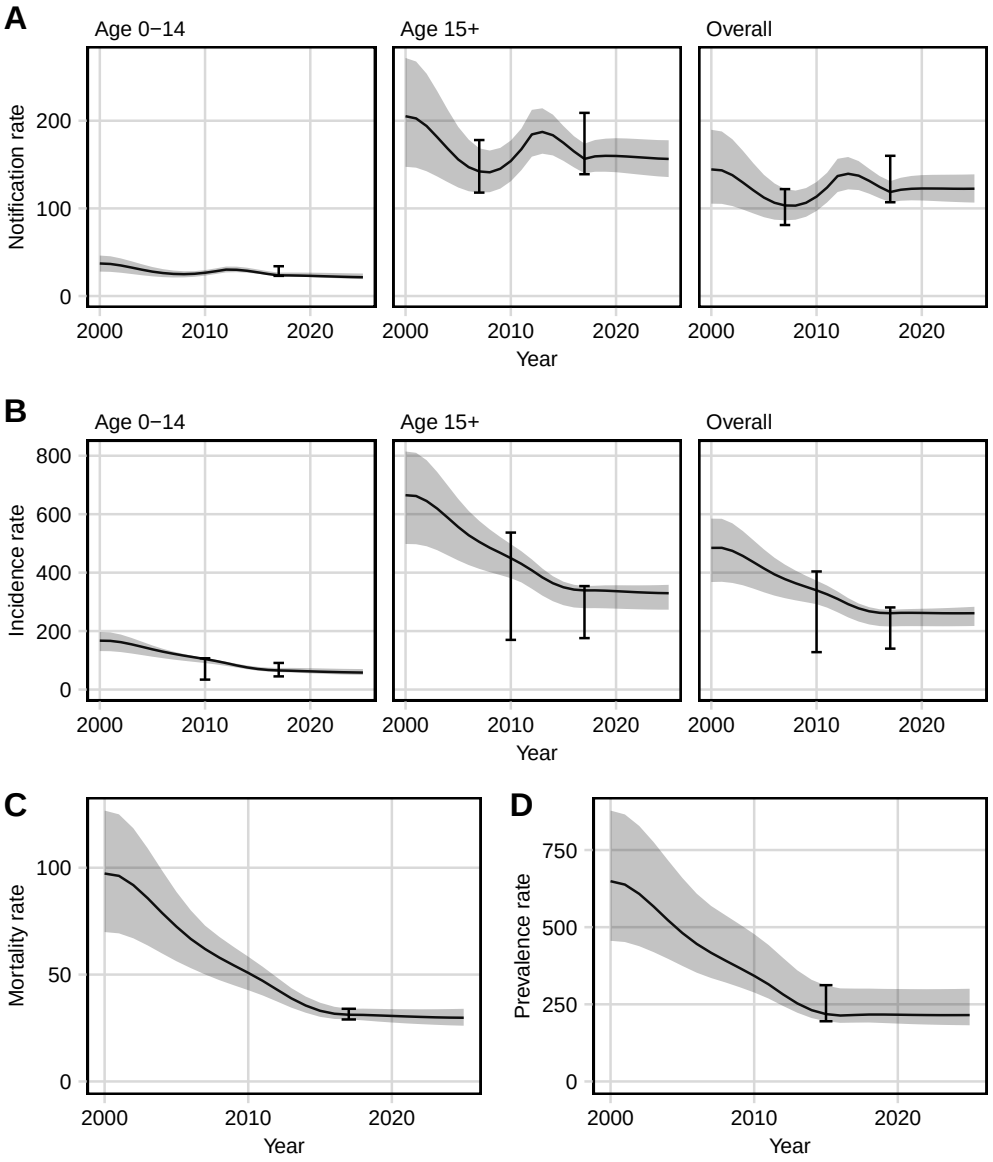

Figure S8: Calibration Results–All Tuberculosis in India. **A**: TB case notifications. **B**: Incidence rate for all TB. **C**: TB mortality. **D**: TB prevalence. All rates are presented per 100,000 population. Line represents median trajectory; ribbons represent minimum and maximum trajectories and error bars represent calibration targets.

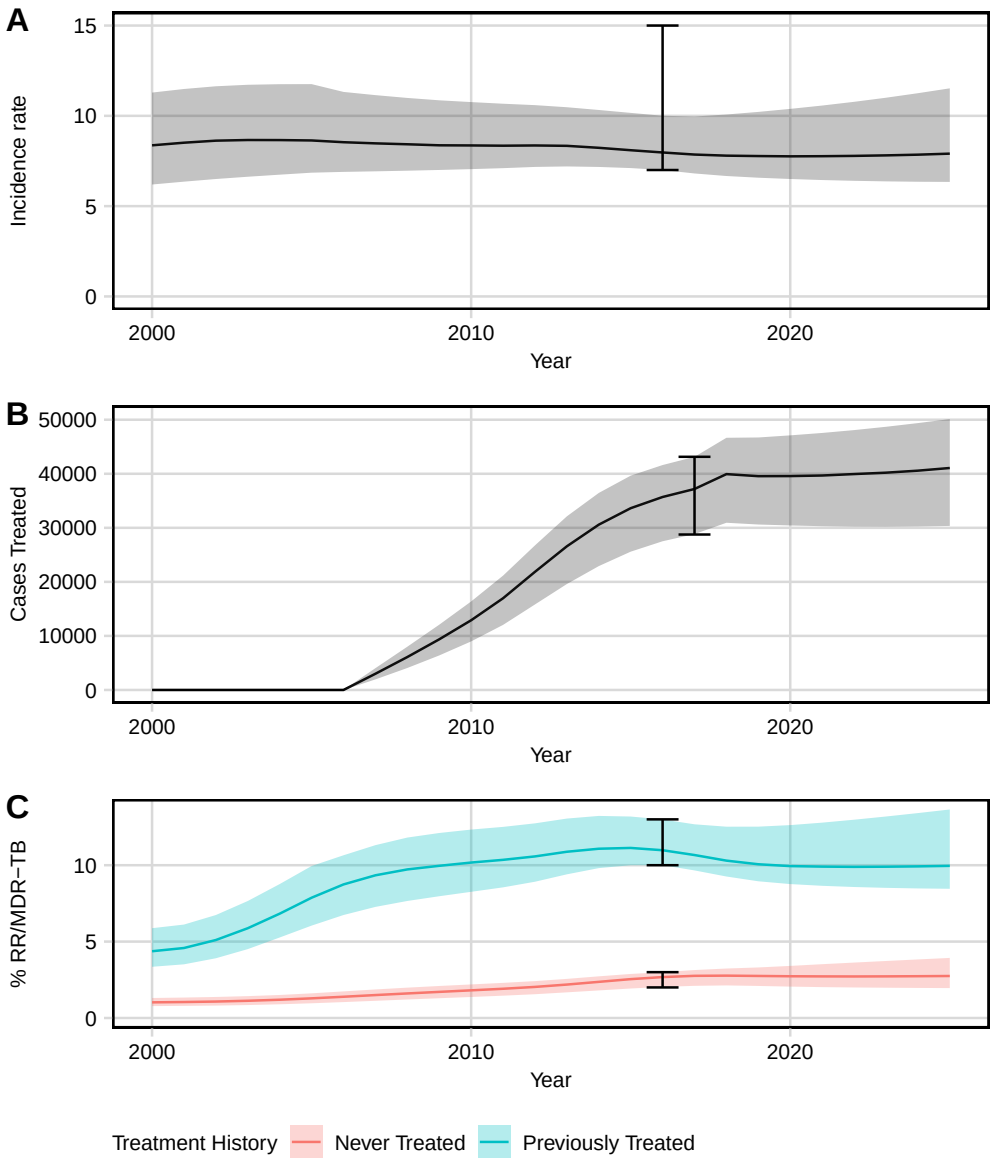

Figure S9: Calibration Results—RR/MDR-TB in India. **A**: RR/MDR-TB incidence rate. **B**: Number of laboratory confirmed treatments for RR/MDR-TB in the public sector. **C**: % of RR/MDR-TB among all TB case notifications, disaggregated by previous treatment. Line represents median trajectory; ribbons represent minimum and maximum trajectories and error bars represent calibration targets.

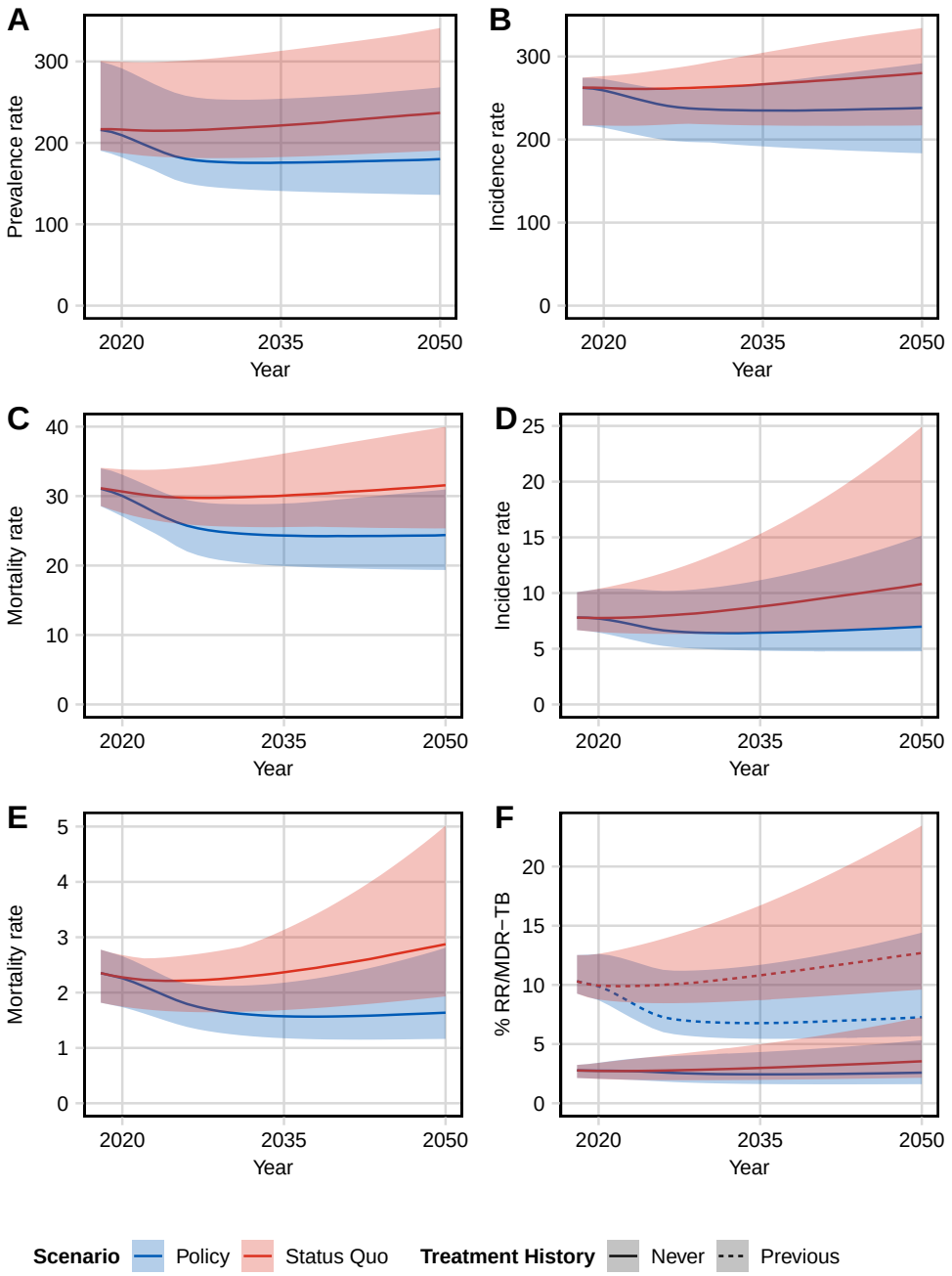

Figure S10: Baseline (no vaccine) projections–India. **A:** All TB Prevalence rate. **B**: All TB Incidence rate. **C**: All TB mortality rate. **D**: RR/MDR-TB incidence rate. **E**: RR/MDR-TB mortality rate. **F**: Proportion RR/MDR-TB cases among notifications, stratified by treatment history. All rates are expressed per 100,000 population.

2050; correspondingly, the proportion among previously treated TB notifications was predicted to be 27% [UI 26–28] in 2018 and 50% [UI 44–53] in 2050 (Figure S14F).

In the "Policy" baseline scenario with scaled up programmatic TB management, all TB burden remained relatively stable compared to 2018. All TB prevalence, incidence and mortality rates in 2050 were predicted to be 74 [UI 67–80] per 100,000, 56 [UI 54–60] per 100,000 and 2.5 [UI 1.6–3.5] per 100,000 respectively (Figure S14A-C). RR/MDR-TB incidence and mortality rates were predicted to be 9 [UI 7–9] per 100,000 and 0.5 [UI 0.3–0.7] per 100,000 by 2050 respectively (Figure S14D and E). The proportion of RR/MDR-TB among never treated and previously treated notifications in 2050 was predicted to be 17% [UI 14–19] and 32% [UI 25–33] respectively (Figure S14F).

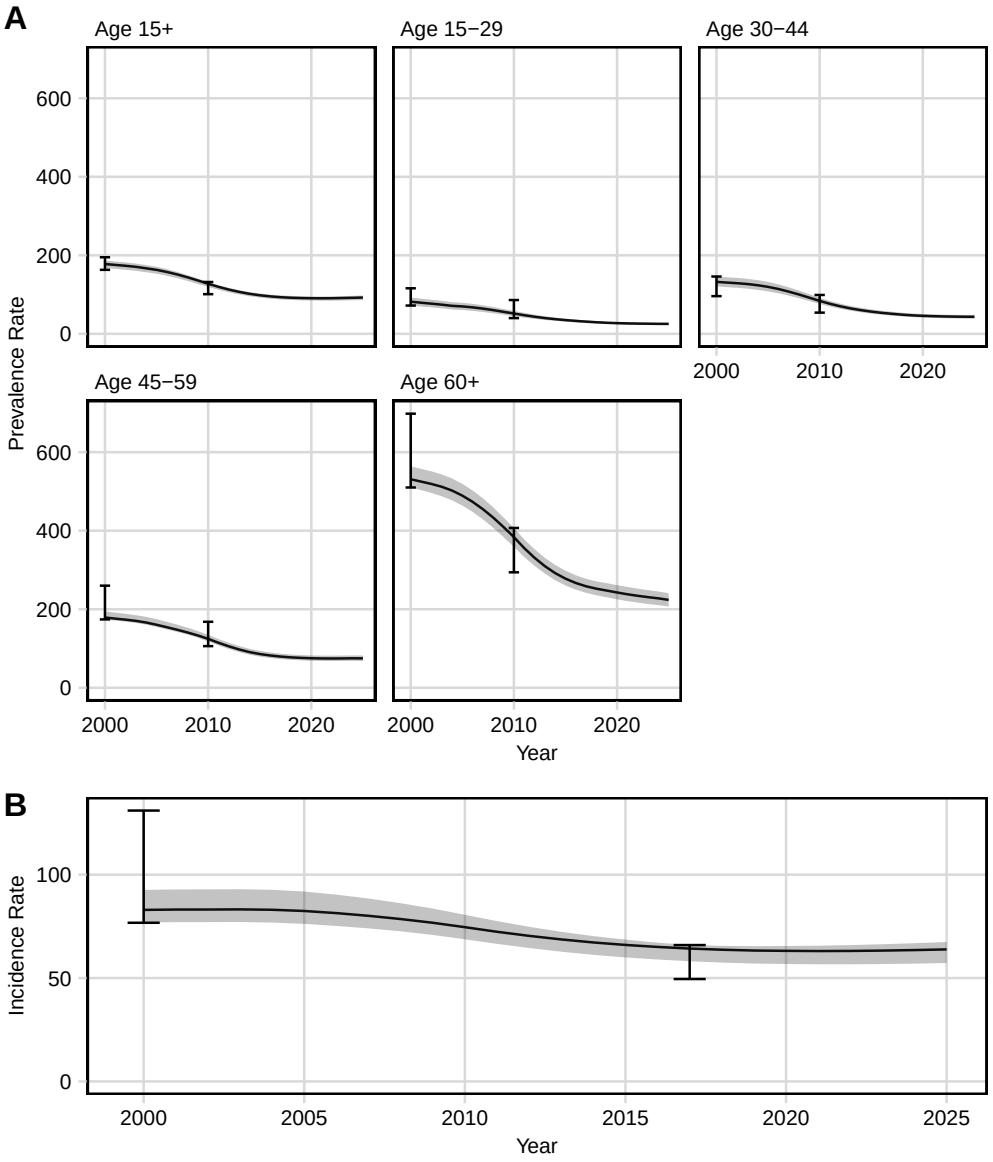

Figure S11: Calibration Results—All TB in China. **A**: All TB prevalence rate, by age. **B**: All TB incidence rate, all ages. All rates are presented per 100,000 population. Line represents median trajectory; ribbons represent minimum and maximum trajectories and error bars represent calibration targets.

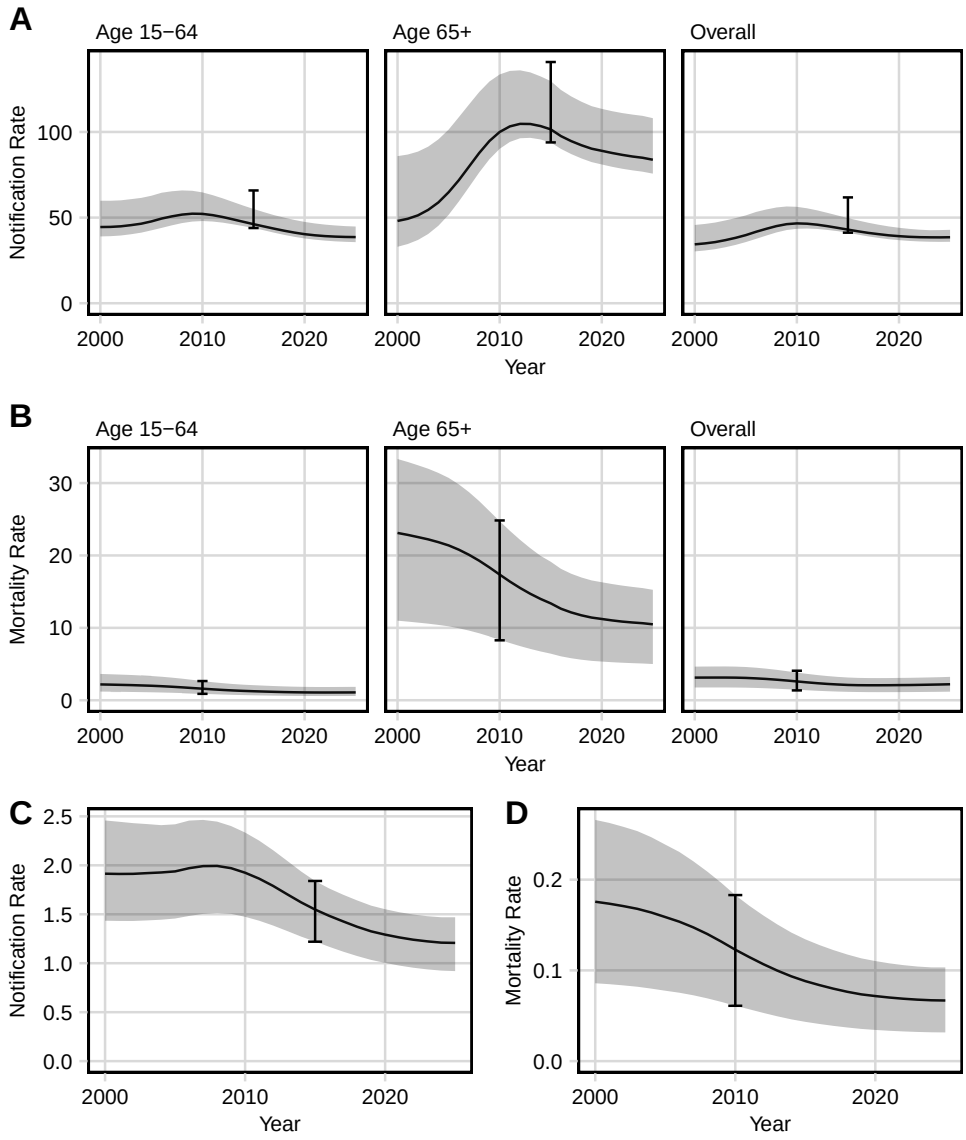

Figure S12: Calibration Results—Notifications and Mortality of All TB in China. **A**: All TB notification rate, by age. **B**: All TB mortality rate, by age. **C**: Notification rate for **Age**$\leq$ 14 **years**. **D**: Mortality rate for **Age**$\leq$ 14 **years**. All rates are presented per 100,000 population. Line represents median trajectory; ribbons represent minimum and maximum trajectories and error bars represent calibration targets.

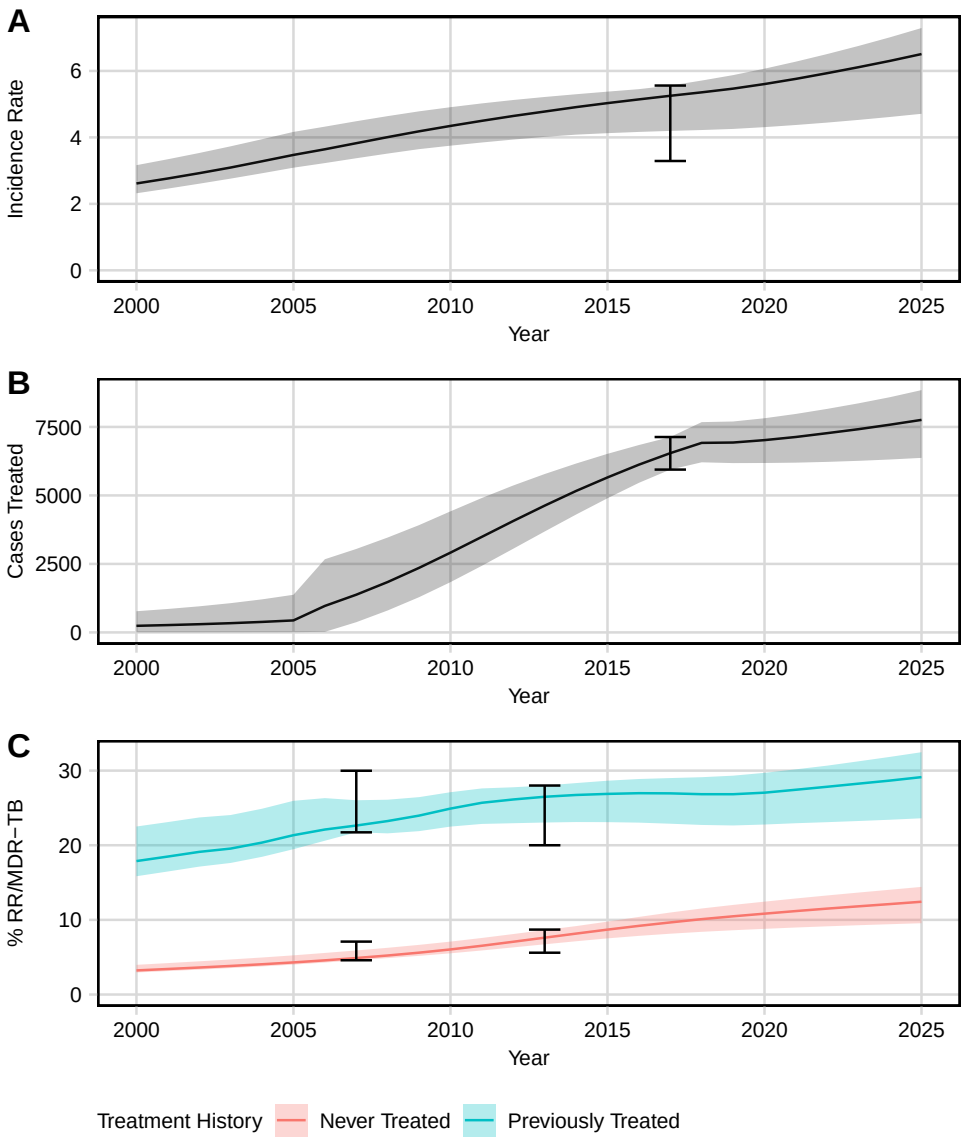

Figure S13: Calibration Results—RR/MDR-TB in China. **A**: RR/MDR-TB incidence rate. **B**: Number RR/MDR-TB treatments in the Chinese Center for Disease Control and Prevention system. **C**: % of RR/MDR-TB among all TB case notifications, disaggregated by previous treatment for tuberculosis. Line represents median trajectory; ribbons represent minimum and maximum trajectories and error bars represent calibration targets.

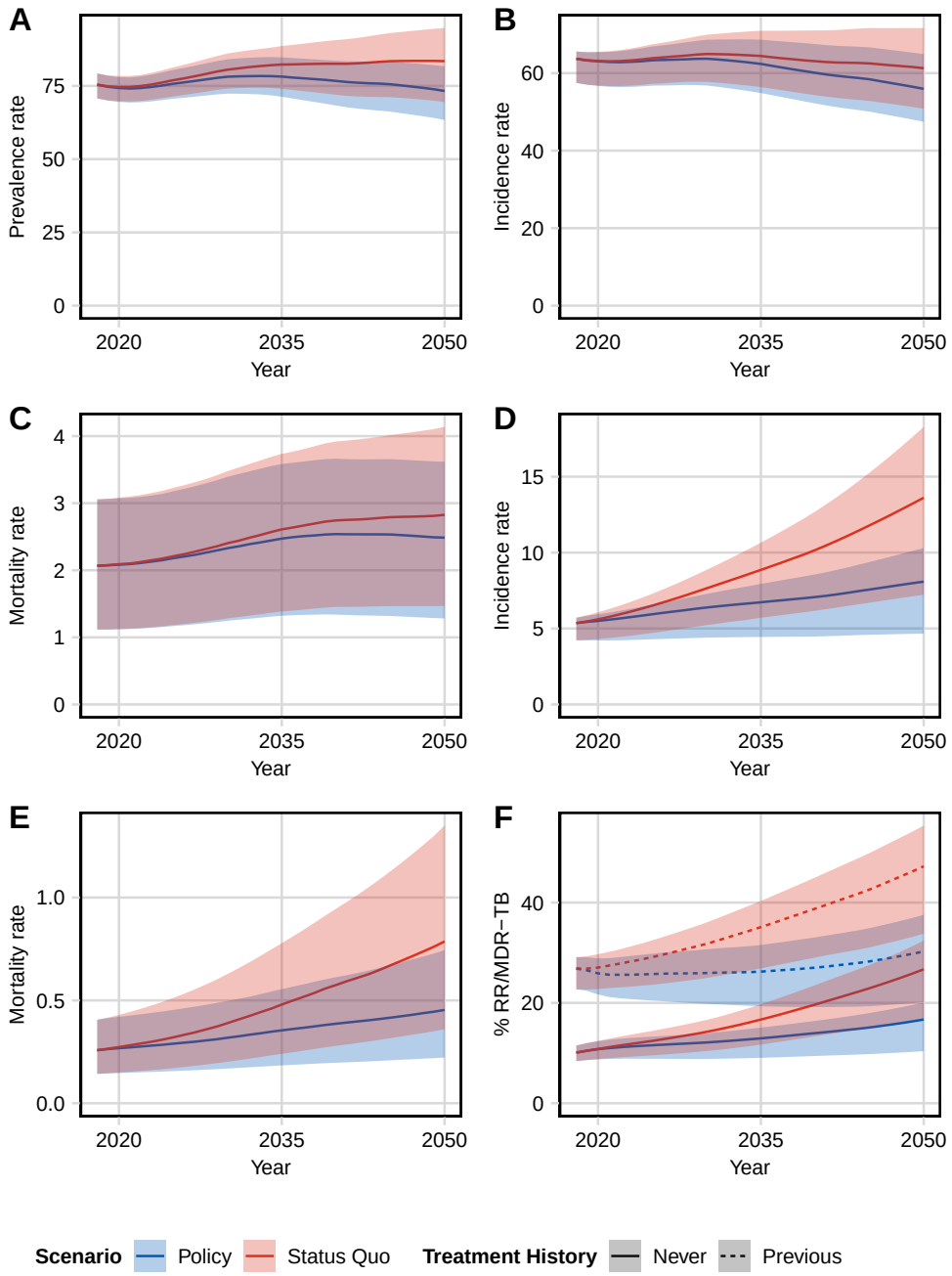

Figure S14: Baseline (no vaccine) projections–China. **A:** All TB Prevalence rate. **B**: All TB Incidence rate. **C**: All TB mortality rate. **D**: RR/MDR-TB incidence rate. **E**: RR/MDR-TB mortality rate. **F**: Proportion RR/MDR-TB cases among notifications, stratified by treatment history. All rates are expressed per 100,000 population.

7 Vaccine Impact

7.1 Vaccine Efficacy and Duration of Protection

Following their introduction in 2027, across both baseline scenarios and over all endpoints—incidence and mortality rate reductions, cases and deaths averted and averted RR/MDR-TB treatment—we found increasing duration of protection and vaccine efficacy led to greater vaccine impact by 2050. As expected, by 2030 both 5-year and 10-year duration of protection vaccines had identical impact as no waning of vaccination had occurred in any cohort which received the vaccine.

7.2 Host-Infection Status Required for Vaccine Efficacy

We found that pre– and post– infection (P&PI) vaccines had a greater impact than pre-infection (PRI) vaccines or post-infection (PSI) vaccines (sections 7.4 and 7.5). PRI vaccines had a comparable or lower impact than PSI vaccines on all TB in India and China and RR/MDR-TB in India. In China, the PRI effect on RR/MDR-TB was greater than PSI effect. Moreover, the impact of PSI vaccines on RR/MDR-TB was substantially higher in India than China (Table S16), whereas the impact of P&PI vaccines was comparable. In contrast, the impact of both P&PI and PSI vaccines on all TB was only modestly greater in India than China.

Two key differences between the TB epidemics in China and India contributed to these differences. First, the prevalence of latent tuberculosis infection (LTBI) (Fig S15) is substantially higher in India (~40–50%) than China (~10–15%). Second, the composition of incident tuberculosis in terms of *pathway to arrival at active disease*—for both overall and RR/MDR—differed substantially between China and India. We disaggregated incident TB into the following streams:

1. Active disease due to fast progression following infection (NP), which is further disaggregated into:
    a) Active disease due to fast progression following infection of *susceptible* (NP-S)
    b) Active disease due to fast progression following **re**-infection of *latent* or *recovered* (NP-LR)
2. Reactivation or relapse to active disease from *latent* or *recovered* populations (RR).

RR/MDR-TB RR/MDR-TB incidence in India driven by approximately equal proportions of NP-S, NP-LR and RR streams (Table S17 and Figure S16). In China, RR/MDR-TB incidence was driven by the NP-S stream, which was approximately twice the proportion of RR, with a very small contribution from NP-LR.

All Tuberculosis In India, the NP stream (the sum of NP-LR and NP-S) was the dominant component of all TB incidence, whereas in China the RR stream was the dominant component (Table S17 and Figure S16). Furthermore, following from the higher prevalence of LTBI in India, the contribution of the NP-LR stream to incidence was substantially higher (median 19.6–21.8%) than in China (median 1.5–1.9%).

Differential Vaccine Efficacy Post-infection vaccine efficacy was mediated by two separate mechanisms (1) reduced fast progression to active disease, following re-infection by *M. tuberculosis*

Table S16: Vaccine impact: Tuberculosis incidence rate reduction (uncertainty interval) in 2050 compared to no-vaccine "Status Quo" baseline, by 50% efficacy, 10-year pre- and post-infection (P&PI), pre-infection (PRI) and post-infection (PSI) efficacy vaccination in India and China.

		P&PI	PRI	PSI
India	RR/MDR-TB	72% (65–77)	46% (31–54)	47% (37–58)
	All TB	67% (59–71)	40% (27–47)	44% (39–49)
China	RR/MDR-TB	73% (66–76)	59% (49–64)	29% (27–31)
	All TB	56% (53–59)	30% (24–35)	37% (35–38)

Table S17: Incidence of TB disaggregated by origin. Values presented are *median [uncertainty interval]* proportions of the incidence streams, as a percentage, *over* 2027–2050.

Country	Resistance Status	Incidence Stream		
		NP-LR	NP-S	RR
RR/MDR-TB	India	28.1% [27.2−30.9]	37.7% [33.8−39.9]	34.3% [33.0−35.3]
	China	3.3% [2.8−4.0]	64.9% [63.9−67.8]	31.9% [28.2−33.3]
All TB	India	20.2% [19.6−21.8]	39.2% [34.4−41.6]	40.9% [39.2−44.1]
	China	1.6% [1.5−1.9]	37.1% [36.0−38.4]	61.3% [59.7−62.4]

in individuals who are in the latent or recovered states and; (2) reduced rate of reactivation and relapse from the latent and recovered states, respectively. In contrast, pre-infection vaccine efficacy was mediated by reduced fast progression following infection by *M. tuberculosis* of susceptible individuals.

In India, the proportion of RR/MDR-TB incidence "avertible" by PSI vaccine efficacy (the sum of RR + NP-LR) was considerably larger than China (Table S17). PSI vaccines reduce incidence in the NP-LR and RR streams—and therefore force of infection—more in India than China, leading to a greater estimate of vaccine impact (Table S16).

In China, a greater proportion of RR/MDR-TB incidence is "avertible" by PRI efficacy (the NP-S substream) than PSI efficacy (NP-LR + RR) (Table S17). Consequently, PRI vaccines lead to a greater reduction in RR/MDR-TB incidence than PSI vaccines. The opposite is true for all TB, where incidence avertible by PSI vaccination (NP-LR + RR) is greater than avertible by PRI vaccination (NP-S) (Table S17).

7.3 Scenario Analyses: Variable Mass Vaccine Campaign Coverage

Percent reduction in incidence rate in 2050 by vaccination for both RR/MDR-TB and all TB in India and China are presented in Figures S17 and S18, respectively. As expected across all vaccine types and efficacies, reduced vaccine campaign coverage leads to lower incidence rate reduction.

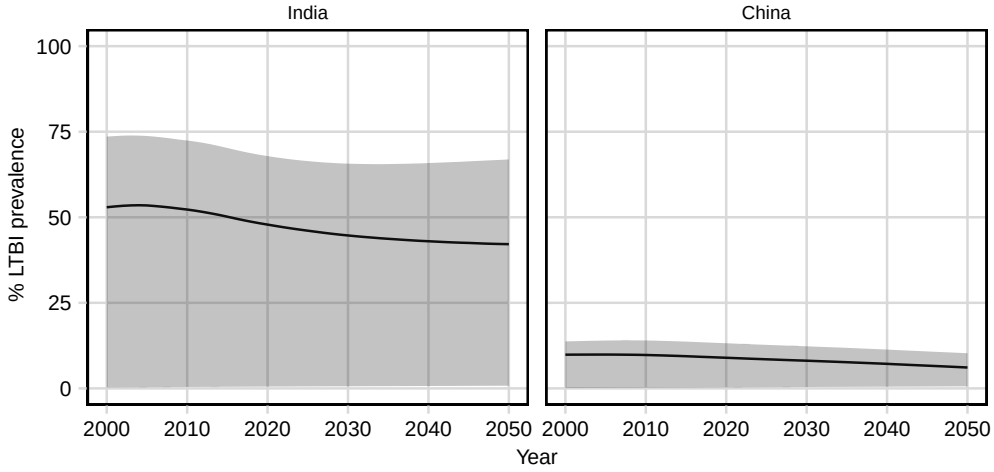

Figure S15: Latent tuberculosis infection in the baseline scenario—India & China, 2025–2050

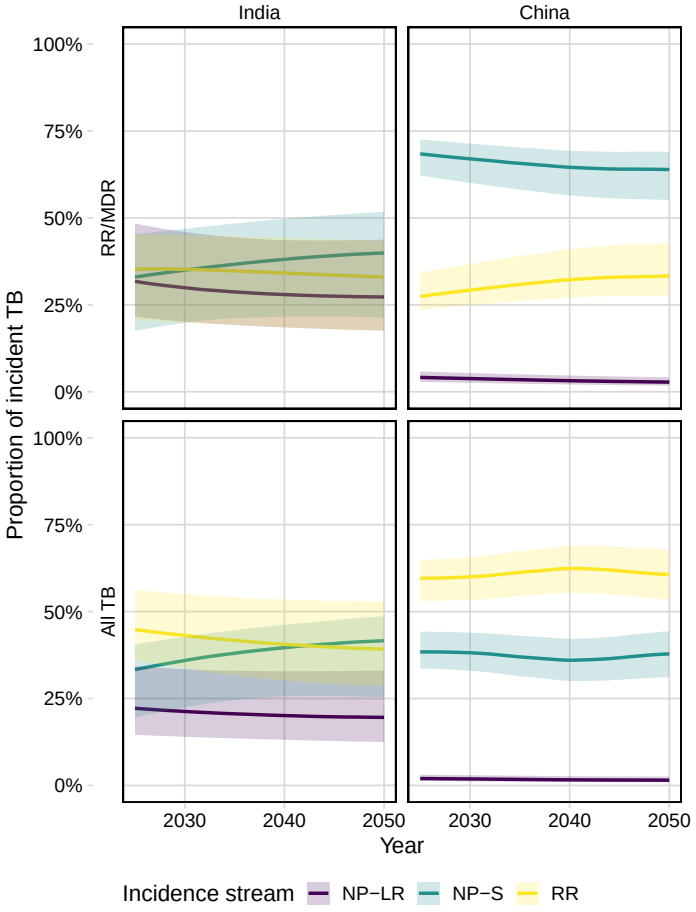

Figure S16: Incident tuberculosis, disaggregated by incidence source in the baseline scenario—India & China, 2025–2050. Lines represent median proportion. Ribbons represent uncertainty.

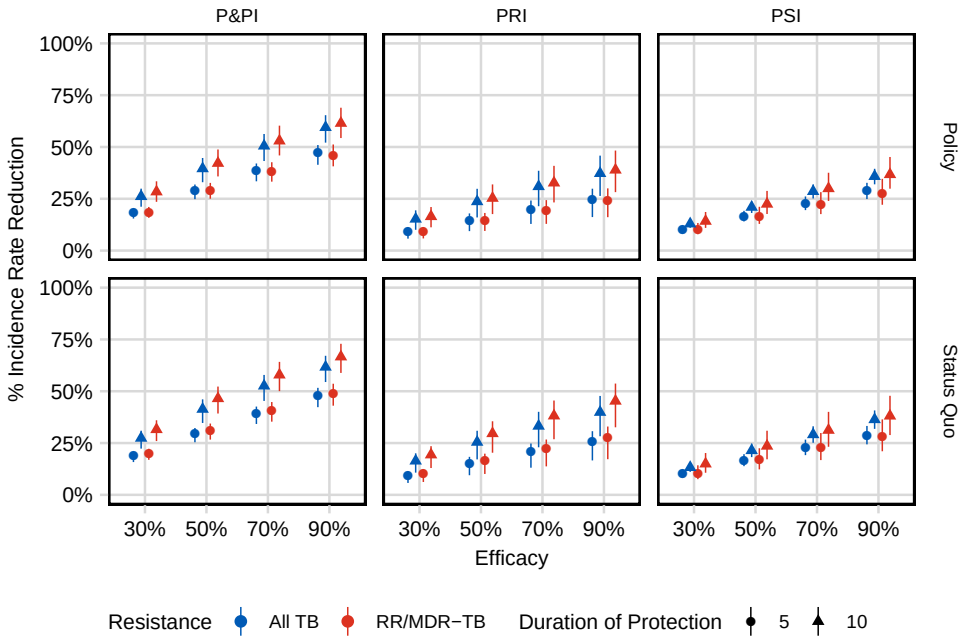

Figure S17: Percent Incidence Rate Reduction in India in 2050 by vaccination, where mass vaccination of ages 10 and above at 30% coverage and routine vaccination of 9-year olds at 80% coverage. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets represent drug resistance status. Vaccine provides 10-years of protection.

7.4 Scenario Analyses: Tuberculosis Incidence and Mortality Rate Reduction

Percent reduction in incidence rate and mortality rate in 2030 and 2050 by vaccination for both RR/MDR-TB and all TB in India are presented in Figures S19 and S20, respectively. Percent reduction in incidence rate and mortality rate in 2030 and 2050 by vaccination for both RR/MDR-TB and all TB in China are presented in Figures S21 and S22, respectively.

7.5 Scenario Analyses: Tuberculosis Cases and Deaths Averted

The number of averted RR/MDR-TB cases and deaths averted by vaccination by 2030 and 2050 in India are presented in Figures S23 and S24. The number of averted all TB cases and deaths averted by vaccination by 2030 and 2050 in India are presented in Figures S25 and S26.

The number of averted RR/MDR-TB cases and deaths averted by vaccination by 2030 and 2050 in China are presented in Figures S27 and S28. The number of averted all TB cases and deaths averted by vaccination by 2030 and 2050 in China are presented in Figures S29 and S30.

7.6 Scenario Analyses: Averted Anti-tuberculosis Therapy

The number of averted RR/MDR-TB and DS-TB treatment regimens averted by 2030 and 2050 by vaccination in India is presented in Figures S31 and S32. The number of averted RR/MDR-TB and DS-TB treatment regimens averted by 2030 and 2050 by vaccination in China is presented in Figures S33 and S34.

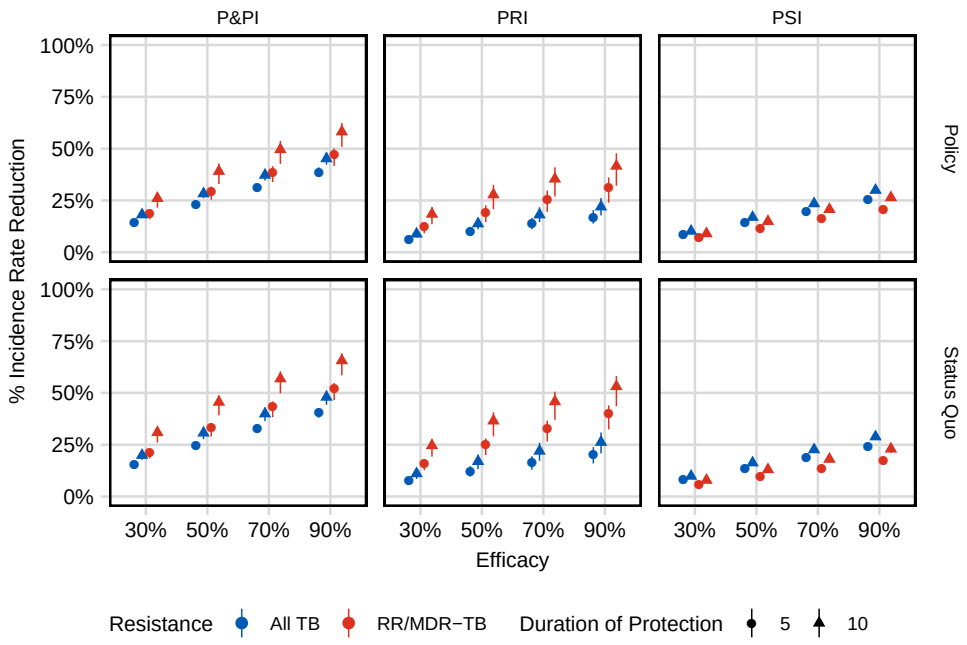

Figure S18: Percent Incidence Rate Reduction in China in 2050 by vaccination, where mass vaccination of ages 10 and above at 30% coverage and routine vaccination of 9-year olds at 80% coverage. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets represent drug resistance status. Vaccine provides 10-years of protection.

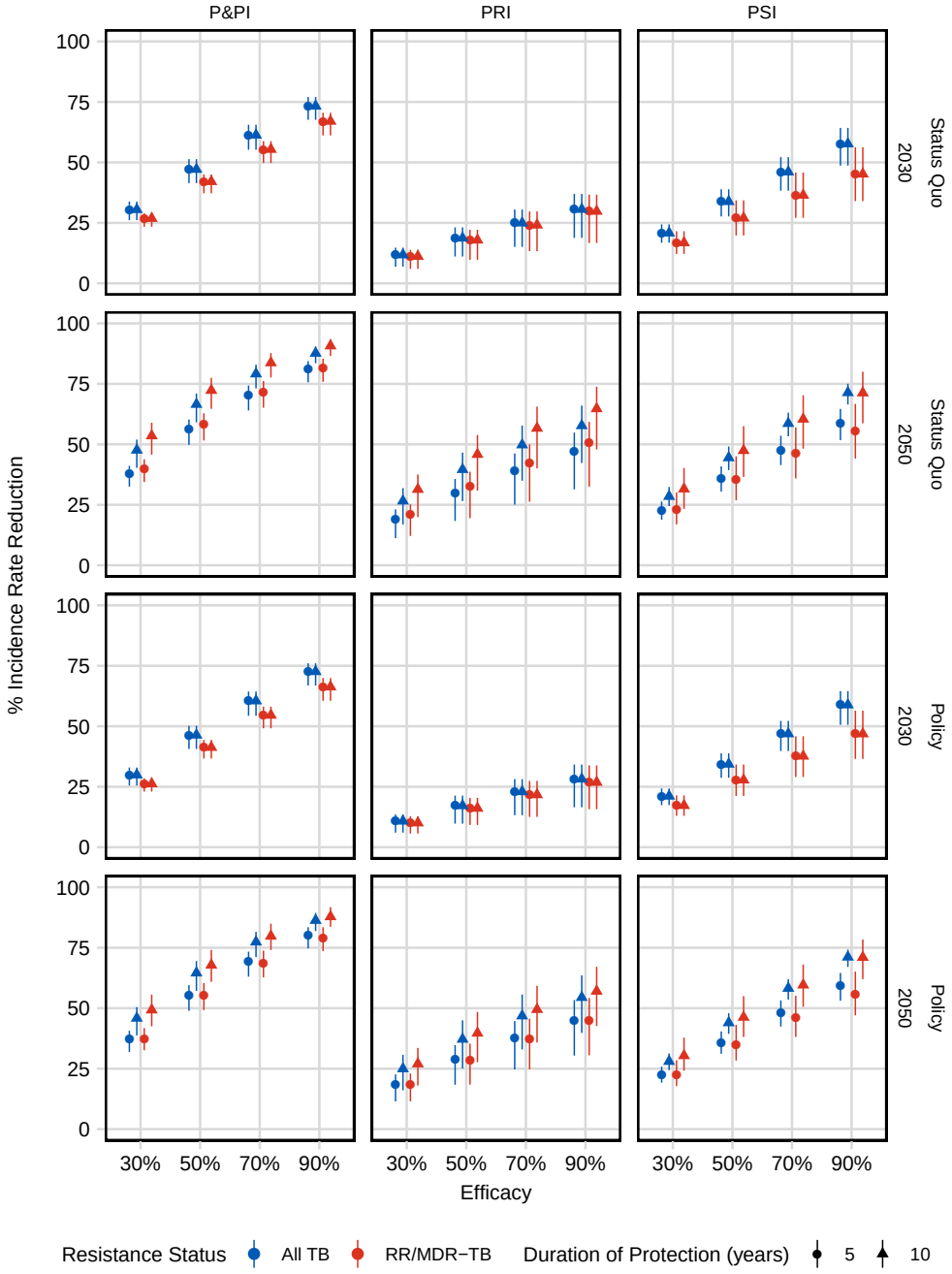

Figure S19: Percent Incidence Rate Reduction in India by vaccination. Colors represent drug-resistance status. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

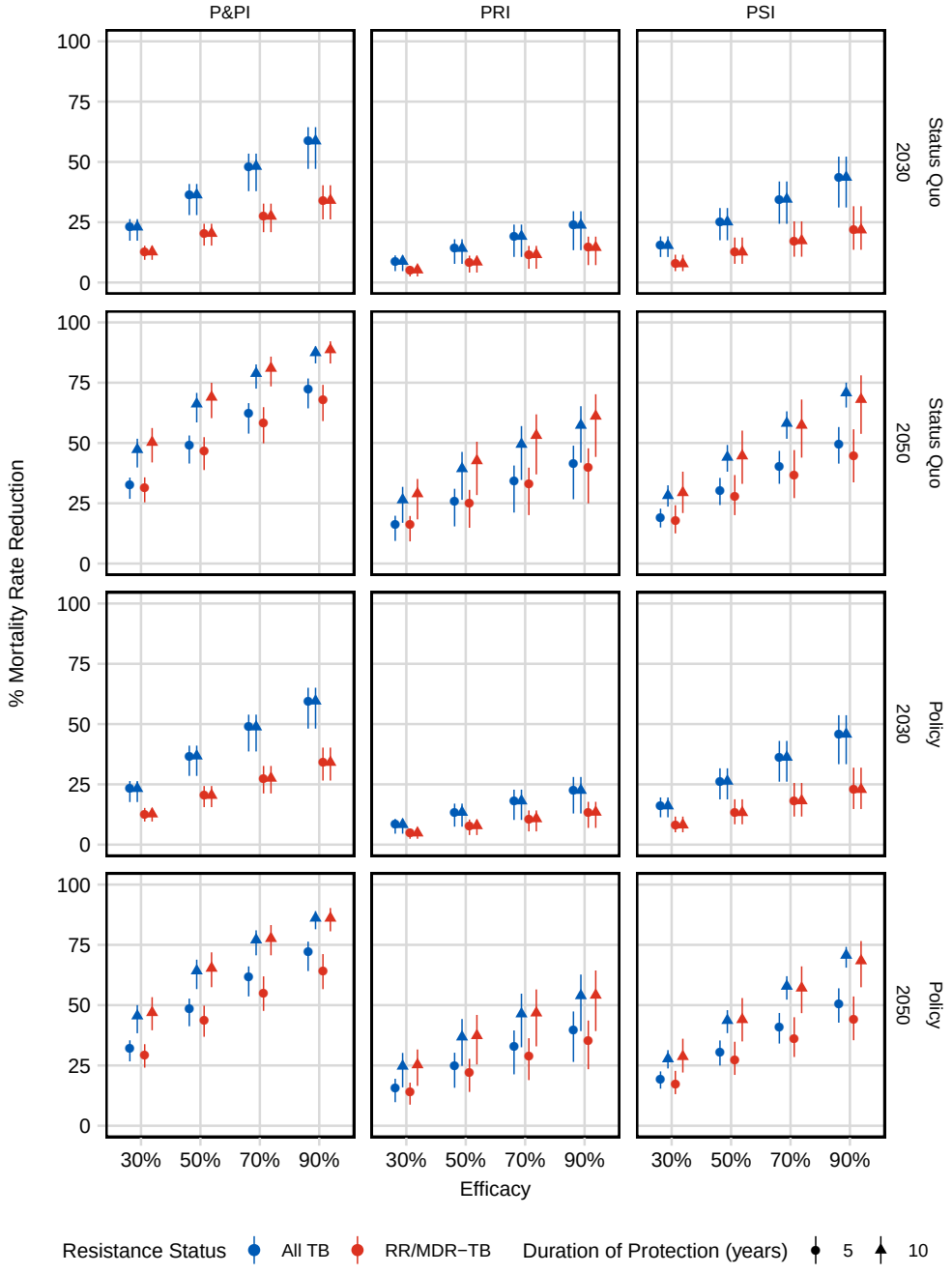

Figure S20: Percent Mortality Rate Reduction in India by vaccination. Colors represent drug-resistance status. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

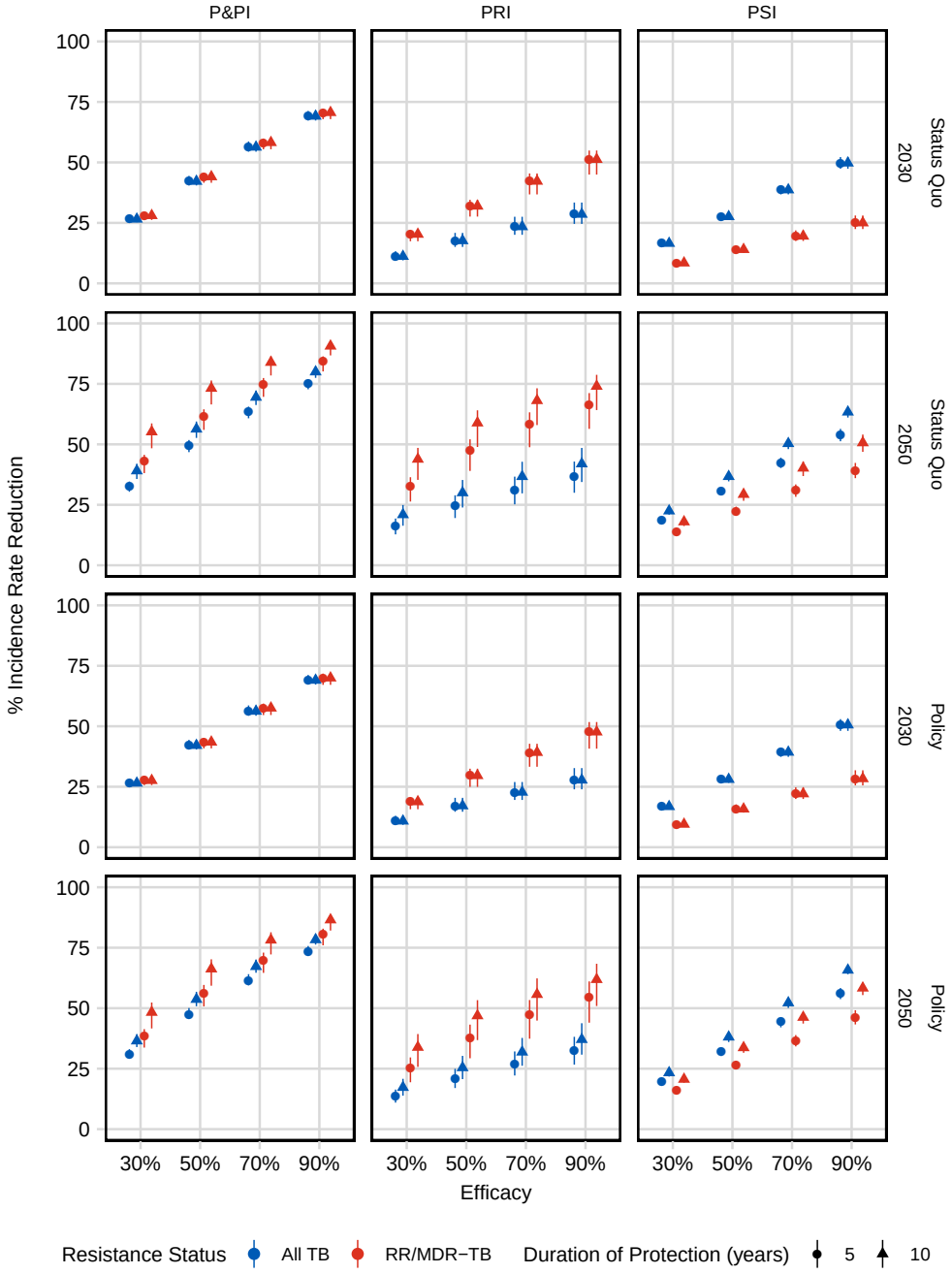

Figure S21: Percent Incidence Rate Reduction in China by vaccination. Colors represent drug-resistance status. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

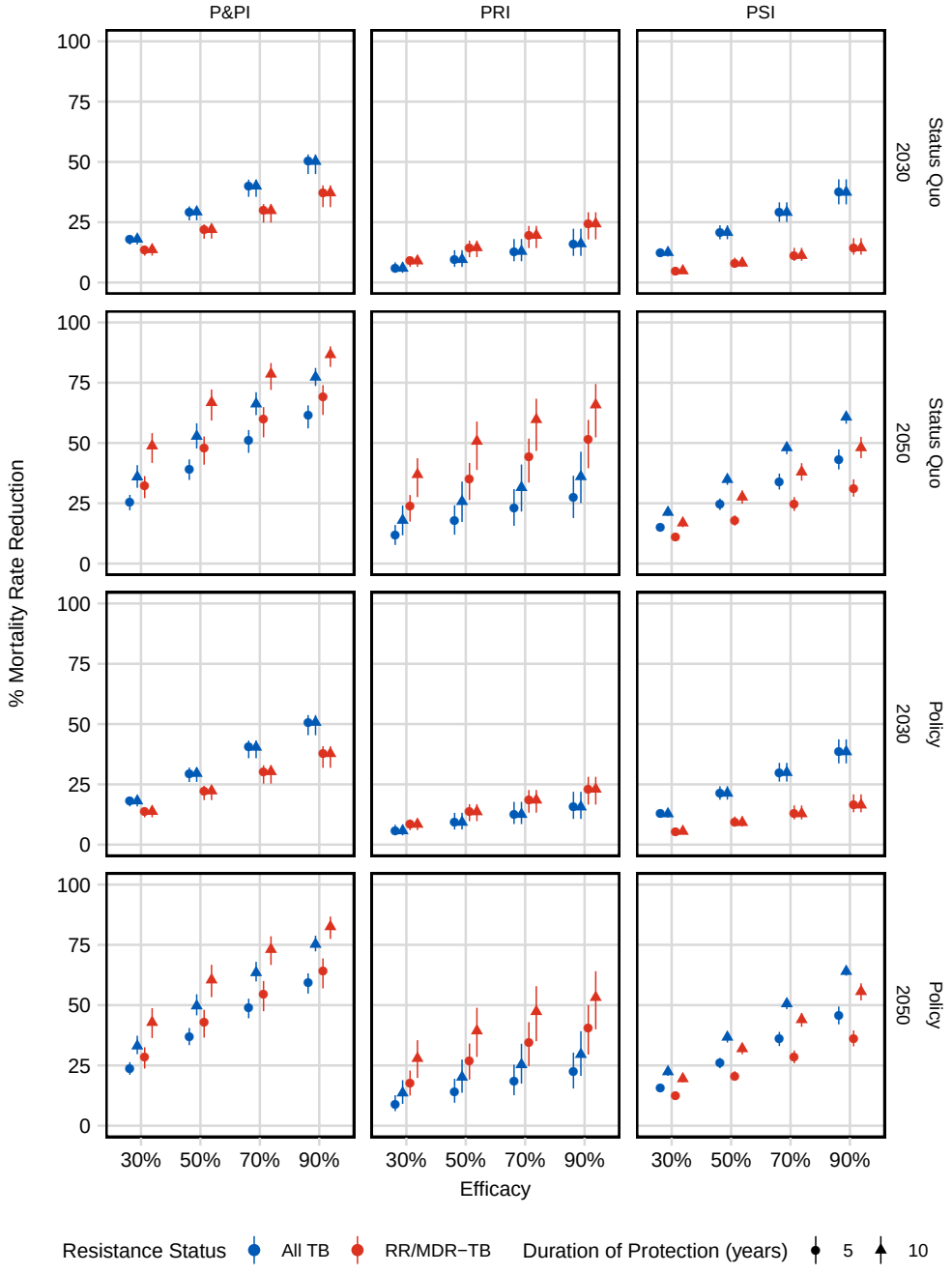

Figure S22: Percent Mortality Rate Reduction in China by vaccination. Colors represent drug-resistance status. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

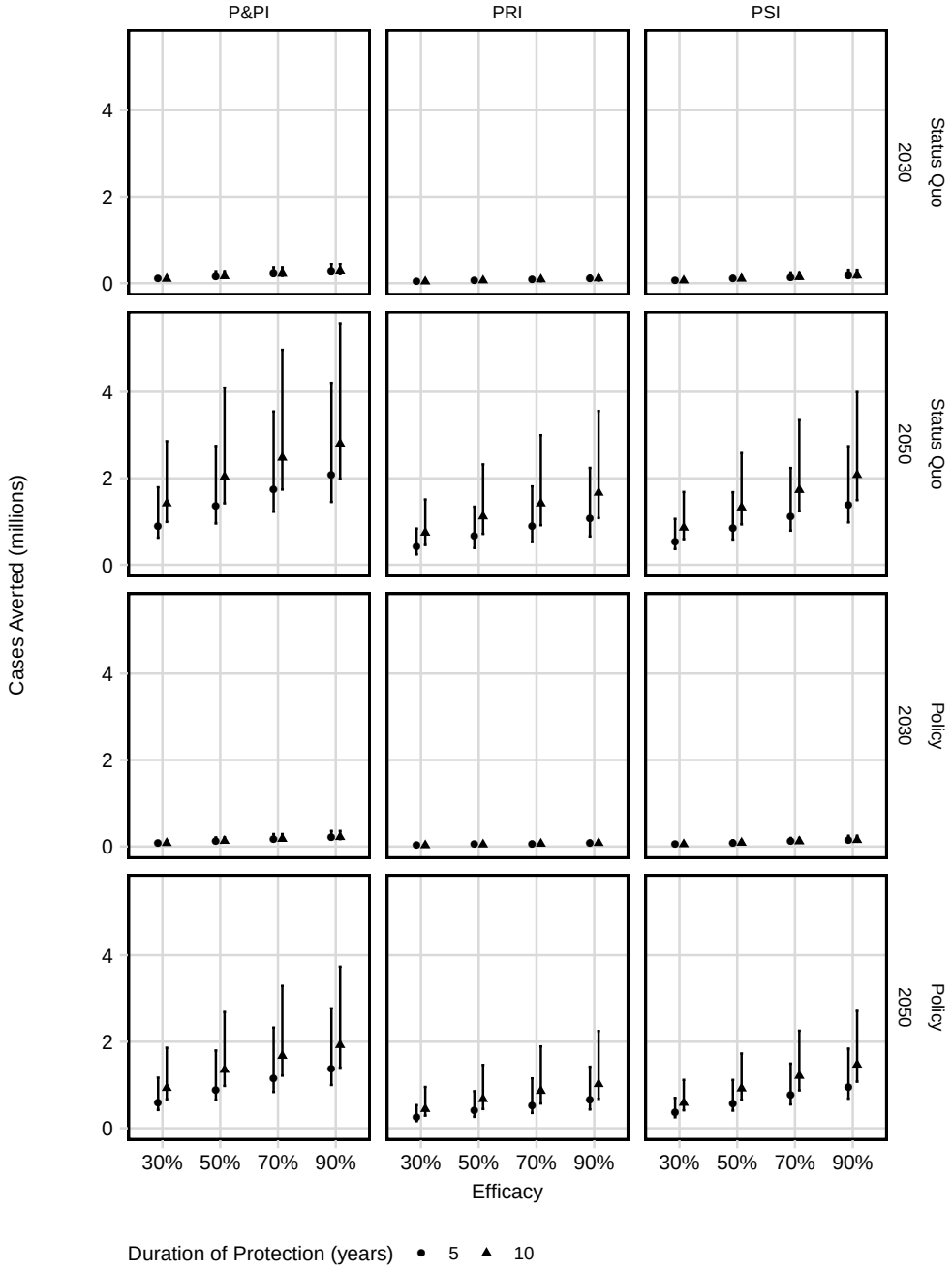

Figure S23: RR/MDR-TB Cases Averted in India by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

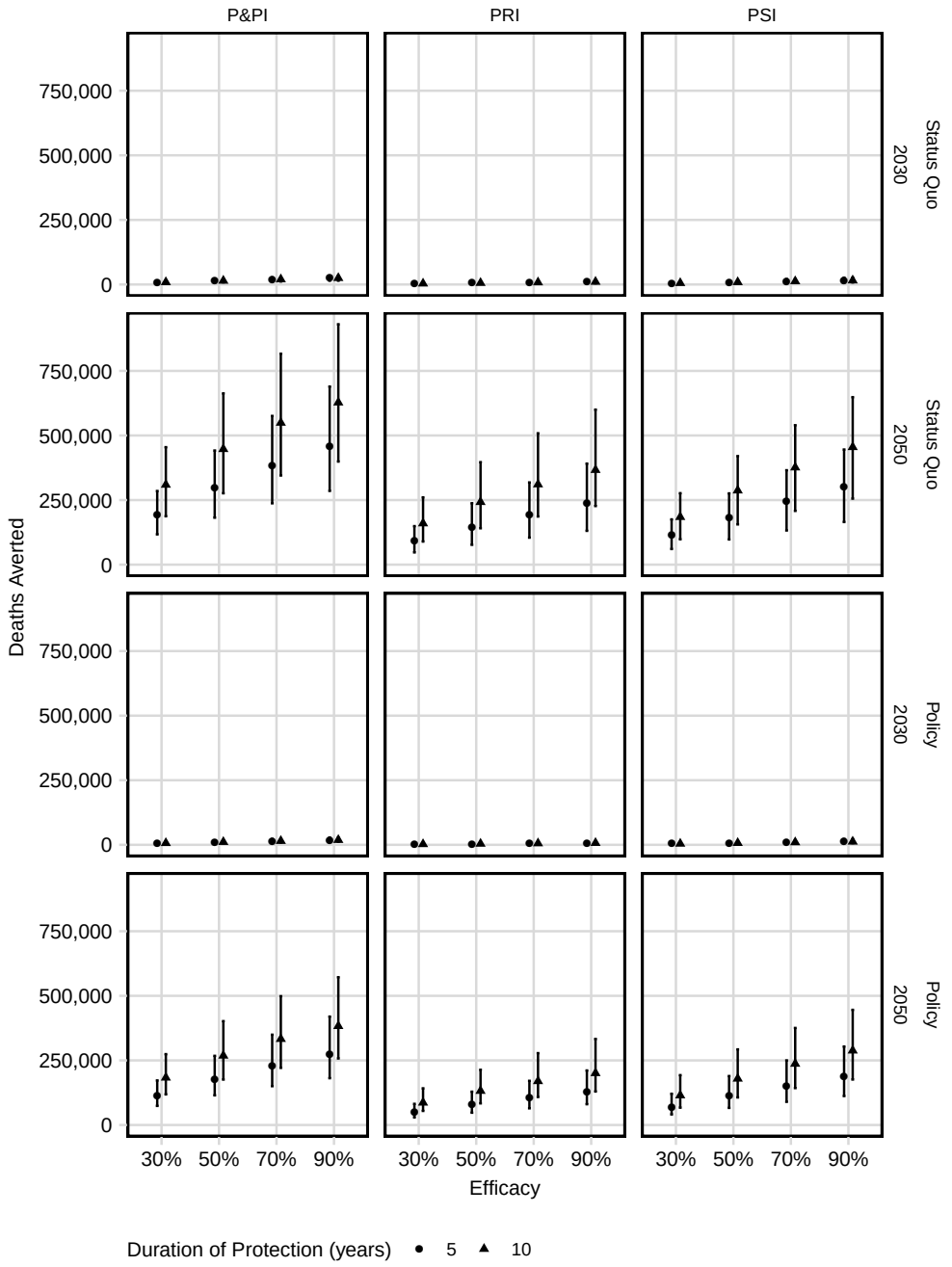

Figure S24: RR/MDR-TB Deaths Averted in India by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

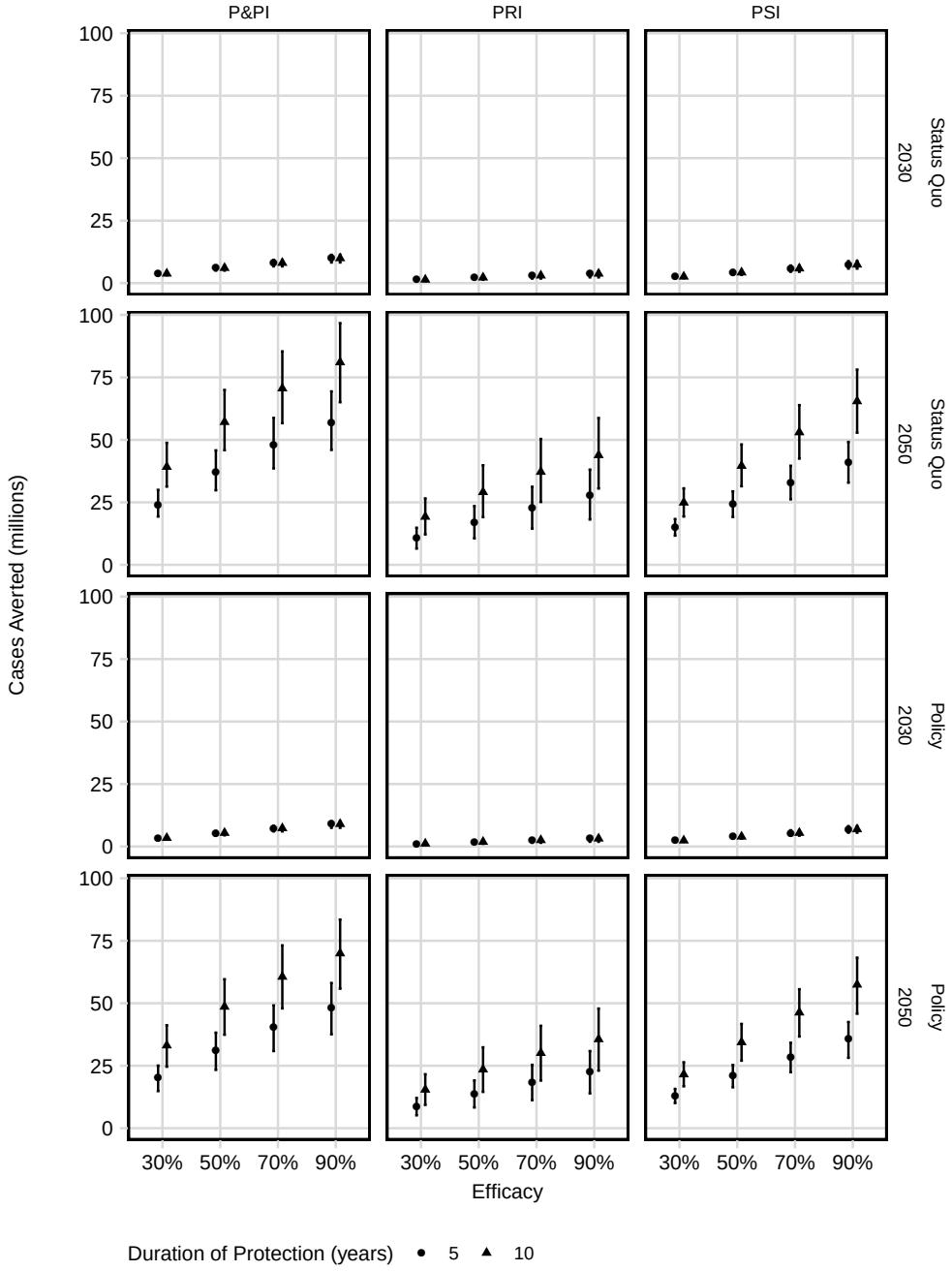

Figure S25: All TB Cases Averted in India by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

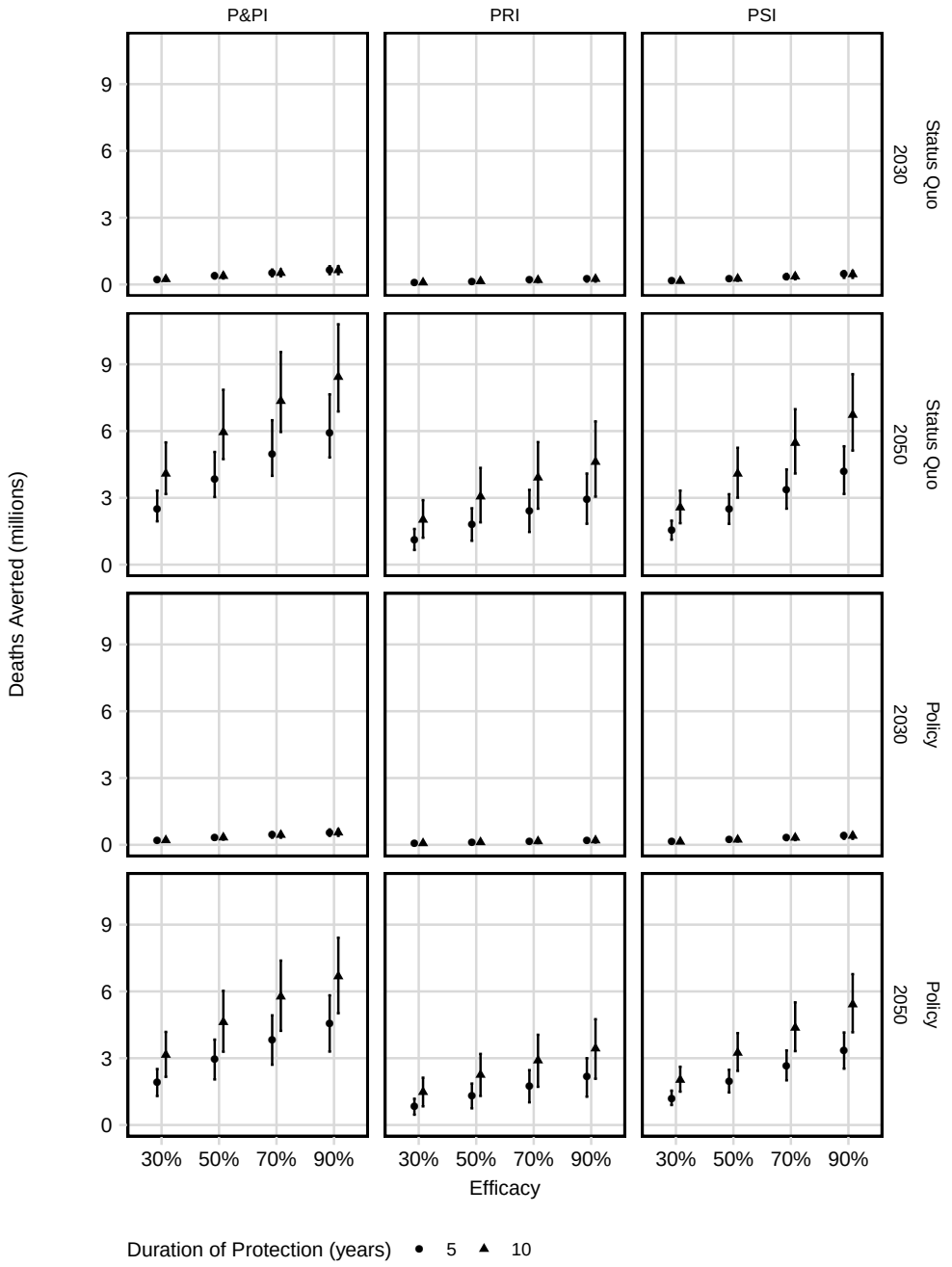

Figure S26: All TB Deaths Averted in India by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

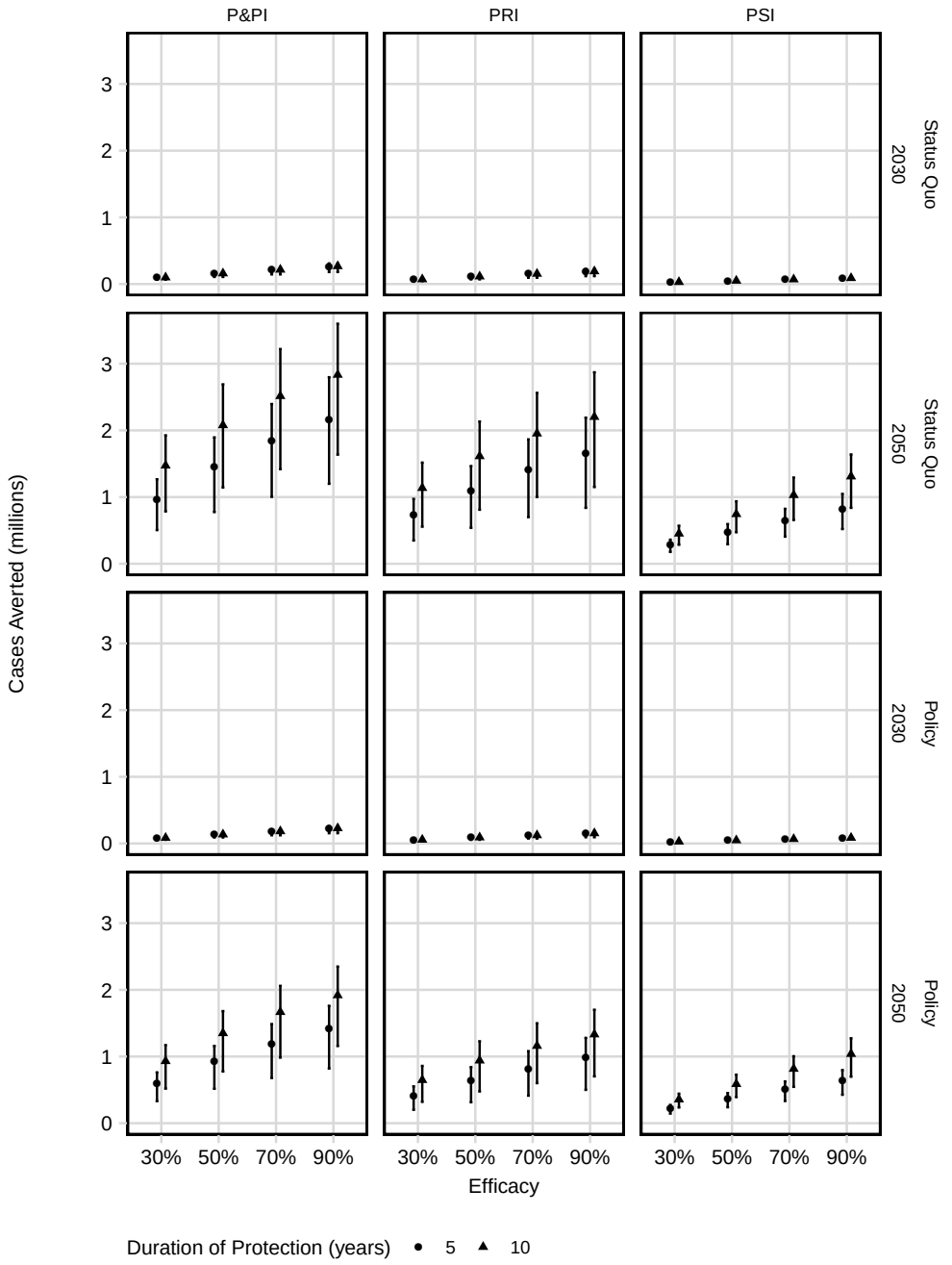

Figure S27: RR/MDR-TB Cases Averted in China by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

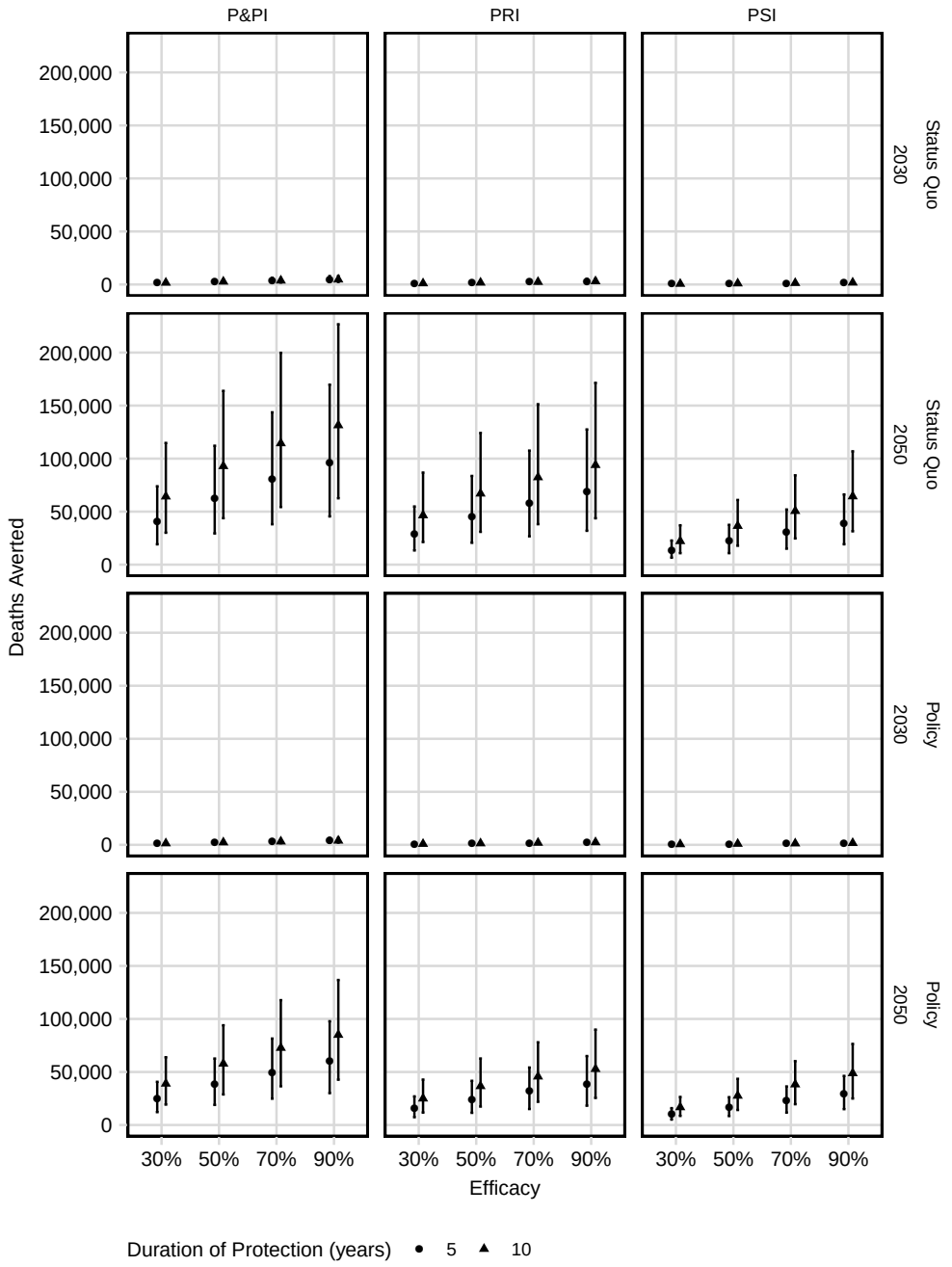

Figure S28: RR/MDR-TB Deaths Averted in China by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

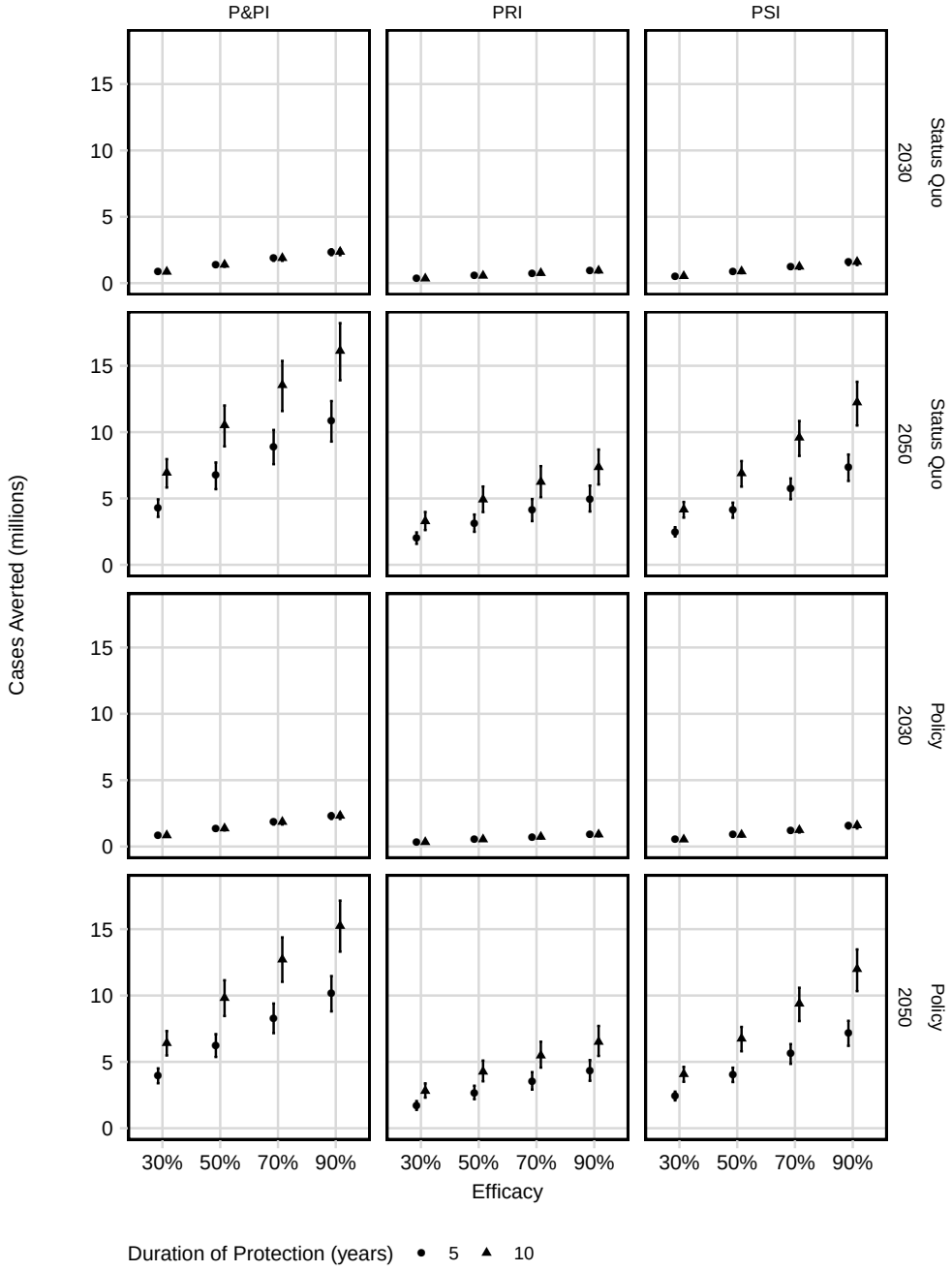

Figure S29: All TB Cases Averted in China by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

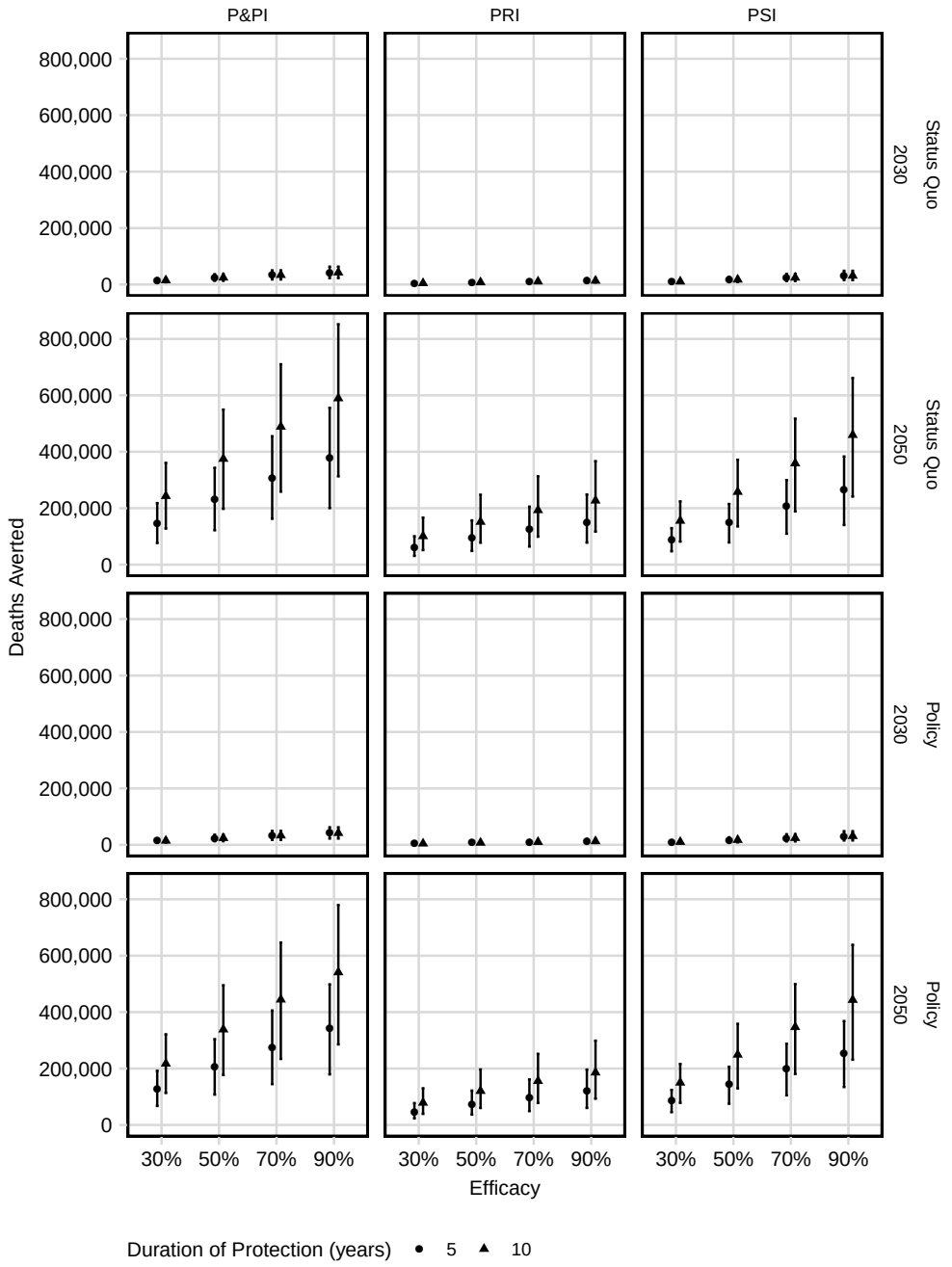

Figure S30: All TB Deaths Averted in China by vaccination by 2030 and 2050. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

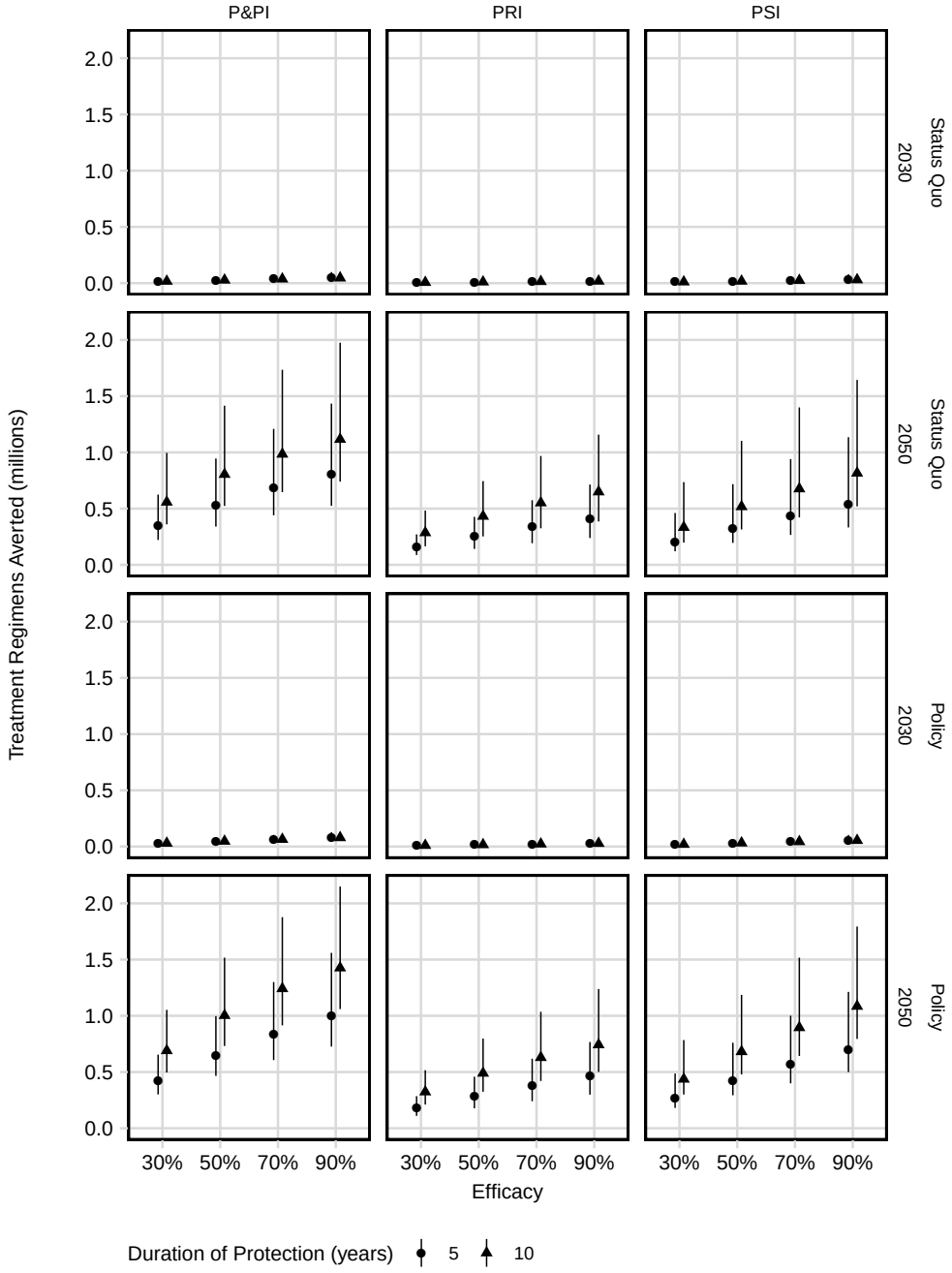

Figure S31: RR/MDR-TB Treatment Regimens Averted by 2030 & 2050 in India. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

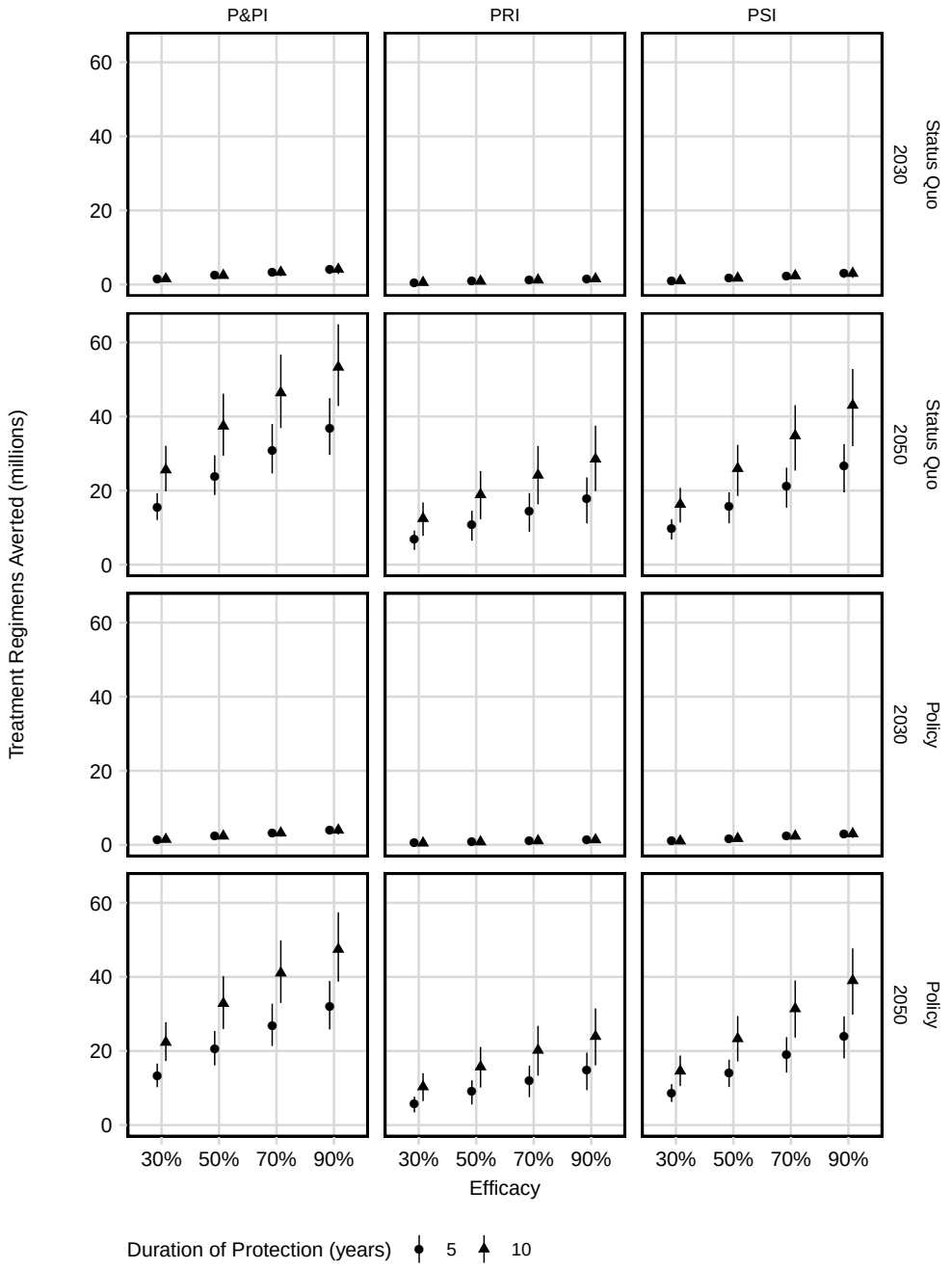

Figure S32: DS-TB Treatment Regimens Averted by 2030 & 2050 in India. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

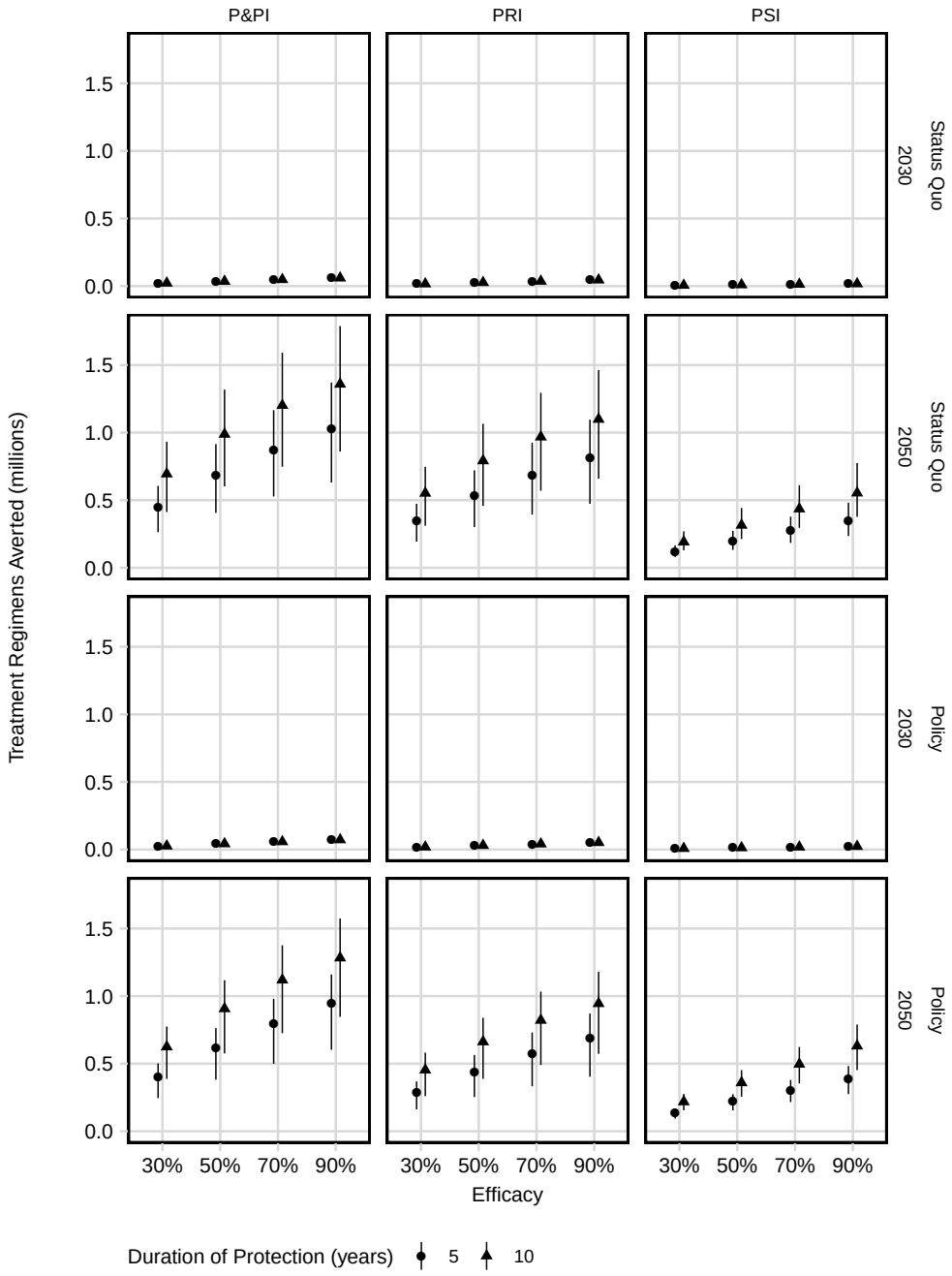

Figure S33: RR/MDR-TB Treatment Regimens Averted by 2030 & 2050 in China. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

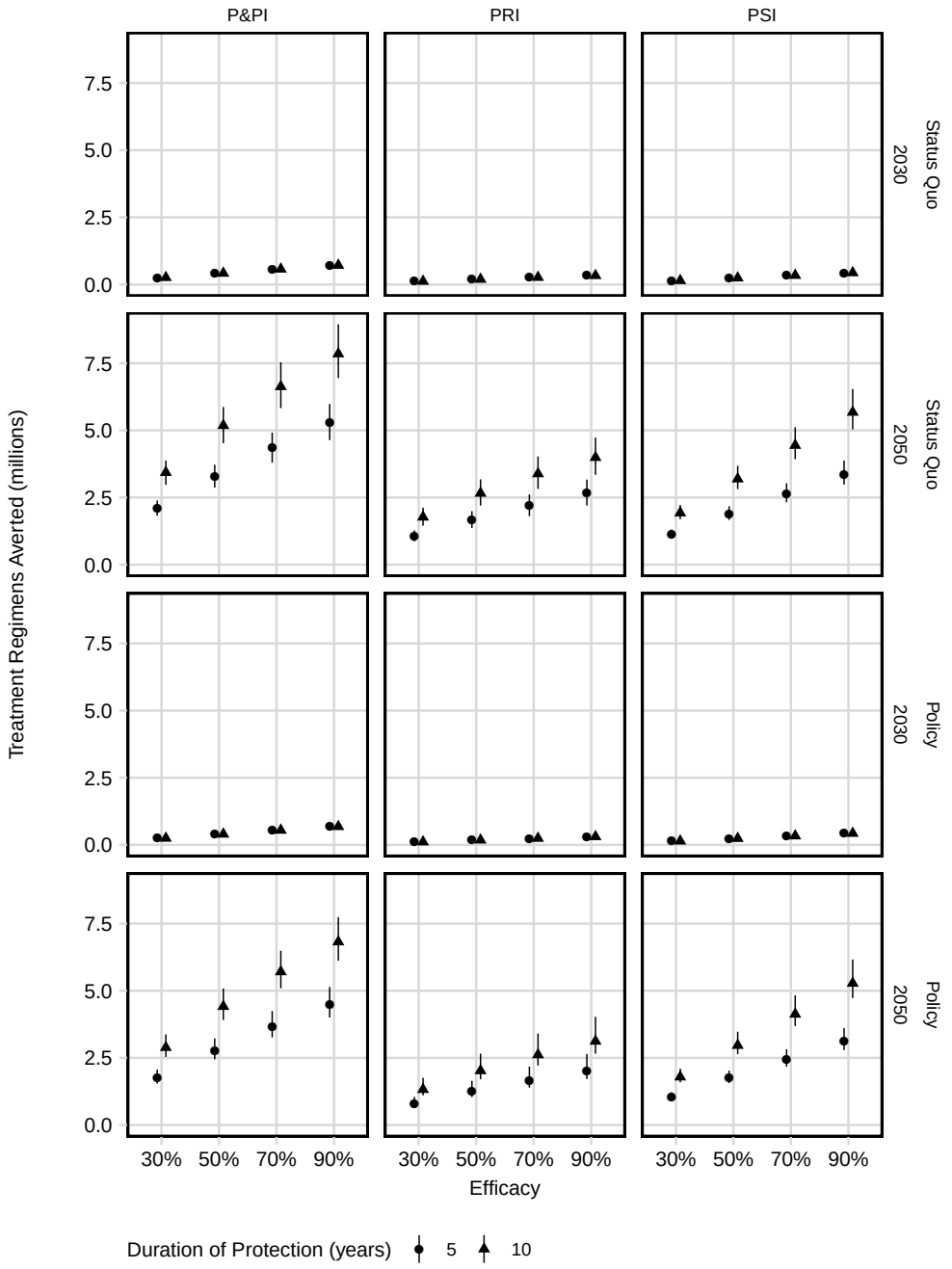

Figure S34: DS-TB Treatment Regimens Averted by 2030 & 2050 in China. Points represent median value. Bars represent the uncertainty interval. P&PI - pre and post-infection efficacy; PSI - post-infection efficacy; PRI - pre-infection efficacy. Horizontal facets show baseline scenarios.

8 Cost-effectiveness

8.1 Incremental Cost Effectiveness Ratios

Estimated incremental cost-effectiveness ratios for USD 10 and USD 30 vaccines are presented in Figures S35 and S36 for India and Figures S37 and S38 for China, respectively.

DALYs averted and costs are affected differently in the discounted analyses as benefits of vaccination are realised later compared to costs, which are incurred earlier. Consequently, we find that ICERs in discounted analyses to be greater than undiscounted analyses across both countries and over the range of vaccine characteristics. Further, in both countries, we found that ICERs for vaccination in the "Policy" scenario to be greater than in the "Status Quo" scenario, consistent with the lower absolute averted burden of disease by vaccination (section 7.5).

Estimated incremental cost-effectiveness ratios for USD 10 vaccines, delivered with routine vaccine coverage of 80% but mass campaign coverage of 30% for India and China are presented in Figures S39 and S40 respectively.

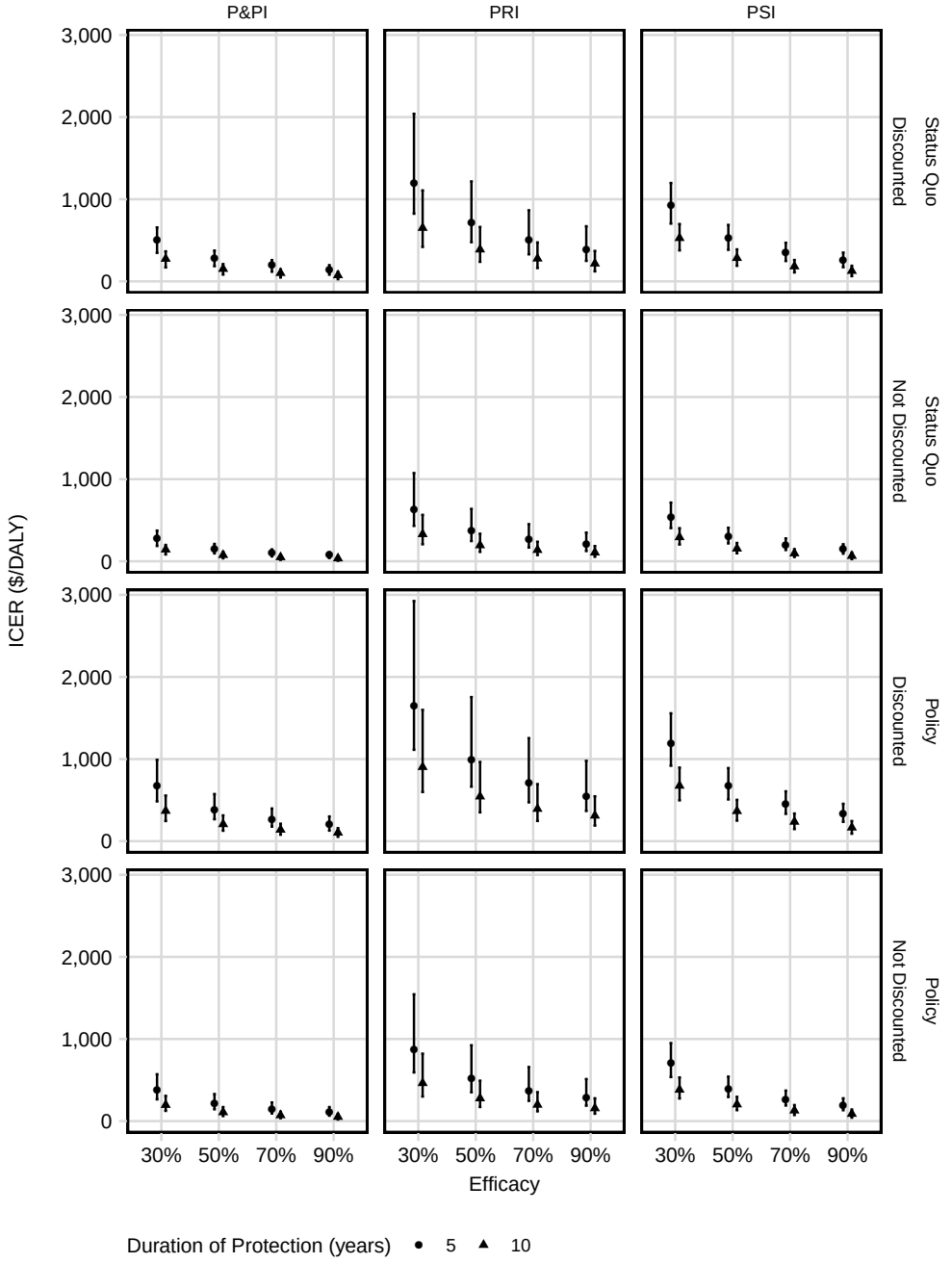

Figure S35: ICER (USD per DALY averted) for vaccination in India over 2027–2050 at USD 10 per vaccine. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

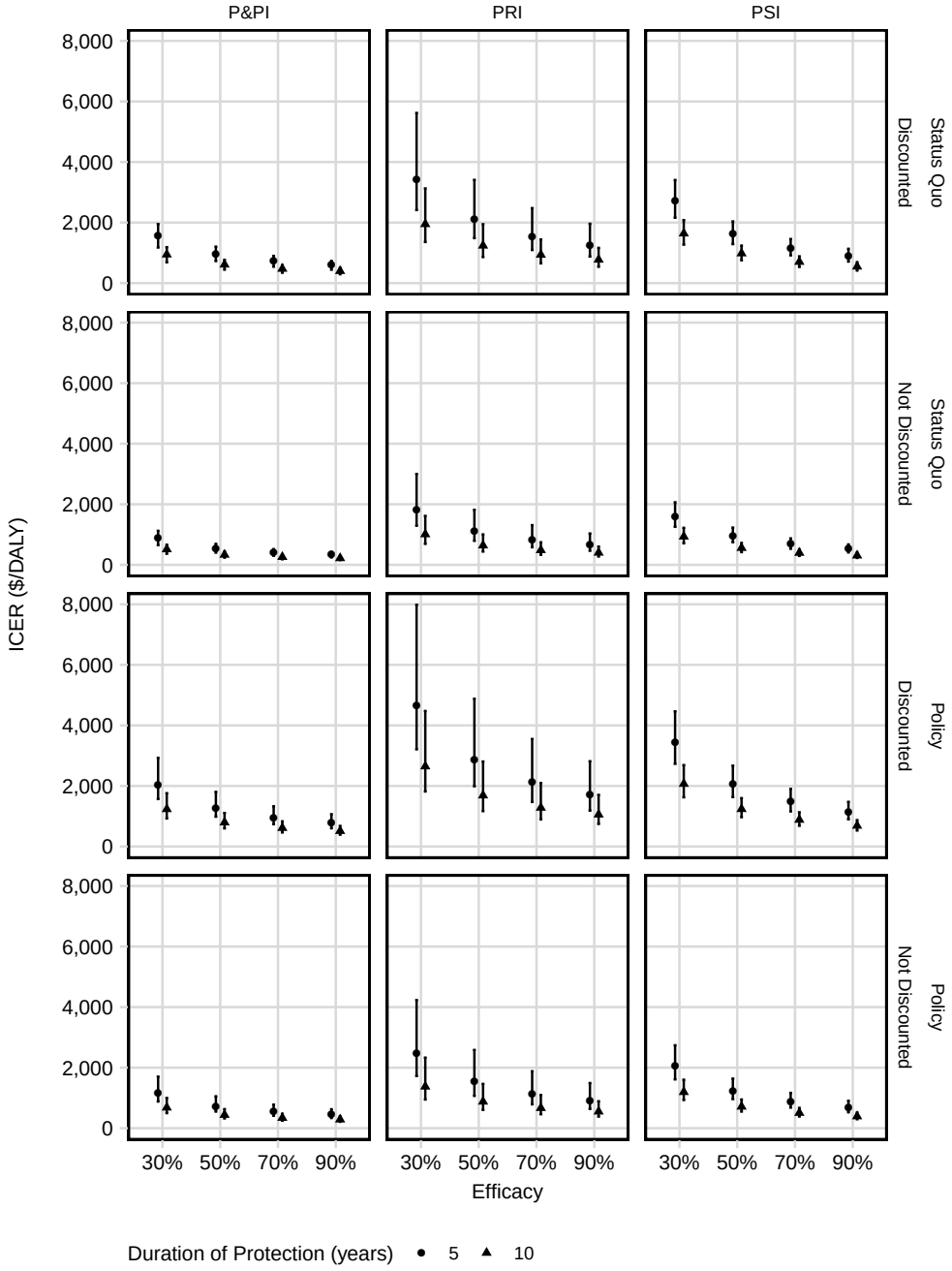

Figure S36: ICER (USD per DALY averted) for vaccination in India over 2027–2050 at USD 30 per vaccine. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

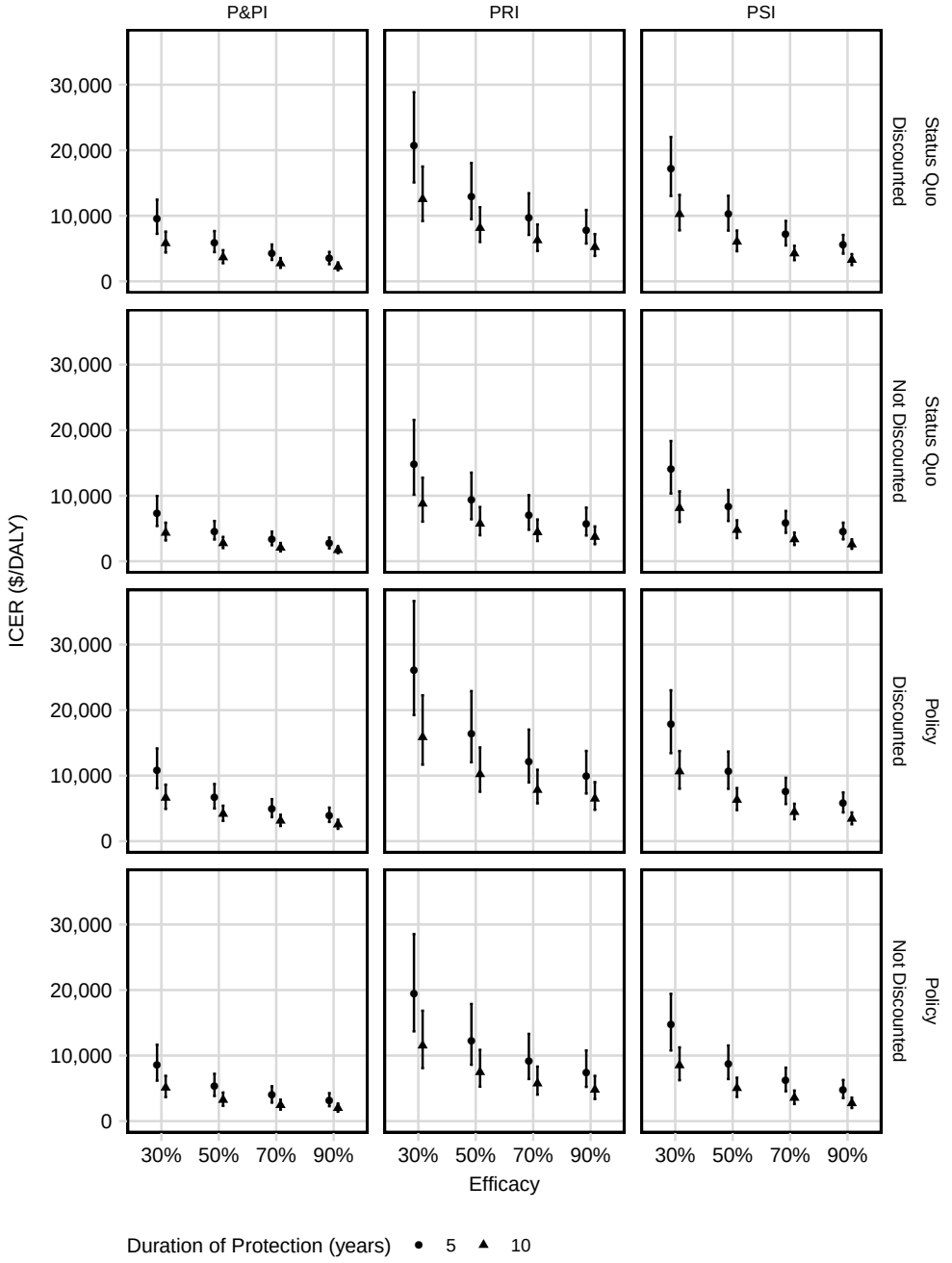

Figure S37: ICER (USD per DALY averted) for vaccination in China over 2027–2050 at USD 10 per vaccine. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

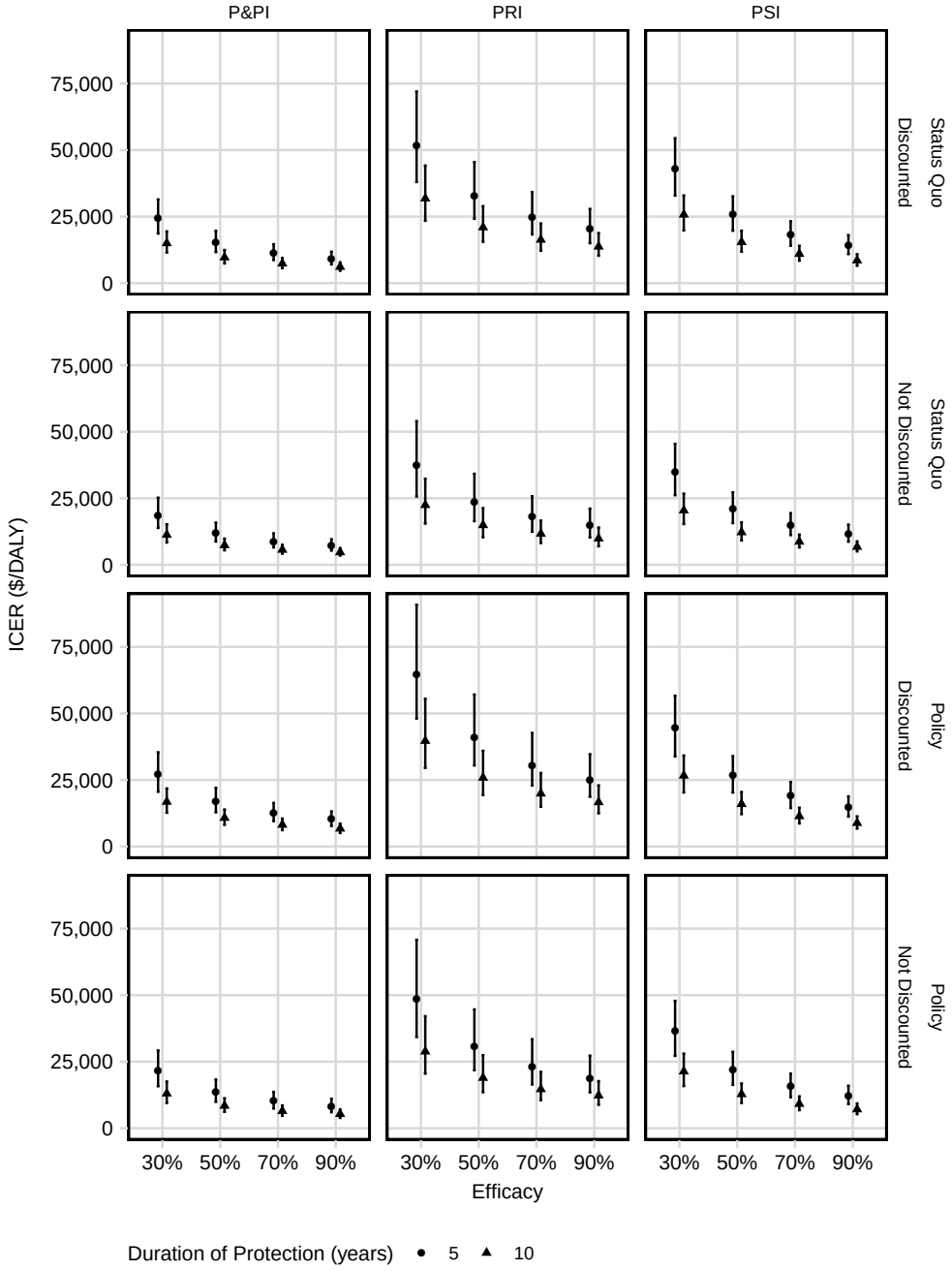

Figure S38: ICER (USD per DALY averted) for vaccination in China over 2027–2050 at USD 30 per vaccine. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

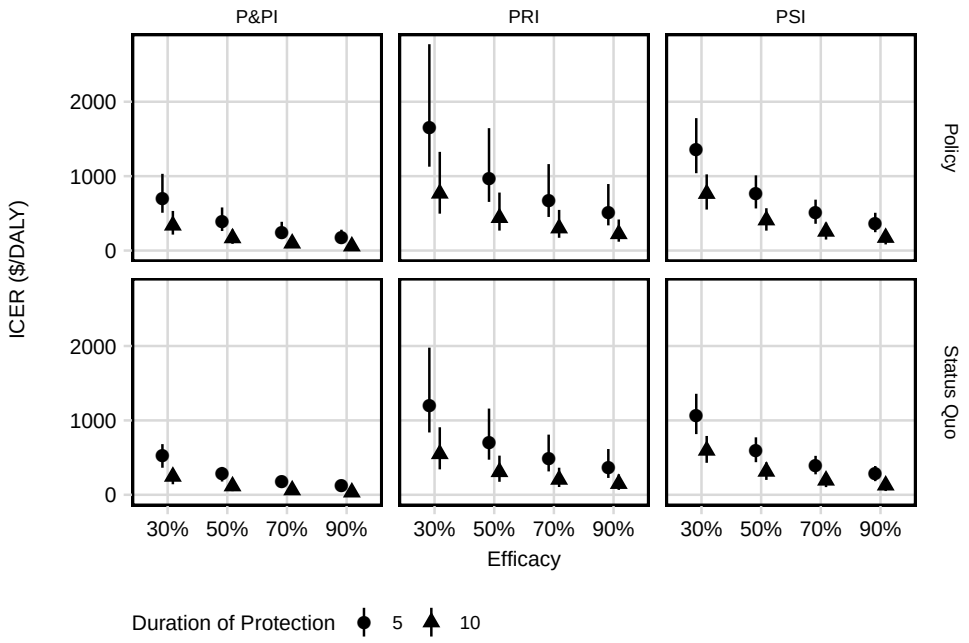

Figure S39: ICER (USD per DALY averted) for vaccination in India over 2027–2050 at USD 10 per vaccine and 30% mass campaign coverage. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

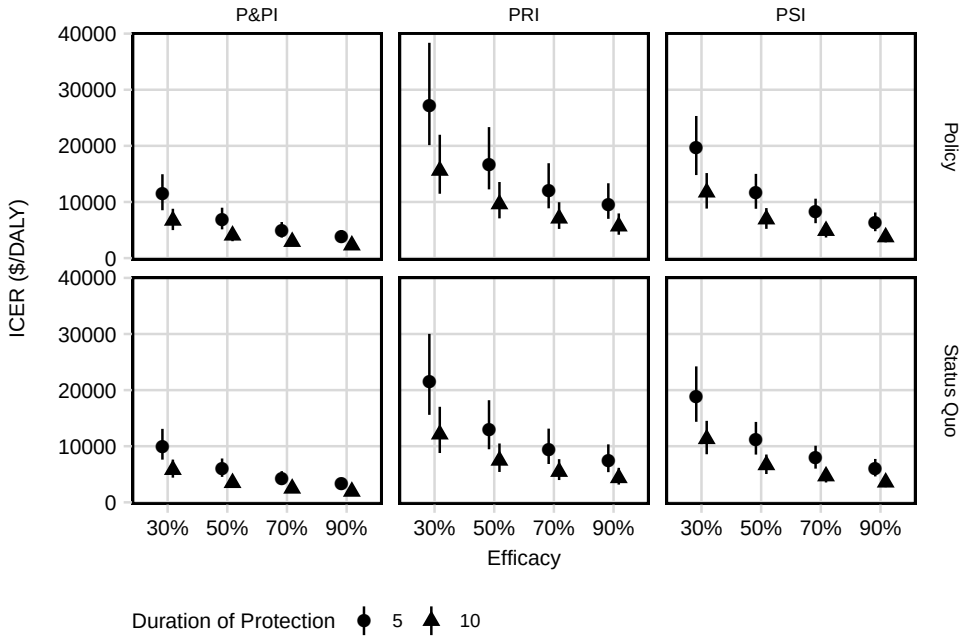

Figure S40: ICER (USD per DALY averted) for vaccination in China over 2027–2050 at USD 10 per vaccine and 30% mass campaign coverage. Points represent median value. Bars represent the uncertainty interval. P&PI: pre and post-infection efficacy; PSI: post-infection efficacy; PRI: pre-infection efficacy. Horizontal facets show baseline scenarios.

9 Budget Impact

For the immunisation programme, we present the total costs incurred through instantaneous deployment of the vaccine. In India, for a 50% efficacy, 10-year duration of protection PSI vaccine priced at USD 10, the model predicted costs for instantly deployed mass campaigns in 2027, 2037 and 2047 of USD 10.2 billion, USD 11.2 billion and USD 12.0 billion respectively. In China, for a 50% efficacy, 10-year duration of protection P&PI vaccine priced at USD 10, the model predicted slightly higher costs for instantly deployed mass campaigns in 2027, 2037 and 2047 of USD 12.7 billion, USD 12.8 billion and USD 12.6 billion, respectively. The corresponding median cost for routine annual vaccination was US$218.2 million (UI: 197.4–229.1) and US$138.1 million (UI: 131.7–166.1) in India and China respectively.

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3.3 New Developments

Two important developments took place between when Research Paper 2 was conceived and published. Firstly, Fu et al.[1] published a contemporary study in 2021 investigating the impact of a post-exposure vaccine on rifampicin-resistant TB across 30 countries, including India and China. Secondly, in October 2021, investigators presented preliminary results from the TB-PRACTECAL study, which investigated the efficacy of a new all-oral six-month drug regimen for MDR/RR-TB , at the International Union of Tuberculosis and Lung Disease World Lung Health 2021 conference[2,3]. I briefly describe these developments and their implications for the results in sections §3.1 and 3.1.

3.3.1 New modelling studies

Key differences and similarities between my study in section §3.1 (Weerasuriya et al.) and that by Fu et al. are summarised in 3.1.

Fu et al. estimated how a 50% efficacy, post-exposure vaccine conferring 10 years of protection would affect rifampicin-resistant tuberculosis (RR-TB) incidence and mortality among the 30 countries that suffer 90% of global RR-TB . They modelled vaccination of all 15-year-olds annually from 2025, with two-year catch-up campaigns every 5 years to all adults >15 years, achieving peak coverage of 72–76%.

Fu et al. estimated that a new TB vaccine would avert 10% (95% credible interval: 9.7–11%) of RR-TB cases and 7.3% (6.6–8.1%) of deaths over 2025–2035, with most contributions from India, China, Indonesia, Pakistan, and the Russian Federation. This result assumed that programmatic MDR/RR-TB management remained unchanged after 2020 ("Status Quo" scenario). Fu et al. also modelled an alternative baseline future scenario with 85% drug sensitivity testing and 75% RR-TB treatment success rates. Combined improvements to MDR/RR-TB management and vaccination was predicted to avert 14% (12–16%) and 31% (29–33%) of cases and deaths, respectively, compared to the unvaccinated Status Quo baseline.

The most comparable outcome measure between Fu et al. and Weerasuriya et al. is the number of MDR/RR-TB cases averted by a 50% efficacy post-infection efficacy (PSI) vaccine in their respective Status Quo scenarios. In Weerasuriya et al., vaccination was predicted to avert 1,300,000 (uncertainty range UR: 900,000–2,600,000) cases in India and 700,000 (UR: 500,000–900,000) cases in China, over the 24 year period 2027–2050. In contrast, in Fu et al., a similar vaccine averted 201,000 (95% credible interval 116,000–428,000) and 86,000 (95% CI: 55,000–133,000) cases in India and China, respectively, over the 10 year period 2025–2035. Both studies found that improved diagnosis and treatment of drug-resistant TB reduced the absolute impact of vaccination compared to a status quo baseline.

Table 3.1: Key differences between Weerasuriya et al. and Fu et al. CrI=credible interval

Weerasuriya et al February 2021	**Fu et al January 2021**
Modelling methods	
Setting	
India and China	30 countries including India and China
Model details	
Age-, treatment-history, drug-resistance stratified compartmental model	Age-, drug-resistance stratified compartmental model. HIV+ strata in some countries (not India or China)
Resistance model	
Acquired and transmitted	Acquired and transmitted
Demographic model	
Single year age compartments	Two age compartments: children (aged<15) and adults (aged≥15)
Data driven annual birth and all-cause death rates	Time invariant fitted birth and ageing rates Time invariant data derived all-cause death rate
Calibration	
Calibrated to overall TB incidence, mortality, prevalence, notifications, DRTB incidence and proportion DRTB among notifications, stratified by treatment history	Calibrated to overall TB incidence, mortality, DRTB incidence, demography
Alternative baseline scenario	
Specific to each country per expert opinion and national plans	Generic improvement in drug sensitivity testing and DRTB treatment success applied to all countries
Vaccine details	
Vaccine time horizon	
2027–2050 (24 years)	2025–2035 (10 years)
Vaccine characteristics (central example)	
POD vaccine	POD vaccine with no impact on disease relapse
P&PI and PSI vaccines	Post-exposure (=PSI) vaccine
50% efficacy	50% efficacy
10-year rectangular duration of protection	10-year truncated average duration of protection
Vaccine implementation	
Annual childhood vaccination (age 9)—coverage 80%	Annual adolescent vaccination (age 15)—coverage 60-80%
Three adult mass campaigns (age ≥10) in 2027, 2037, and 2047—coverage 70%	Two adult (age ≥15) catch up campaigns in 2025/26 and 2030/31—coverage 72–76% Gradual mass campaign scale up
Results	
Averted cases	
2027–2050 (24 years): India: 1,300,000 (UR 900,000–2,600,000) China: 700,000 (UR 500,000–900,000)	
Scaled to 10 years*: India: 541,667 (UR 375,000–1,083,333) China: 291,667 (UR 208,333–375,000)	2025–2035 (10 years) India: 201,000 (95% CrI 116,000–428,000) China: 86,000 (95% CrI 55,000–133,000)
* See text for scaling assumptions	

The estimates of averted cases are not directly comparable as vaccine time horizons differed between Fu et al. (10 years) and Weerasuriya et al. (24 years). Due to time and computational resource constraints, I did not rerun the Weerasuriya et al. model over a 10-year period to match the Fu et al. time horizon exactly. However, I speculate that we can make useful inferences by approximately scaling the results from Weerasuriya et al. to match the time horizon of Fu et al. First, we determine that the vaccine time horizon of Fu et al. is 41% (≈10/24) of Weerasuriya et al. Then we make the *strong assumption* that cases averted in Weerasuriya et al. accumulated linearly with time after vaccine introduction. Under this assumption, we would expect that, over 10 years, vaccines in Weerasuriya et al. would avert approximately 541,667 (UR: 375,000–1,083,333) and 291,667 (UR: 208,333–375,000) cases in India and China, respectively. The approximately scaled results from Weerasuriya et al. are likely underestimates for two reasons: (i) as it is a dynamic model, vaccine impact is likely to behave non-linearly over time as the indirect (transmission) effects propagate through the population and (ii) vaccine is scaled up instantaneously, so most cases are averted soon after vaccine introduction, with accumulation plateauing thereafter. Because the scaled estimates are still greater than those by Fu et al. despite this underestimation, different vaccine time horizons are unlikely to be the only cause of the difference in observed vaccine impact.

The models in Weerasuriya et al. and Fu et al. differ in how they represent TB natural history and treatment. Therefore, it is difficult to pinpoint a single or dominant cause for the greater vaccine impact predicted by Weerasuriya et al. However, I hypothesize that two groups of assumptions contributed to this difference: (i) more optimistic vaccine characteristics and deployment in Weerasuriya et al. and (ii) more optimistic baseline burden projections in Fu et al. (i.e. lower vaccine avertible TB burden).

Vaccine Deployment and Characteristics Both Fu et al. and Weerasuriya et al. modelled 50% efficacy M72/AS01$_E$-like PSI vaccines with a durability of 10 years, but vaccination in Weerasuriya et al. conferred more protection through two mechanisms. First, Weerasuriya et al. assumed that vaccination protected against relapse from the recovered state, whereas Fu et al. did not. Second, the average vaccinee received more protection in Weerasuriya et al. than Fu et al. Durability in Weerasuriya et al. was 'rectangular' in shape. Each effectively vaccinated individual was protected for the *total duration* of protection; protection was then lost instantly at the end of this period. In contrast, Fu et al. modelled 10 years of protection *on average* per recipient, truncated in those still protected at the end of 10 years. In this model, each year, 10% of the remaining vaccinated cohort lost protection; all individuals still protected at 10 years lost protection at this point. Vaccine delivery was also more optimistic in Weerasuriya et al. than Fu et al. Weerasuriya et al. modelled higher coverage (80%) in a larger adult/adolescent cohort (aged ≥10 years) than Fu et al., who modelled 72–76% peak coverage in those aged ≥15 years. Maximum coverage was achieved instantly in the former, but through catch-up campaigns lasting two years in the latter.

Baseline Burden Fu et al. modelled a lower baseline future burden of MDR/RR-TB in the Status Quo scenario than Weerasuriya et al., which translated to lower avertible burden by vaccination. Fu et al. modelled a continuous decline in TB burden over time representing expected continuing improvements in living standards and nutritional status. They implemented this trend by applying a continuously decreasing geometric adjustment parameter to the force of infection of drug susceptible TB (DSTB) and RR-TB from 1970 onwards. In contrast, in Weerasuriya et al., I did not externally constrain future MDR/RR-TB burden. Instead, trends in MDR/RR-TB were determined solely by the intrinsic characteristics and programmatic control of MDR/RR-TB .

Taken together, these differences led to

1. vaccine that provides more extended protection, effective in more natural history states, and delivered to a broader population; and
2. higher vaccine avertible burden at baseline,

in Weerasuriya et al., compared to Fu et al.

Weerasuriya et al. and Fu et al. aimed to answer questions with different policy relevance. In Weerasuriya et al., I focused on representing local MDR/RR-TB epidemiology and other local health system features (e.g. case detection rates, treatment success rates, and private sector care provision) to generate estimates that could inform country level decisions. In contrast, Fu et al. assess the potential global impact of a new TB vaccine, maintaining inter-country comparability. Three key differences make Weerasuriya et al. more suitable to inform local decisions: (i) more specific country-specific calibration, (ii) alternative scenarios based on country policy, and (iii) a more accurate demographic model.

In Weerasuriya et al., I calibrated the model to MDR/RR-TB incidence and the proportion of all TB notifications found to be resistant, stratified by treatment history. In contrast, RR-TB was calibrated to a single data point (2018 incidence rate) per country in Fu et al. More generally, I calibrated both country models to TB notification rates to constrain TB case detection (and treatment initiation) in line with World Health Organization (WHO) data.

The alternative baseline scenario ("Policy") in Weerasuriya et al. was constructed with advice from country experts and a published national strategy. Thus, scale-up plans for India and China were substantially different. In contrast, Fu et al. assumed a generic improvement in drug sensitivity testing coverage to 85% and second-line treatment treatment success to 75% in all settings.

Finally, in Weerasuriya et al., I modelled demography with single-year age groups, with time variant birth rates and death rates per World Population Prospects[4]. In contrast, Fu et al. modelled demography using two age compartments (age <15y and age ≥15y), with time invariant average all-cause mortality based on World Population Prospects and time invariant birth and ageing rates calibrated to 2018 demography.

The additional country-specific parameterisation, calibration, and inputs in Weerasuriya et al. are likely to improve the country-specific reliability of the model at the cost of reduced comparability between India and China (particularly in the alternative baseline scenario).

However, despite differences in their structure, vaccine assumptions, and time horizons, both studies predicted that vaccines would substantially reduce MDR/RR-TB burden in India and China. Indeed, because the two studies modelled a range of possible future baseline scenarios, each provided counterfactual results for the assumptions made by the other, reinforcing their mutual conclusions. The final key difference was that the Weerasuriya et al. study included a cost-effectiveness analysis. While it is reasonably certain that, due to the lower burden averted, vaccination in Fu et al. would be less cost-effective, the authors would need to substantively establish this by attaching a cost-model to their study.

3.3.2 Developments in second-line therapeutic regimens

In Research Paper 2, I found that vaccine cost-effectiveness was decreased by introducing a shorter, cheaper standardised MDR/RR-TB treatment regimen in China's alternative "Policy" baseline scenario. We can also expect a more effective second-line regimen to reduce avertible MDR/RR-TB burden, reducing vaccines' epidemiologic impact and cost-effectiveness. In this section, I briefly describe two recent trials that investigated new second-line regimens that are shorter, more-effective, or both: STREAM and TB-PRACTECAL.

STREAM The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) Stage 1 trial investigated the outcomes of a short (9–12 month) standardised regimen for MDR/RR-TB against standard of care. This multicentre, international phase III non-inferiority randomised controlled trial enrolled patients between 2012 and 2015 in Ethiopia, Viet Nam, Mongolia, and South Africa.

STREAM Stage 1 recruited participants with bacteriologically positive rifampicin-resistant but fluoroquinolone and aminoglycoside susceptible TB[5,6]. Patients in the investigational arm received a 9–12 month standardised drug regimen whereas those in the control arm received long (20 month) conventional treatment per 2011 WHO guidelines[7]. The primary outcome was favourable status at 132 weeks, where favourable status was defined as cultures negative for *Mycobacterium tuberculosis* (*Mtb*) at 132 weeks post randomisation, with no intervening positive culture or previous unfavourable outcome. An unfavorable outcome was defined by the initiation of two or more drug therapies that were not included in the assigned regimen, treatment extension beyond the permitted duration, death from any cause, a positive culture from one of the two most recent specimens, or no visit at 76 weeks or later.

Final results from the STREAM Stage 1 trial were published in March 2019[8]. Investigators found that the short standardised regimen was non-inferior to long conventional regimens in both modified Intention to Treat (mITT) and Per-Protocol (PP) analyses. In the mITT analysis, 99/124 (79.8%) patients in the control arm and 193/245 (78.8%) in the investigational arm had favourable outcomes, leading to a final difference of 1.0% (95% CI: (–)7.5–9.5; $p = 0.02$). Similarly, in the PP analysis, 67/83 (80.7%) patients in the control arm and 186/227 (81.9%) in the investigational arm had favourable outcomes, leading to a final difference of –0.7% (95% CI: (–)10.5–9.1).

Incorporating a range of observational data and the results of STREAM Stage 1, the 2019 WHO consolidated guidelines on drug-resistant TB treatment[9] conditionally recommended a 9–12 month short MDR/RR-TB regimen for selected patients. These patients should not have been previously treated for more than 1 month with second-line medicines used in the shorter multidrug-resistant TB (MDR-TB) regimen or should have resistance to fluoroquinolones and second-line injectable agents excluded. STREAM Stage 2, which investigates whether (i) it is possible to replace the injectable aminoglycoside with (oral) bedaquiline and (ii) whether treatment can be further shortened to six months is currently ongoing[6,10].

TB-PRACTECAL The Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) is an ongoing phase II–III randomised clinical trial that compares short (six month) all oral second-line regimens containing bedaquiline, pretomanid, and linezolid (BPaL), with or without additional clofazimine or moxifloxacin, to WHO recommended standard of care for the treatment of bacteriologically confirmed MDR/RR-TB . This multicentre trial is ongoing in Belarus, Uzbekistan, and South Africa. The composite primary endpoint of the phase III component is the percentage of patients who experience unfavourable outcomes (failure, death, treatment discontinuation, recurrence, or loss to follow up at 72-weeks post-randomisation).

Recruitment into TB-PRACTECAL was terminated in March 2021 because predetermined statistically significant differences between the investigational and control arms were met. Preliminary results were presented at the 52nd World Lung Health Conference in October 2021[2,3], where investigators reported that the BPaL + moxifloxacin regimen was non-inferior to the standard of care ($p < 0.0001$). In the mITT analyses, 7/62 (11.3%) patients in the investigational arm (BPaL + moxifloxacin, BPaLM) suffered unfavourable outcomes, compared to 32/66 (48.5%) in standard of care. In the BPaLM arm, 5 patients discontinued treatment and 2 were lost to follow-up, whereas in the SOC arm, 2 patients died, 28 discontinued treatment, and 2 were lost to follow-up. Superiority was demonstrated in the mITT analysis ($p < 0.001$) but not the PP analysis ($p = 0.13$).

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If the results from studies such as STREAM and TB-PRACTECAL translate into routine clinical outcomes, this may represent a pivotal step in MDR/RR-TB treatment while also substantially affecting the impact and cost-effectiveness of new TB vaccines.

As discussed in section §3.1 and section 2.3.1, widespread adoption of a less ineffective new treatment regimen will likely reduce future vaccine-avertible MDR/RR-TB . However, we cannot immediately predict the impact on vaccine cost-effectiveness in the short-medium term.

On the one hand, all else being equal, a six month long all oral drug regimen with no inpatient treatment costs (e.g. TB-PRACTECAL), fewer side effects, and fewer unfavourable outcomes is likely to cost less per patient treated than the current standard of care. If such a treatment were widespread, the financial value of each averted MDR/RR-TB would decline, reducing vaccine cost-effectiveness.

On the other hand, a highly successful treatment might motivate the health systems in India and China to increase their efforts to diagnose and treat MDR/RR-TB . As a result, more patients may be treated, increasing health system costs in the short-medium term. Averting these MDR/RR-TB cases (and costs) in the first place might increase vaccine cost-effectiveness. However, while increased MDR/RR-TB diagnosis might drive costs in the short term, it will also decrease transmission (primary resistance) in the longer term. Thus, over a long time horizon, vaccine cost-effectiveness will likely fall.

The discussion above rests on two assumptions.

First, it assumes that the treatment outcomes observed in trials will translate to routine clinical practice. Under trial conditions, existing second-line treatment regimens have also shown high treatment success rates. However, we have thus far failed to consistently replicate these outcomes programmatically. This difference has been explained by the long duration of conventional second-line regimens, parenteral administration, and drug toxicity—disadvantages which are mitigated by the new short regimens.

Second, it assumes that new drugs will remain effective. Fluoroquinolone resistance is well recognised[11,12] and sporadic instances of bedaquiline resistance have been described[13–16]. The loss of new drugs due to rapidly emerging resistance may increase the relative impact of vaccines over time.

3.4 Future Work

The first aim of this thesis was to integrate context-specific aspects of TB epidemiology and management into vaccine models. To this end, in section §3.1, I have integrated (i) a dynamic representation of MDR/RR-TB calibrated to country epidemiologic data, (ii) country-specific cost models, and (iii) country-specific alternative baseline scenarios. However, TB burden in India and China varies along many axes that might affect overall vaccine impact. These sources of heterogeneity should be incorporated in future studies.

Geographically, burden is higher in Western China[17] and North-Eastern India[18], reflecting in-country differences that include healthcare access and population density. Migration has been implicated in changing burden patterns of MDR/RR-TB: in China, the transregional movement of patients seeking better healthcare to Beijing has been hypothesised to drive ongoing transmission[19].

Comorbidities that drive TB are an important source of heterogeneity; two such sources are diabetes and malnutrition in India.

India is home to 77 million adults with diabetes[20–22], with prevalence (≈7.5% in 2014) is rising rapidly[20,23,24]. Diabetes mellitus is a risk factor for TB disease[25,26] and poorer TB treatment outcomes[27–30]. Some studies have identified it as a risk factor for MDR/RR-TB[30–32]. It has also been associated specifically with infectious TB[26].

Modelling work suggests that one-third of TB incidence and half of TB mortality in India might be attributable to diabetes by 2050[33]. Conversely, 3.1–12.8% of all TB in India in 2050 could be averted by vaccinating 50–60% of individuals with diabetes over 2020–2025 with a 50% efficacy post-exposure vaccine conferring 10-years of protection[34].

Similarly, that malnutrition and TB predispose towards each other is well established[35–38]. Low body mass index (a proxy measure for undernutrition) is consistently associated with TB disease, adverse treatment outcomes, and TB mortality[39], including MDR/RR-TB mortality[40]. Providing nutritional support to TB patients reduces the risk of treatment failure[41]. In addition, improving population nutrition might substantially reduce TB burden: using a model set in Central-Eastern India, Oxlade et al.[42] showed that policies and programs that reduced the prevalence of undernutrition could reduce TB incidence and mortality by 43–71% and 40–68%, respectively.

Nutritional support is an integral part of TB care[36,37] and likely to be an ongoing concern in India, where 15% of the population remained undernourished in 2021[43]. It is important that any improvements in general nutrition and changes to targeted nutritional support for TB patients are integrated into estimates of future vaccine impact.

It is clear that there are locally important factors in the epidemiology of India and China that must be factored into estimates of future vaccine impact. However, it is likely to be more useful to integrate these aspects when (i) more data about how these factors might interact with vaccine are available (e.g. the interaction of diabetes and nutrition with vaccine immunogenicity) and (ii) as more detailed plans for implementation are designed, where considerations such as targeting to these risk groups can be considered.

3.5 Summary

In this chapter, I attempted to satisfy the first and second objectives of this thesis. The first objective was to develop a transmission model of *Mtb* that dynamically modelled drug resistance, calibrated to epidemiologic data from India and China. The second

objective was to use the calibrated model to assess the epidemiologic impact of vaccines on MDR/RR-TB , their overall cost-effectiveness, and how country-specific scale up of programmatic TB management might affect vaccine impact.

Assuming a "Status Quo" baseline and an M72/AS01$_E$-like PSI vaccine conferring 10-years of protection, I estimated that vaccination reduced the 2050 MDR/RR-TB incidence rate by 47% (uncertainty interval, UI: 37–58) and 29% (UI: 27–31) in India and China, respectively. In India, a $10 vaccine was cost-effective at the 1× gross domestic product (GDP) and upper healthcare opportunity cost (HCOC) thresholds. In China, vaccination was cost-effective at the 1× GDP threshold but only 21% likely at the upper HCOC threshold.

Scaling up programmatic (MDR-)TB management reduced the burden averted by vaccination and decreased vaccine cost-effectiveness. In India, over 2027 to 2050, total averted MDR/RR-TB cases declined from 1.3 (UI: 0.9–2.6) million in the Status Quo scenario to 0.9 (UI: 0.7–1.7) million cases in the Policy (scale-up) scenario. The corresponding incremental cost-effectiveness ratio (ICER) for a $10 vaccine increased from $284 (UI: 189–389) to $366 (UI: 250–504). In China over 2027 to 2050, total averted MDR/RR-TB cases declined from 0.7 (UI: 0.5–0.9) million in the Status Quo scenario to 0.6 (UI: 0.4–0.7) million cases in the Policy (scale-up) scenario. The corresponding ICER for a $10 vaccine increased from $6059 (UI: 4591–7749) to $6,310 (UI: 4,745–8,109).

Through a dynamic transmission model calibrated to epidemiologic data from India and China, I found that TB vaccines could substantially reduce future MDR/RR-TB burden over different future baseline scenarios. Consistent with previous studies, adult and adolescent vaccination was likely to be cost-effective. However, decision makers must be vigilant to developments in MDR/RR-TB diagnosis and treatment: as MDR/RR-TB is a major driver of TB related costs, such advancements may disproportionately impact vaccine cost-effectiveness. Finally, I also presented estimates of the volume of second line therapy averted by vaccination and showed that this estimate is likely to rise if MDR/RR-TB diagnosis and treatment are scaled up.

By incorporating MDR/RR-TB epidemiology, country-specific plans to scale up programmatic management, country-specific costs and (in India) the private health sector, this chapter has addressed the first aim of this thesis and contributed to the nascent body of work that incorporates locally important epidemiologic and health system features and their uncertainty into estimates of TB vaccine impact in India and China.

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4 Total Cost and Affordability of Tuberculosis Vaccines

In this chapter, I investigate the total cost and affordability of large-scale cost-effective adult TB vaccination. First, I discuss the basis of cost-effectiveness thresholds (CETs) and why they do not necessarily indicate that health interventions will be affordable at the health system level. I then review the relationship between the expected total cost of an intervention and the CET it is appraised against. In Research Paper 3, I measure the affordability of TB vaccination by estimating the expected maximum cost of TB vaccine programmes whose health benefits are valued at prevailing CET thresholds. Finally, I review the implications of these estimates for decision makers considering TB vaccine deployment.

4.1 Cost-effectiveness thresholds and affordability

Whether a cost-effectiveness analysis (CEA) of a new health intervention that compares its incremental cost-effectiveness ratio (ICER) to a CET to estimate if that intervention might be cost-effective *can* address affordability questions is a matter of ongoing scholarly debate[1–7]. Even under the theoretical conditions where it can, such an analysis requires that the CET is derived using the actual spending and budget constraints of the setting to which it applied. However, it is well recognised that the CETs used *in practice* for CEAs in low- and middle-income countries (LMICs) are not derived from such data. Consequently, health interventions, including TB vaccines, indicated as cost-effective by these analyses may turn out to be unaffordable by health systems[7–13].

4.1.1 Cost-effectiveness thresholds in practice

Previous analyses[14], including chapter 3, predict that hypothetically priced adult and adolescent TB vaccination is likely to be cost-effective in India and China over a range of CETs. These thresholds include those specified as multiples of gross domestic product (GDP) per capita or based on estimates of the marginal productivity of health systems (healthcare opportunity cost).

Cost-effectiveness literature in global health frequently benchmarks new health interventions against CETs of 1–3× GDP per capita. One systematic review found that 66% of

all CEAs set in LMICs between 2000 and 2015 used GDP-based thresholds, providing little justification beyond reference to generic guidelines[12]. The GDP per capita based thresholds originate in the report of the World Health Organization (WHO)'s Commision on Macroeconomics and Health (CMH) in 2001[15]. Importantly, the CMH set out to perform a benefit-cost analysis, comparing the cost of scaling up essential health interventions in LMICs against the *economic value* of disability adjusted life years (DALYs) lost due to disease (assumed to be 1–3× average earnings per capita per DALY). This calculation was used approximate the *direct economic benefit* of investing in health. The threshold values themselves were derived from value per statistical life estimates, which in turn characterise an individuals' willingness to spend on small decreases in mortality risk rather than purchasing goods and services[16]. These threshold values were subsequently adopted by WHO's 'Choosing Interventions that are Cost-Effective'[17] and would go on to become the *de facto* CETs used in global health. As such, the resulting GDP-based CETs had no basis in actual spending by healthcare systems, their capacity, priorities or population preferences for health interventions.

GDP-based thresholds are now considered too high to be useful in LMICs[8,12,18,19] because they render too many health interventions cost-effective, leading to misallocation of resources and net health loss. Nor does demonstrating cost-effectiveness at these thresholds necessarily lead to adoption: one review found that many countries where Human Papillomavirus and rotavirus vaccination were 'cost-effective' by GDP criteria had not introduced them[19].

GDP-based thresholds nominally reflect a 'demand-side' estimation of the CET that reflects society's monetary valuation of health gain[13]. An alternative view holds that CETs should reflect a 'supply-side' estimate, specifically the opportunity costs of healthcare spending. Here, the CET denotes the health benefit *foregone* when a health system spends on a specific intervention *instead* of the *next best* alternative[10,13], i.e. the marginal productivity of the health system. Such a CET that reflects opportunity cost is optimally determined by the "league table" approach[7,8,13]. Here, the budget impacts of funded interventions are ranked in descending order of cost-effectiveness until the budget is exhausted. If the budget is fixed, the least cost-effective intervention that *is* funded will be displaced to fund a new intervention; the ICER of this *least* cost-effective intervention is the CET of the health system. Alternatively, if additional funds can be procured to fund the new intervention, the ICER of the *most* cost-effective *alternative* intervention that is *not yet* funded is the CET of the health system. The league table approach, while theoretically optimal, is impractical. It requires that decision-makers know the available budget, its constraints, and the cost-effectiveness and required scale of all available health interventions for all indications and population subgroups. This information is rarely, if ever, completely available.

Instead, most recent studies have estimated proxy measures for the opportunity cost of spending. For example, Ochalek et al.[20] estimated the DALYs averted by a 1% change in healthcare expenditure across LMICs (including India and China), using a regression

model that incorporated published estimates[21] of the expenditure elasticity of health (the elasticity of the effects of government health expenditure on health outcomes). The reciprocal of this result (cost per DALY averted) estimates the marginal productivity of the health system, i.e. the opportunity cost of healthcare spending. The input data into this model includes country-specific estimates of health spending, epidemiology, and demographics. However, while superior to GDP-based thresholds, the Ochalek thresholds still only indirectly and approximately reflect budgetary constraints in their respective settings.

Given the limitations of CETs that underlie prior TB vaccine economic evaluations, there is a need to assess whether the vaccine programmes found cost-effective are affordable by estimating the total costs implied by these analyses.

4.1.2 Constant Thresholds and Budget Impact

Section 4.1.1 addressed where CETs used in practice for CEAs in LMICs originate. In this section, I discuss whether these CETs can be held constant as the budget impact of a proposed new health intervention grows.

Paulden et al.[22] use a graphical model of the idealised ICER-ordered process described in section 4.1.1 (the league table approach), termed the "cost-effectiveness bookshelf", to describe the impact of introducing a new intervention into a health system with a constrained budget. This is the same abstraction as the "league table" approach to establishing the healthcare opportunity cost-based threshold at the margin of healthcare spending. They use this model to describe how the budget impact of a proposed new health intervention might affect the cost-effectiveness threshold against which it should be appraised.

Central to this model is the non-linearity of the relationship between health expenditure and health outcomes: the opportunity cost of spending changes disproportionately to the expected budget impact of a new intervention. As noted above, a new intervention can be funded either by disinvesting from existing interventions and services, keeping the overall budget fixed, or increasing the overall budget. The opportunity cost of a new intervention is the value foregone from the displaced interventions when the budget is fixed, or the value that could have been gained if the funds were spent elsewhere when the budget can be increased. The underlying dynamics of the CET with budget impact are the same in both cases.

This model includes a number of assumptions underlying this model that should be stated up front:

- The ICERs and total costs of all current and possible interventions are known to decision-makers.

- Decision-makers aim to maximise overall health, and select interventions based on this criterion alone. Interventions are funded from most- to least- cost-effectiveness until the budget is exhausted. Conversely, interventions are defunded or displaced in reverse order from least to most cost-effective.
- Interventions are either completely funded or not at all.
- Disinvestment from existing interventions incurs no costs.
- Interventions do not affect the efficacy, requirement for, or cost of other interventions.

I first discuss the case where the budget is fixed, then the case where the budget may be increased.

The "cost-effectiveness bookshelf" is presented in figure 4.1A. Here, the x-axis represents total expenditure by the health system, with vertical dashed line B as the budget line. Each rectangle ("book") represents a health intervention; the width of each "book" represents the total cost of that intervention. The y-axis shows the ICER for each intervention. The available interventions are placed in order of cost-effectiveness, from most to least cost-effective (lowest to highest ICER). Interventions to the left of dashed line B (green rectangles) are funded, whereas those to the right are not (orange rectangles).

If the budget is fixed, the CET equals the ICER of the least cost-effective funded intervention, i.e. T1. figure 4.1B and figure 4.1C show two vaccine deployments with equal ICER values ($ICER_V$) but with different budget impacts.

In figure 4.1B, the total cost of vaccination V equals that of D (the least cost-effective intervention). As $ICER_V < T1$, displacing D with V results in net health gain by the health system (more DALYs are averted for the same amount of money spent).

In figure 4.1C, the total cost of vaccination equals that of B, C, and D combined. $ICER_V < T1$ but funding vaccine would defund B, C, and D. The 'aggregate' ICER for B, C, and D is the weighted average of their individual ICERs, represented by T3. T3 is lower than both T1 and $ICER_V$. Thus, appraising vaccine against T1 but spending an amount equal to that for B + C + D would lead to a net loss of health for the health system.

Now consider the case where the budget is increased to fund vaccination (figure 4.1D–F).

If there were no vaccine and the budget was increased from B to AF (figure 4.1D), the next most cost-effective non-vaccine intervention that the health system could buy is intervention E (figure 4.1D). Intervention E has an ICER T2, which is the CET.

As $ICER_V < T2$, the health system would gain heath by spending an equal amount on vaccine over intervention E (figure 4.1D). The opposite is true where $ICER_V > T2$ (figure 4.1E): here, spending on (not cost-effective) vaccination results in net health loss.

In the final scenario the budget is increased further to AF2 (figure 4.1F). $ICER_V$ remains greater than T2. Based on threshold criteria alone, vaccine is not cost-effective compared

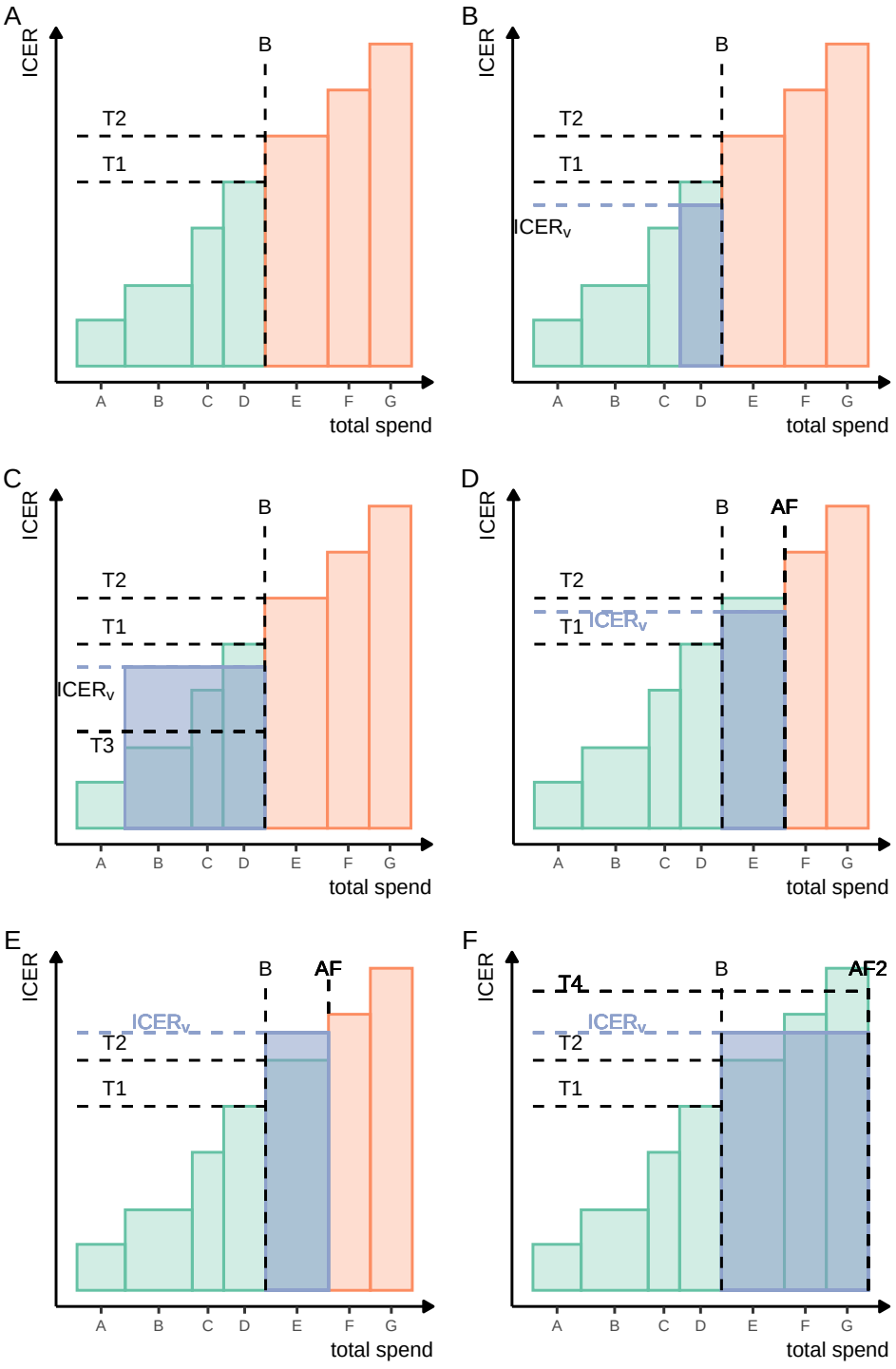

Figure 4.1: Cost-effectiveness Thresholds and Budget Impact. Each rectangle represents a hypothetical health intervention. Green=funded; orange=not funded; purple overlay=vaccination. T1–T4=cost-effectiveness thresholds (see text). A–F represent different scenarios of funding (displace existing interventions or increase budget) and total vaccine cost.

to investing in E and should not be funded. However, if instead of vaccine, the health system invests in E, F, and G, then the aggregate ICER of all three new interventions (T4) is higher than $ICER_V$. Thus, at this scale, investing in $ICER_V$ would have gained greater net benefit for the system, despite the fact that vaccine had a higher ICER than the next most cost-effective option (E).

This model highlights the relationship between the ICER of a proposed new intervention, its expected budget impact, and why the CET against which it should be appraised might change.

Taking a fixed budget as an example, under this model, as the expected budget impact of a new intervention grows, we should appraise it against a progressively lower cost-effectiveness threshold as the ICER of displaced interventions is progressively decreased.

4.2 Research Paper 3

In Research Paper 3, I quantify the expected total costs of large scale adult vaccination. However, there is no data to substantiate TB vaccine prices or large-scale adult mass vaccination to date (other than COVID-19, which does not represent typical funding circumstances). Instead, in this analysis, I attempt to answer the following: if the DALYs averted by vaccination are valued at prevailing cost-effectiveness thresholds, what is the maximum cost of a vaccination programme to the health system?

Research Paper 3 is cited as:

> Weerasuriya, C.K.; Harris, R.C.; Quaife, M.; McQuaid, C.F.; White, R.G.; Gomez, G.B. Affordability of Adult Tuberculosis Vaccination in India and China: A Dynamic Transmission Model-Based Analysis. *Vaccines* **2021**, *9*, 245. https://doi.org/10.3390/vaccines9030245

> **Terminology** Some authors use the term "willingness-to-pay threshold" to refer exclusively to demand-side thresholds (e.g. GDP-based thresholds), rather than supply-side thresholds. In the following research paper, willingness-to-pay threshold and cost-effectiveness threshold are used interchangeably.

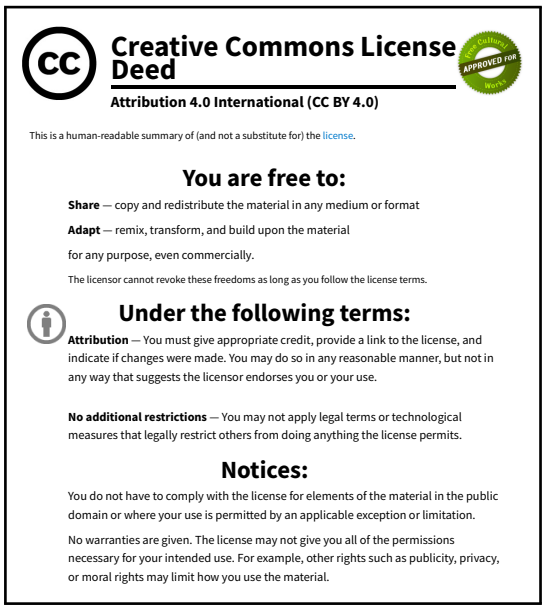

Figure 4.2: Research Paper 3: Creative Commons License

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SECTION A – Student Details

Student ID Number	1604836	**Title**	DR
First Name(s)	CHATHIKA KRISHAN		
Surname/Family Name	WEERASURIYA		
Thesis Title	ADVANCING MATHEMATICAL MODELS OF MYCOBACTERIUM TRANSMISSION TO SUPPORT VACCINE INTRODUCTION		
Primary Supervisor	PROFESSOR RICHARD G WHITE		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	VACCINES		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study and designed the research question. I collected the relevant epidemiologic data from literature. I designed the epidemiologic and health-economic model, programmed it in software (R), calibrated the model(s), simulated baseline and vaccination scenarios, computed outcomes (vaccine impact, total costs, vaccines per DALY averted), and analysed and visualised the results. I wrote the first full draft and edited all subsequent drafts of the manuscript and appendices, submitted the manuscript for publication including writing all correspondence to the journal, wrote responses to reviewers and revised the manuscript as necessary.

SECTION E

Student Signature	[redacted]
Date	08 DECEMBER 2021

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Date	14 DECEMBER 2021

vaccines

MDPI

Article

Affordability of Adult Tuberculosis Vaccination in India and China: A Dynamic Transmission Model-Based Analysis

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Abstract: New tuberculosis vaccines have made substantial progress in the development pipeline. Previous modelling suggests that adolescent/adult mass vaccination may cost-effectively contribute towards achieving global tuberculosis control goals. These analyses have not considered the budgetary feasibility of vaccine programmes. We estimate the maximum total cost that the public health sectors in India and China should expect to pay to introduce a M72/AS01$_E$-like vaccine deemed cost-effective at country-specific willingness to pay thresholds for cost-effectiveness. To estimate the total disability adjusted life years (DALYs) averted by the vaccination programme, we simulated a 50% efficacy vaccine providing 10-years of protection in post-infection populations between 2027 and 2050 in India and China using a dynamic transmission model of *M. tuberculosis*. We investigated two mass vaccination strategies, both delivered every 10-years achieving 70% coverage: Vaccinating adults and adolescents (age $\geq$10y), or only the most efficient 10-year age subgroup (defined as greatest DALYs averted per vaccine given). We used country-specific thresholds for cost-effectiveness to estimate the maximum total cost (C_{max}) a government should be willing to pay for each vaccination strategy. Adult/adolescent vaccination resulted in a C_{max} of \$21 billion (uncertainty interval [UI]: 16–27) in India, and \$15B (UI:12–29) in China at willingness to pay thresholds of \$264/DALY averted and \$3650/DALY averted, respectively. Vaccinating the highest efficiency age group (India: 50–59y; China: 60–69y) resulted in a C_{max} of \$5B (UI:4–6) in India and \$6B (UI:4–7) in China. Mass vaccination against tuberculosis of all adults and adolescents, deemed cost-effective, will likely impose a substantial budgetary burden. Targeted tuberculosis vaccination, deemed cost-effective, may represent a more affordable approach.

Keywords: tuberculosis; vaccine; model; affordability; budget; cost-effectiveness

Citation: Weerasuriya, C.K.; Harris, R.C.; Quaife, M.; McQuaid, C.F.; White, R.G.; Gomez, G.B. Affordability of Adult Tuberculosis Vaccination in India and China: A Dynamic Transmission Model-Based Analysis. *Vaccines* **2021**, *9*, 245. https://doi.org/10.3390/vaccines9030245

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1. Introduction

New tuberculosis vaccines have made substantial progress in the clinical development pipeline [1]. The phase IIb trial of M72/AS01$_E$ reported vaccine efficacy of 49.7% at 36 months in preventing pulmonary tuberculosis in adults with a previous history of tuberculosis infection [2]. Previous modelling studies suggest that new tuberculosis vaccines, particularly when delivered to adults or the elderly, may substantially contribute towards achieving global tuberculosis control targets [3–5].

These findings have renewed interest in deploying anti-tuberculosis vaccination to support achieving global tuberculosis control goals [6]. Previous studies of new or repurposed tuberculosis vaccines have consistently projected that vaccination is likely to be cost-effective [3,7].

Most studies that analysed cost-effectiveness have used willingness-to-pay (WTP) thresholds that only indicate if an intervention is good (or poor) value for money at the margin [8]. Historically, such analyses have used demand-side thresholds (e.g., multiples of gross domestic product per capita). Demand-side thresholds have been criticized for not reflecting country-level affordability of interventions. Alternative methods have been recently proposed, such as supply-side country-level WTP thresholds based on the marginal productivity of their respective healthcare systems [9,10].

Despite these developments, most studies that establish cost-effectiveness have not assessed the affordability of vaccination programmes [11]. Affordability is particularly relevant to vaccination programmes, which while often cost-effective, must be deployed at a large scale. Discrepancies between cost-effectiveness and affordability may arise due to the methods of WTP threshold estimation. Demand-side thresholds are typically exogenously determined, without consideration of other interventions provided by the health system, the overall healthcare budget, or the different timing of costs and benefits of vaccination. Supply-side WTP thresholds, although linked to local healthcare budgets, have raised concerns of transferability across settings. Widely cited examples of such conflicting results include the provision of directly acting antiviral drugs for Hepatitis C [12,13] and the use of Gene Xpert rapid molecular diagnostic testing for tuberculosis [14,15].

Tuberculosis vaccination delivered to adults is likely to require large-scale mass campaigns. This represents a very large target population for two of the countries with the greatest number of incident TB cases: China and India. While previous studies have found that adult and elderly TB vaccination may be cost-effective [3,7], no studies have investigated whether mass vaccination programmes costed based on their maximum cost-effective value to the healthcare systems could be affordable.

In this study, we estimate the maximum cost of a cost-effective, large-scale adult TB vaccine programme in China and India, assuming country-specific willingness to pay per DALY averted thresholds under varying vaccine implementations. Finally, we discuss the affordability implications of these estimates in the context of tuberculosis-specific and general expenditure by the public health sectors of India and China.

2. Materials and Methods

2.1. Transmission Model

We developed an age-, treatment-history and drug-resistance stratified compartmental dynamic transmission model of tuberculosis. The model, parameters, calibration and data sources are described in full elsewhere [7]. Briefly, uninfected (susceptible) individuals who acquired *Mycobacterium tuberculosis* (M. tb) infection could transition directly to active (infectious or non-infectious disease) or to latent tuberculosis infection (LTBI). Individuals with LTBI could reactivate to active disease. From active disease, individuals could be initiated on TB treatment, self-cure or die. Following successful treatment or self-cure, individuals transitioned to the resolved state from where they could relapse back to active disease. Individuals could also be infected by drug-susceptible TB and develop drug-resistance on treatment or be infected by drug-resistant M. tb. A diagram detailing model compartments and flows is presented in Weerasuriya et al. [7] (additional File 1, Figure S1). We calibrated the model to historical epidemiologic data in India and China from 2000 to 2018 and projected TB epidemiology over 2018 to 2050, in line with TB control milestones and timelines specified in the WHO End TB goals [16–18]. In the baseline (no-vaccine) scenario, programmatic management of TB was unchanged after 2018. Final projections were derived through the aggregation of results from 1000 fully calibrated parameter sets.

2.2. Vaccine Implementation

We simulated vaccination from 2027 onwards and compared the vaccine-enabled model output with corresponding unvaccinated baseline model output to estimate vaccine impact over 2027–2050. We assumed characteristics aligned with M72/AS01$_E$ and modelled a vaccine with 50% efficacy conferring 10-years of protection. The vaccine protected against

disease, but not infection by M. tb, and was assumed to be effective only in those with a previous history of infection by M. tb (referred to as a "post-infection" efficacy vaccine). We did not explicitly model existing neonatal Bacillus Calmette–Guérin (BCG) immunisation programmes, as the effect of BCG was assumed to be reflected in the baseline epidemiology through model calibration targets. The vaccine was administered to individuals with neither active disease nor who were receiving treatment for TB and mediated its effect through reducing the rate of progression to active disease following infection and reducing the rate of reactivation or relapse from latent disease or a recovered state. Vaccine waning was assumed to be instant at the end of the duration of protection.

We investigated two scenarios of adult and adolescent mass vaccination: "all age" and "targeted".

2.2.1. All-Age Vaccination

In all age vaccination, vaccination was delivered to all ages ≥10 years through mass campaigns delivered in 2027, 2037 and 2047. Vaccines were assumed to be delivered within a single calendar year. As there was no direct analogue for all-age mass vaccination of adults in India or China on which to base probable vaccine coverage, we assumed a value of 70% based on a composite of sources: (a) Menafrivac campaigns delivered to 1–29-year-olds in South Africa, which achieved coverage of 70–98% [19]; (b) routine influenza vaccination in China [20,21], achieving coverage of 36–49%; and (c) Japanese encephalitis mass adult vaccination campaigns in India [22], achieving coverage of 58%. Both influenza and Japanese encephalitis campaigns were delivered to populations that included the elderly. Since the all-age vaccination strategy we modelled also included the elderly, we opted for the lower estimate of Menafrivac coverage but performed sensitivity analyses by simulating coverage of 10% and 90%.

2.2.2. Targeted Vaccination

In the "targeted" scenario, vaccination was delivered to a 10-year wide age band through similar mass campaigns. For each country, this group was chosen by segmenting the population between 10 and 99 years into 10-year wide groups and identifying the group with the highest vaccination efficiency (defined as the number of DALYs averted per vaccine given). We assumed vaccine coverage of 70% to maintain comparability to the "all-age" strategy.

2.3. Vaccine Programme Cost Estimation

2.3.1. TB Programme Cost Model

We used an ingredients-based approach to estimate the (non-vaccine) TB control programme costs from the public healthcare sector perspective. We applied country-specific unit costs to diagnosis, including drug-sensitivity testing and treatment for both drug-sensitive and drug-resistant TB. For India, we additionally included costs borne by the public healthcare sector for nutritional support to TB patients on treatment and incentive payments to the private healthcare sector. A full description of unit costs, including sources, is given in Weerasuriya et al. [7]. The cost-model was restricted to direct costs to the TB programme.

2.3.2. Costs and Benefits of Vaccines and Vaccine Programmes

We measured the health benefit of vaccination in disability-adjusted life years (DALYs) lost by tuberculosis. DALYs were calculated by applying disability weights for tuberculosis per the Global Burden of Disease study [23] and conditional life expectancy per the UN World Population Prospects [24]. The effectiveness of vaccination was then estimated as DALYs averted comparing the vaccine scenario to the baseline (non-vaccine) scenario.

We estimated the maximum total cost of a vaccination programme the public health sector should be willing to pay, thus the intervention remained cost-effective given our

assumed vaccine characteristics and implementation strategies. The maximum total cost of a vaccination programme (C_{max}) was calculated as follows:

$$C_{max} = (WTP \times \Delta DALYs) - (C_V - C_B) \quad (1)$$

Where WTP is the willingness to pay threshold per DALY averted; ΔDALYs are the DALYs averted comparing the vaccine scenario to the baseline (non-vaccine) scenario; and C_v and C_B are the total costs of the TB programme in the vaccine and baseline scenarios, respectively. The term WTP×ΔDALY represents the monetary value of DALYs averted by vaccination, whereas the term (C_V-C_B) represents the net cost-savings in the TB programme due to reduced TB burden. C_{max} represents the maximum incremental cost the buyer should be willing to pay for vaccination. The incremental cost-effectiveness ratio for vaccination is equal to the willingness-to-pay threshold. A particular vaccine implementation that averted more DALYs would lead to a higher C_{max} value, reflecting greater value provided to the health system.

We also calculated the maximum total cost per course of vaccination (including dose, delivery and programmatic costs) that the public health sector should be willing to pay, subject to assumptions above, as C_{max} divided by the number of vaccines delivered. For a given WTP threshold, a higher cost per vaccine course was interpreted as the additional cost per course that a payer should be willing to pay for the greater number of DALYs averted per vaccine course.

The country-specific willingness-to-pay thresholds were taken from Ochalek et al. [9]. This study estimated the elasticity of mortality outcomes, survival and morbidity burdens of disease with respect to public healthcare expenditure to derive the estimated number of DALYs averted by a 1% change in healthcare expenditure. The reciprocal of this value—the cost per DALY averted—estimated the marginal productivity of the health system, i.e., the opportunity cost of healthcare spending on a given intervention. These values represented a supply-side estimate of willingness-to-pay per DALY averted grounded in country-specific healthcare expenditure and budgets. Ochalek el al. provided 4 estimates per country, reflecting slightly different assumptions in their calculations. In this analysis, we used the lowest and highest estimates, for India estimated at $264 and $363 and for China at $3650 and $5669 per DALY averted, respectively. Given that WHO now encourages the use of country-based thresholds instead of GDP-based thresholds [8], and given that the country-specific thresholds are substantially lower than GDP per capita estimates for both India and China, demand-side thresholds based on GDP per capita were excluded from our analysis.

We discounted costs and health benefits at 3% to 2018 values in the base case analysis, per standards from the Gates reference case for economic evaluation [25]. Rates were set at 3% in both India and China to ensure comparability. Undiscounted results were presented as a sensitivity analysis in supplementary material section 1.1, Figures S1 and S2, and Table S1. All costs are presented in USD.

2.4. Baseline Scenario Analysis

To capture uncertainty in future health system investments, we defined an alternative "Policy" baseline scenario, representing a scale-up of programmatic TB management for each country.

For China, the Policy scenario was informed by country expert opinion [7] and comprised 2 changes. First, we linearly scaled-up drug-susceptibility testing coverage to 90% from 2018 to 2036. Second, we introduced a standard 9-month RR/MDR-TB treatment besides the baseline 24-month regimen, maintaining the same treatment success rate across both regimens. The proportion of drug-resistant TB treated with the 9-month regimen was linearly increased to 40% of all second-line therapy from 2018 to 2036.

For India, we used the National Strategic Plan of the Indian Revised National Tuberculosis Control Programme [26] to inform the Policy scenario. We implemented three changes: (a) Increased case detection rate (combined across private and public sectors)

from approximately 60% to 85%; (b) increased drug-susceptibility testing coverage among public sector notifications to 100%; and (c) increased proportion of notifications originating from the private sector to 35%, all from 2018 to 2025.

2.5. Patient and Public Involvement

Patients were not involved in the conduct of this study.

3. Results

3.1. All-Age Vaccination

3.1.1. Averted Burden

A post-infection 50% efficacy vaccine conferring 10-years of protection, delivered to all adults (aged ≥10 years) at 10-yearly intervals at coverages of 10%, 70% and 90%, was predicted to avert 8.3 (Uncertainty Interval [UI]: 6.5–10.5) million, 52.7 (UI 42.8–65.2) million and 65.7 (UI 53.6–80.9) million DALYs by 2050 in India, corresponding to 0.021 (UI 0.016–0.026), 0.019 (UI 0.015–0.023) and 0.018 (UI 0.015–0.023) DALYs averted per vaccine delivered.

In China, vaccination at coverages of 10%, 70% and 90%, was predicted to avert 0.5 (UI 0.4–0.7) million, 3.8 (UI 3.0–4.9) million and 4.8 (UI 3.8–6.3) million DALYs by 2050, corresponding to 0.001 (UI 0.001–0.002), 0.001 (UI 0.001–0.002) and 0.001 (UI 0.001–0.002) DALYs averted per vaccine delivered.

3.1.2. Maximum Vaccination Programme Cost

The maximum total cost of a vaccination programme for all age vaccination to remain cost-effective and the predicted total cost per vaccine course are presented in Table 1, Figures 1 and 2, respectively.

In India, mass vaccination of all adults at 70% coverage was predicted to cost up to $21 (UI 16–27) billion and $26 (UI 21–33) billion at the lower and upper WTP thresholds of $264 and $363 per DALY averted, respectively. This corresponded to a maximum total cost per course of $7 (UI 6–10) and $9 (UI 7–12) for the approximately 3 (UI 3–3) billion vaccines delivered to remain cost-effective.

In China, mass vaccination of all adults at 70% coverage was predicted to cost up to $15 (UI 12–19) billion and $23 (UI 18–29) billion at the lower and upper WTP thresholds of $3650 and $5669 per DALY averted, respectively. This corresponded to a maximum total cost per course of $5 (UI 4–7) and $8 (UI 7–11) for the approximately 3 (UI 3–3) billion vaccines delivered to remain cost-effective.

Table 1. Mass vaccine campaigns. Targeted vaccination in India was delivered to ages 50–59 and in China to ages 60–69. Results are aggregated over three campaigns delivered in 2027, 2037 and 2047. Averted DALYs and estimated net vaccine implementation costs are discounted to 2018 values at 3% per year. WTP: Willingness to pay.

Country	Campaign	Averted DALYs (Total) [a]	Averted DALYs (per Vaccine)	Vaccinations Delivered [b]	WTP Threshold (DALY Averted)	Maximum Total Vaccine Programme Cost	Maximum Total Cost per Vaccine Course
India	All Ages	52.67M (42.79–65.18)	0.019 (0.015–0.023)	2.79B (2.78–2.80)	$264 $363	$21B (16–27) $26B (21–33)	$7 (6–10) $9 (7–12)
	Targeted	12.69M (10.27–15.46)	0.031 (0.025–0.038)	0.41B (0.41–0.41)	$264 $363	$5B (4–6) $6B (5–8)	$13 (10–16) $16 (12–20)
China	All Ages	3.79M (2.96–4.89)	0.001 (0.001–0.002)	2.75B (2.75–2.75)	$3650 $5669	$15B (12–19) $23B (18–29)	$5 (4–7) $8 (7–11)
	Targeted	1.40M (1.03–1.79)	0.003 (0.002–0.004)	0.45B (0.45–0.45)	$3650 $5669	$6B (4–7) $8B (6–10)	$12 (9–15) $19 (14–23)

[a] M = millions; [b] B = billions.

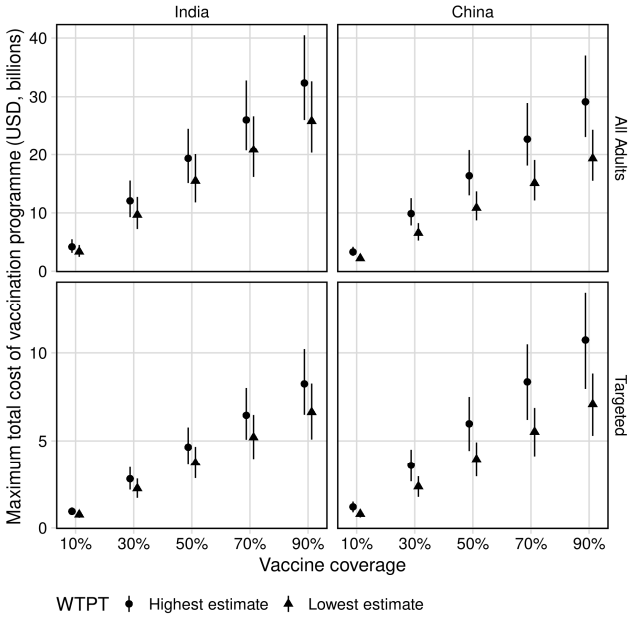

Figure 1. Maximum total vaccine programme cost. Top panels represent all-age vaccination (adults ≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = willingness to pay thresholds per Ochalek et al. [9], estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs discounted to 2018 values.

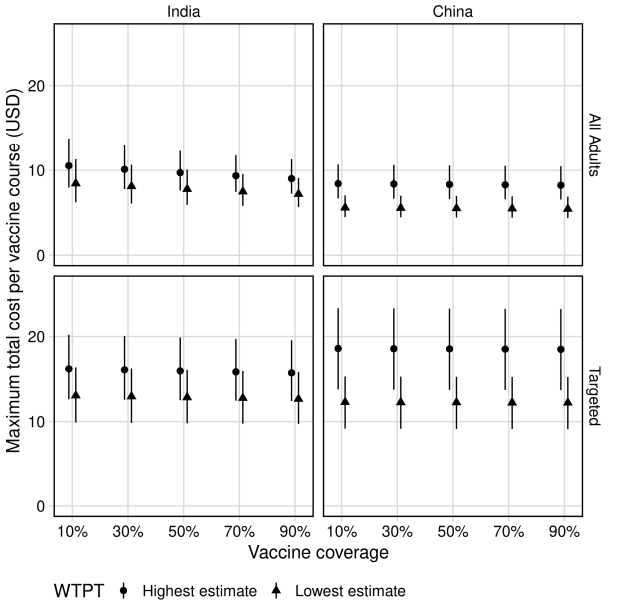

Figure 2. Maximum total cost per vaccine course. Top panels represent all-age vaccination (adults ≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = country-specific willingness to pay thresholds per Ochalek et al. [9], estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs discounted to 2018 values.

3.2. Targeted Vaccination

3.2.1. Optimal Target Age Groups and Averted Burden

The predicted efficiency of vaccination (in terms of DALYs averted per vaccine delivered) is presented in Table 1 and Figure 3. Age-specific TB prevalence in the underlying transmission model is presented in supplementary material section 1.2, Figures S3 and S4.

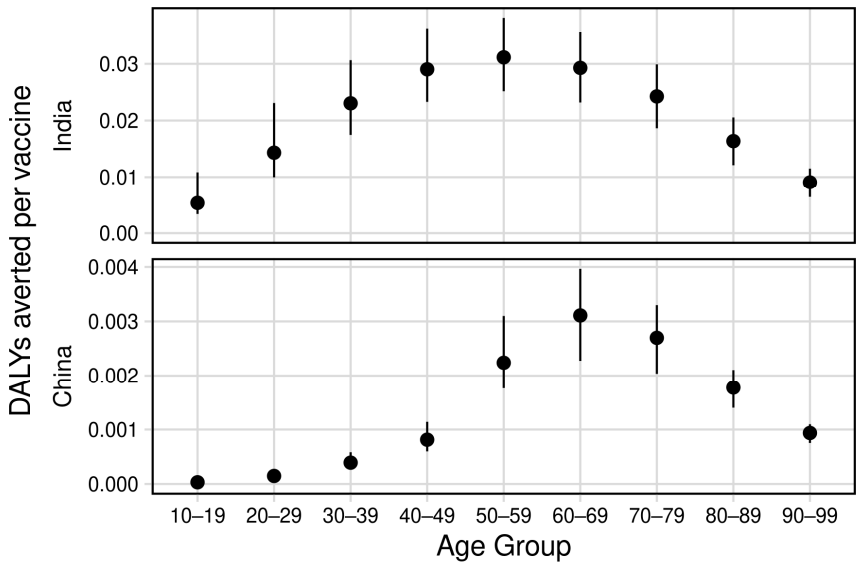

Figure 3. Vaccination efficiency by target age group. Efficiency is defined as the number of DALYs averted per vaccine delivered. Mass vaccine campaigns were deployed at 70% coverage to each age group.

In India, we found that vaccination of 50–59-year-olds was most efficient (Figure 3), with 70% vaccine coverage averting 12.7 (UI 10.3–15.5) million DALYs by 2050, corresponding to 0.031 (UI 0.025–0.038) DALYs averted per vaccine delivered over 407 (UI 405–410) million vaccines. Vaccination of the adjacent age groups 40–49 and 60–69 years yielded similar efficiencies of 0.031 (UI 0.025–0.038) and 0.031 (UI 0.025–0.038) DALYs averted per vaccine delivered, respectively.

In China, we found that the most efficient age group for vaccination was older, between 60–69-year-olds, averting 1.4 (UI 1.0–1.8) million DALYs by 2050, corresponding to 0.003 (UI 0.002–0.004) DALYs averted per vaccine delivered over 451 (UI 451–452) million vaccines. In contrast to India, the optimum age group was more sharply defined, with a greater difference compared to vaccination of adjacent age groups (Figure 3). Fewer DALYs were averted per vaccine delivered across all age-groups in China compared to India.

3.2.2. Maximum Vaccination Programme Cost

The maximum total cost of a vaccine programme for targeted vaccination to remain cost-effective and the predicted total cost per vaccine course are presented in Table 1, Figures 1 and 2, respectively.

In India, mass vaccination of adults aged 50–59 at 70% coverage was predicted to cost up to $5 (UI 4–6) billion and $6 (UI 5–8) billion at the lower and upper WTP thresholds of $264 and $363 per DALY averted, respectively. This corresponded to a maximum total course per vaccine course of $13 (UI 10–16) and $16 (UI 12–20) for the approximately 407 (UI 405–410) million vaccines delivered to remain cost-effective.

In China, mass vaccination of adults aged 60–69 at 70% coverage was predicted to cost up to $6 (UI 4–7) billion and $8 (UI 6–10) billion at the lower and upper WTP thresholds of $3650 and $5669 per DALY averted, respectively. This corresponded to a total cost per

vaccine course of $12 (UI 9–15) and $19 (UI 14–23) for approximately 451 (UI 451–452) million vaccines delivered to remain cost-effective.

3.3. Policy Scenario Analysis

In India, when (non-vaccine) TB programme activities were scaled up, targeted vaccination at 70% coverage was predicted to cost up to $5 (UI 4–7) billion and $4 (UI 3–5) billion at the upper and lower WTP thresholds, respectively, corresponding to a maximum total cost per vaccine course of $13 (UI 10–16) and $11 (UI 8–13). In China, targeted vaccination at 70% coverage was predicted cost up to $8 (UI 6–10) billion and $5 (UI 4–7) billion at the lower and upper WTP thresholds, respectively, corresponding to a maximum total cost per vaccine course of $18 (UI 13–23) and $12 (UI 9–15). In both countries, the maximum costs for a cost-effective vaccination programme in the policy scenario were lower than for the baseline scenario without TB programme scale-up, reflecting a lower avertible burden of TB by vaccination. This effect was substantially smaller in China than India. This reflected the future TB programme scale-up strategy, which in China focused on increased case detection and treatment of drug-resistant tuberculosis, while in India was focussed on both drug-sensitive and drug-resistant tuberculosis. Complete results for the policy scenario are given in supplementary material section 1.3, Figures S5–S9, and Tables S2 and S3.

4. Discussion

Cost-effective mass vaccination of adults and adolescents aged $\geq$10 years against tuberculosis in India was estimated to cost $26B and $21B at high ($363/DALY averted) and low ($264/DALY averted) willingness-to-pay (WTP) thresholds, respectively, over 2027–2050, corresponding to a total cost per vaccine course (including dose, delivery and programmatic costs) of $9 and $7, respectively. In China, cost-effective mass vaccination using the same strategy was predicted to cost $23B and $15B at high ($3650/DALY averted) and low ($5669/DALY averted) WTP thresholds, respectively, corresponding to a total cost per vaccine course of $8 and $5, respectively. Cost-effective mass vaccination of a targeted high-efficiency age group was predicted to incur lower total costs but higher costs per course of vaccine than mass vaccination of all ages. In India, vaccinating ages 50–59 was predicted to cost $6B and $5B at the high and low thresholds, respectively, over 2027–2050, corresponding to a total cost per course of $16 and $13. In China, vaccinating ages 60–69 was predicted to cost $8B and $6B at the high and low thresholds, respectively, by 2050, corresponding to a maximum total cost per vaccine course of $19 and $12.

Increased investment in the (non-vaccine) TB programme led to substantial reductions in the estimated maximum vaccination programme costs in India, with moderate reductions in China. This follows from lower TB case detection rates in India [16] than China of both drug-sensitive and drug-resistant TB at baseline, which translates into a greater burden of averted disease due to programmatic scale up. Moreover, the planned scale-up of programmatic TB management was greater in India than in China.

Each vaccine course averted more DALYs and delivered more value to the health system in the targeted vaccination scenario compared with the "all-age" scenario. Therefore, at a given willingness to pay threshold, the total cost per vaccine course that the health system should be willing to pay was correspondingly higher in the targeted than all age scenarios. Assuming the vaccine price borne by the health system is independent of the implementation scenario, this would translate to proportionately more funds available for programmatic aspects of vaccination (e.g., logistics, campaign organisation).

4.1. In Context

Our study suggests that an all-age adult and adolescent mass tuberculosis vaccination programme, considered cost-effective at country-specific cost-effectiveness thresholds, would impose a substantial budgetary burden on the health system in India and China. We estimated the maximum cost of such a vaccination programme at the lowest WTP threshold to be $21B (UI 16–27) and $15B (UI 12–19) in India and China, respectively, for

three vaccination campaigns in 2027, 2037 and 2047. In comparison, annual universal infant vaccination programmes in India and China are estimated to cost approximately $700 million (2013–14 levels, adjusted to 2017 prices) [27] and $1B (2015 levels) [28], respectively, while the World Health Organization estimates the total annual budgets available for national strategic plans for tuberculosis in India and China at $583 million and $719 million in 2019, respectively. In this context, targeted vaccination may represent a more affordable approach. The maximum cost of a cost-effective vaccination programme targeted to the highest efficiency 10-year age group was estimated at between $5B (UI 4–6) and $6B (UI 4–7) in India and China, respectively, for three vaccination campaigns over 2027–2050. While routine infant vaccination is not a direct comparator to spaced adult and adolescent mass vaccination campaigns, this approximate comparison suggests that the maximum estimated costs of cost-effective targeted TB vaccination may be comparable to existing and funded health interventions. However, routine infant vaccination provides multiple doses against multiple conditions per fully immunised child.

Our findings suggest that cost-effectiveness estimates, even with supply-side WTP thresholds, will likely provide an incomplete assessment of the economic feasibility of mass TB vaccination in India and China to decision makers, as they do not reflect the probable budget impact of such a programme. Further, marginal WTP thresholds may inadequately capture the health opportunity costs of interventions, which incur very high expenditures [29]. Decision makers should, therefore, carefully assess the appropriateness of WTP thresholds used in the economic evaluation of TB vaccines. This study also demonstrates the use of a dynamic model to identify a high-efficiency subgroup for vaccine targeting. While age alone may be an insufficient criterion on which to base targeting strategies, this approach may be generalisable to identify other risk groups or stratifications, which can maximise efficiency.

We present total cost-estimates of national vaccination programmes in both India and China. Both countries have complex health systems with healthcare provisions devolved to subnational administrative divisions, with variation in TB epidemiology, costs of providing programmatic TB management and immunisation services. Regional affordability of mass vaccination is likely to be sensitive to these local factors. Future studies could explore such factors to assess affordability at the regional level.

4.2. Willingness to Pay Thresholds

In this study, we used healthcare opportunity cost-based willingness to pay thresholds substantially lower than demand-side WTP thresholds (for example, based on GDP per capita) for India and China. If country decision makers were to adopt thresholds higher than the supply-side estimates we used in decision-making around tuberculosis vaccine programme financing, our cost estimates would be conservative. However, given that our total vaccination programme costs estimates were still substantial, this suggests that TB vaccines or vaccination cost-effective at GDP thresholds would be infeasible without substantial increases in healthcare expenditure beyond current levels, particularly in India.

4.3. Strengths and Limitations of This Study

We highlight two main limitations in our estimates of vaccine impact: (a) Paucity of data to substantiate vaccine deployment scenarios and their costs; (b) limitations in the deployed vaccine scenario.

There is no existing precedent for large, national, all-adult and adolescent vaccination campaigns in India or China. Assumptions around achievable coverage (particularly by age) are extrapolated from experience in other settings or age groups. We implemented mass vaccine campaigns within a single year rather than as a gradual scale-up of coverage and presented the maximum total cost of vaccination over three mass campaigns. The budget impact of the vaccination programme during each one of these three campaign years is considerable and not directly comparable to savings in the non-vaccine TB programme during inter-campaign years. Despite recent examples of COVID-19 vaccination rates, large-

scale adult mass vaccination for tuberculosis may be delivered in multi-year campaigns. This would distribute budget impact over time. Vaccine waning is modelled as instant at the end of the duration of protection. This underestimated ongoing waning during inter-campaign years and during phased multi-year campaigns, leading to a likely overestimate of averted burden and of total maximum cost.

Our estimates of vaccine efficiency by 10-year age groups may also be affected by the lack of age-specific TB burden data. The underlying transmission model [7] was calibrated to age-specific data (children aged <15 years and adults aged ≥15 years) in both India and China. We found good concordance between empirical and modelled TB prevalence estimates by 10-year age group in China (Figure S1). However, nationally representative age-specific empirical estimates for India do not currently exist. Although TB prevalence predicted by the model for India (Figure S2) is consistent with *a priori* assumptions regarding the age-distribution of disease burden, these may be an over- or under-estimate. Without further data, it is difficult to deduce how this might bias our estimated total cost of "targeted" mass vaccination.

We selected an age-group for the "targeted" implementation scenario based solely on vaccine efficiency. Total cost estimates may be an underestimate, as our analysis does not consider other priorities, e.g., targeting at-risk groups or equity considerations, which are often important features of vaccination programmes. As there is no data to inform this relationship, we assume that vaccine efficacy is invariant with age. Higher rates of vaccine failure and poorer vaccine responses are reported for influenza, pneumococcal and herpes zoster vaccines, amongst others [30]. If such a phenomenon were reported for new TB vaccines, the highest efficiency age groups may change.

A strength of this study is that we make no assumptions regarding the composition of vaccination programme costs (e.g., unit or programmatic costs), nor how this composition might vary with implementation (e.g., at different coverage levels, or by targeting to specific age groups). By modelling vaccines through a dynamic transmission model, we capture both the direct and indirect (transmission) effects of vaccination on TB burden and the corresponding impact on changes to the non-vaccine TB programme, which are incorporated into our estimates of total cost. Furthermore, our estimates incorporated the (averted) costs of drug-resistant tuberculosis: The underlying transmission model included a fully dynamic representation of resistance acquisition and transmission. The model was calibrated to rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) incidence and notification data in India and China. The underlying cost-model included country-specific estimates of RR/MDR-TB diagnosis and treatment costs and drug-sensitivity testing costs.

5. Conclusions

We found that cost-effective mass vaccination against tuberculosis of all adults and adolescents will likely impose a substantial budgetary burden on health systems in India and China. Cost-effective targeted tuberculosis vaccination, for example, by age, may represent a more affordable approach while also allowing greater expenditure per vaccine course delivered.

Supplementary Materials: The following are available online at https://www.mdpi.com/2076-393X/9/3/245/s1, Figure S1: Prevalence rate of tuberculosis in China in 2000, 2010 and 2050. Figure S2: Prevalence rate of tuberculosis in India in 2000, 2010 and 2050. Figure S3: Maximum total vaccine programme cost in the Policy baseline scenario. Figure S4: Maximum total cost per vaccine course in the Policy baseline scenario. Figure S5: Vaccination efficiency by target age group in the Policy scenario. Figure S6: Maximum total vaccine programme cost. Figure S7: Maximum total cost per vaccine course. Figure S8: Maximum total vaccine programme cost in the Policy scenario. Figure S9: Maximum total cost per vaccine course in the Policy scenario. Table S1: Mass vaccine campaigns (undiscounted). Table S2: Mass vaccine campaigns in the Policy scenario. Table S3: Mass vaccine campaigns in the Policy scenario (undiscounted).

Author Contributions: C.K.W. undertook conceptualisation, study design, programming, analysis, and manuscript writing. G.B.G. and R.G.W. contributed to conceptualisation. R.C.H., M.Q., C.F.M., R.G.W., and G.B.G. contributed to results interpretation and manuscript writing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: G.B.G. and R.C.H. report currently being employed at Sanofi Pasteur, unrelated to this work or TB. Sanofi Pasteur did not provide funding for this work and had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All other authors declare no competing interests.

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4.3 Online Supplementary Material

Reprint Notes The online supplementary materials were published in *Vaccines* with Research Paper 3. It is reprinted here as is. The original published version is available online at:
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Affordability of New Tuberculosis Vaccines in India and China: a Dynamic Transmission Model-based Analysis
Online Supplementary Materials

1 Additional results

1.1 Undiscounted Analysis

Total maximum undiscounted costs for the vaccine programme and per vaccine course are presented in Figure S1, Figure S2 and Table S1.

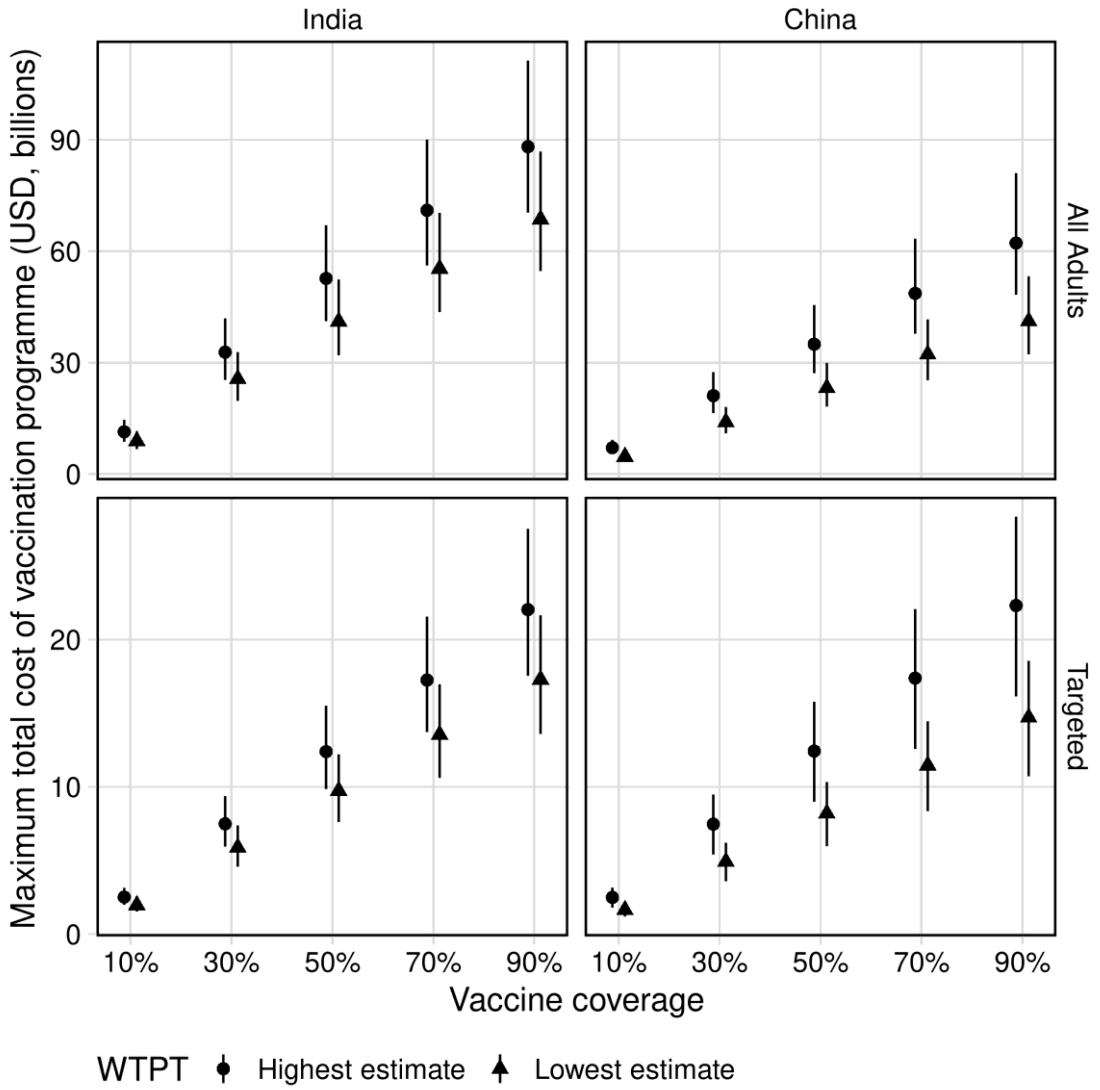

Figure S1: Maximum total vaccine programme cost. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs undiscounted.

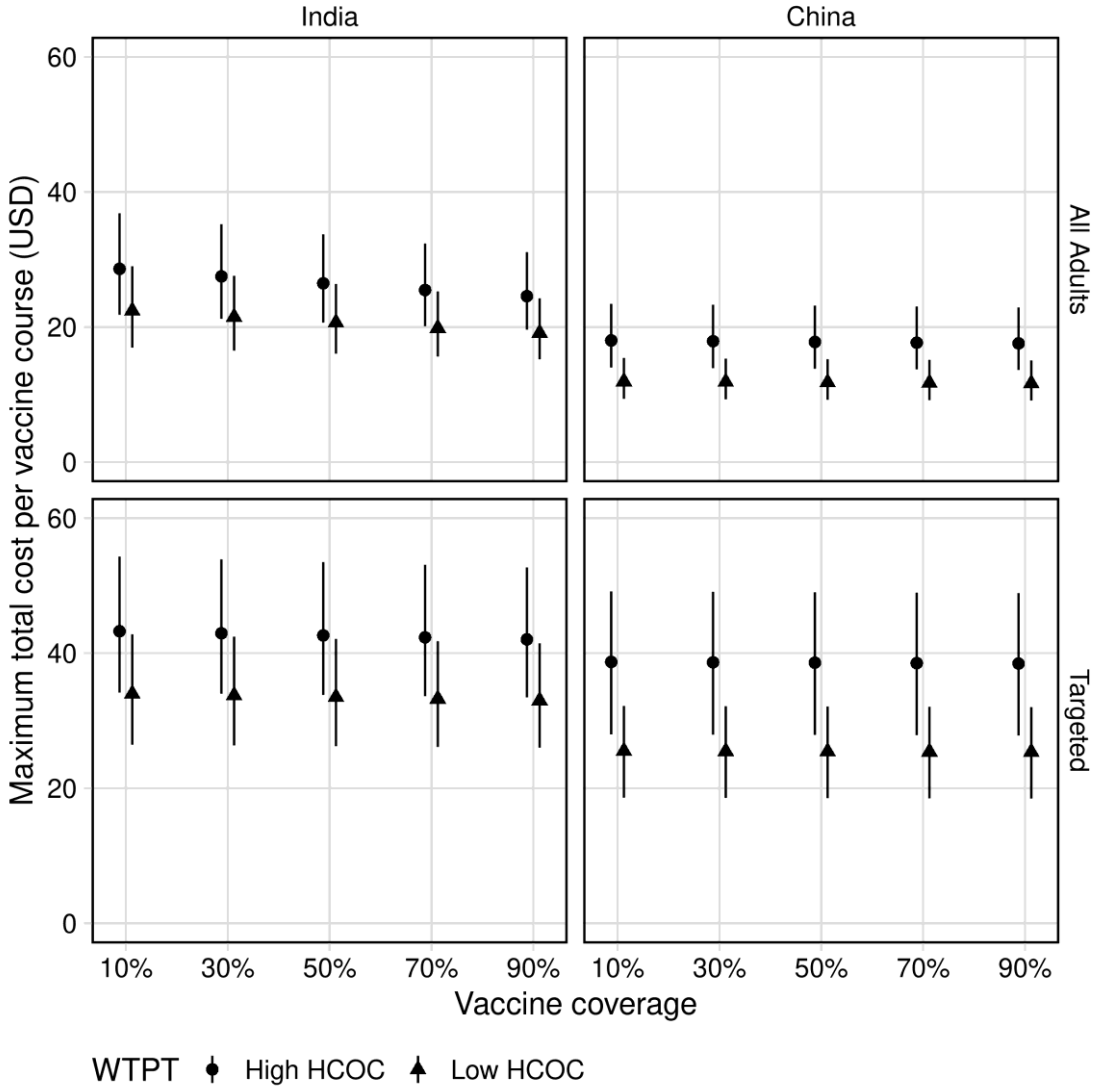

Figure S2: Maximum total cost per vaccine course. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = country-specific willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs undiscounted.

Table S1: Mass vaccine campaigns. Targeted vaccination in India was delivered to ages 50–59 and in China to ages 60–69. Results are aggregated over three campaigns delivered in 2027, 2037 and 2047. Averted DALYs and estimated net vaccine implementation costs are undiscounted. WTP: willingness to pay

Country	Campaign	Averted DALYs (total)[a]	Averted DALYs (per vaccine)	Vaccinations Delivered[b]	WTP	Maximum Total Cost of Vaccination Programme[b]	Maximum Total Cost per Vaccine Course
India	All Ages	158.21M (125.43–199.14)	0.057 (0.045–0.072)	2.79B (2.78–2.80)	264	$55B (44–70)	$20 (16–25)
					363	$71B (56–90)	$25 (20–32)
	Targeted	37.44M (29.15–46.41)	0.092 (0.071–0.114)	0.41B (0.41–0.41)	264	$14B (11–17)	$33 (26–42)
					363	$17B (14–22)	$42 (34–53)
China	All Ages	8.14M (6.21–10.76)	0.003 (0.002–0.004)	2.75B (2.75–2.75)	3,650	$32B (25–42)	$12 (9–15)
					5,669	$49B (38–63)	$18 (14–23)
	Targeted	2.93M (2.09–3.77)	0.007 (0.005–0.008)	0.45B (0.45–0.45)	3,650	$11B (8–14)	$25 (18–32)
					5,669	$17B (13–22)	$39 (28–49)

[a]M=millions

[b]B=billions

1.2 Age-specific prevalence

Model estimates of age-specific prevalence rates for tuberculosis in 2000, 2010 and 2050 are provided in Figures S3 (China) and S4 (India). In both countries, prevalence rate fell continuously from 2000 to 2050. In China (Figure S3), model estimates are shown against age-specific empirical estimates of TB prevalence rate derived from data underlying nationally representative TB prevalence surveys in 5-year age-groups in 2000 and 2010. We found good concordance between available data and model estimates in most age-groups, with slightly higher divergence in the elderly.

Figure S4 shows the age-specific prevalence rates estimated for India. There are no currently available nationally representative age-stratified estimates for TB prevalence, therefore corresponding empirical data are not shown. Similar to the pattern seen in China, the prevalence rate increased with age; however, the relative burden in the elderly (age≥65) was not as great in India.

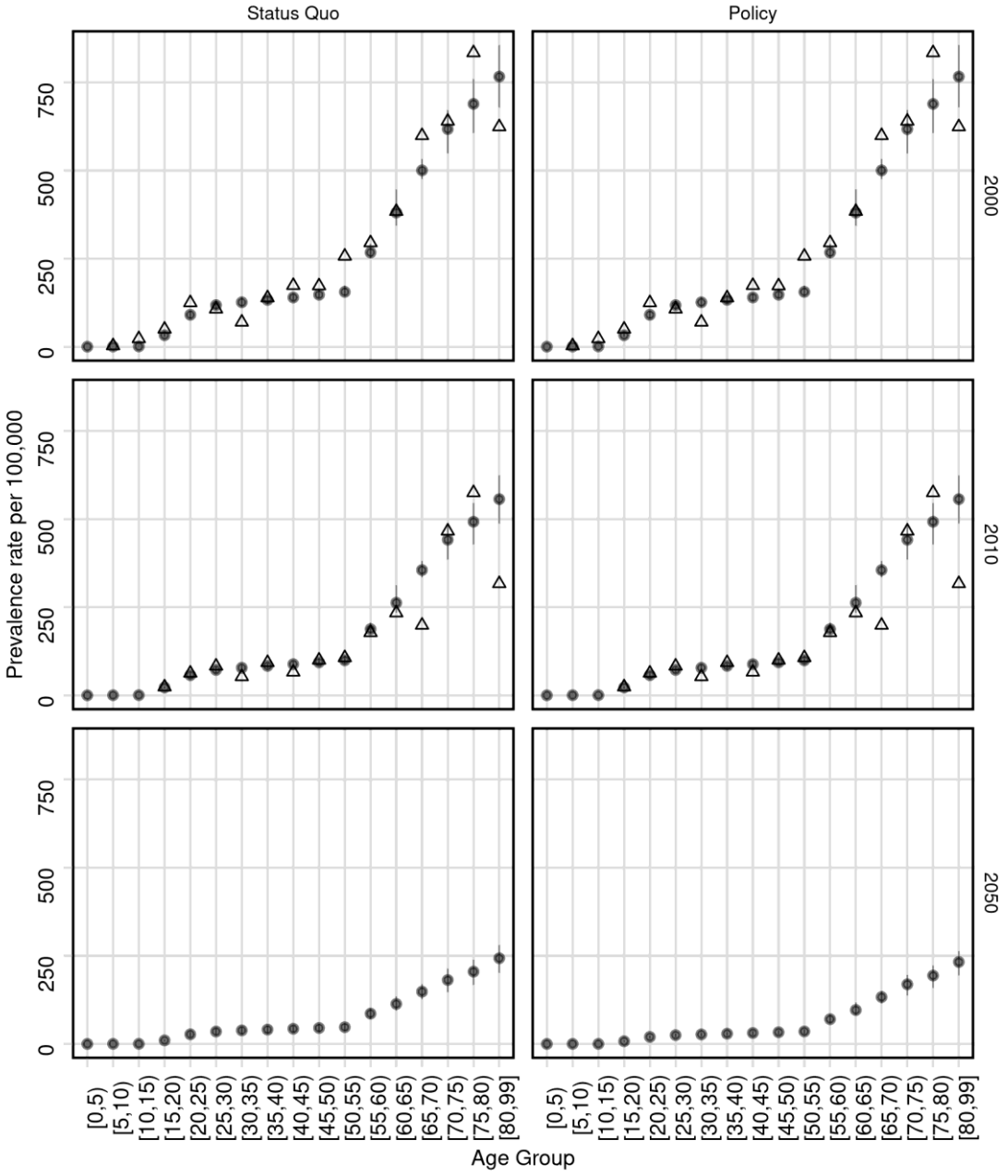

Figure S3: Prevalence rate of tuberculosis in China in 2000, 2010 and 2050. Points represent median model estimates, bars represent uncertainty. Triangles represent empirical estimates.

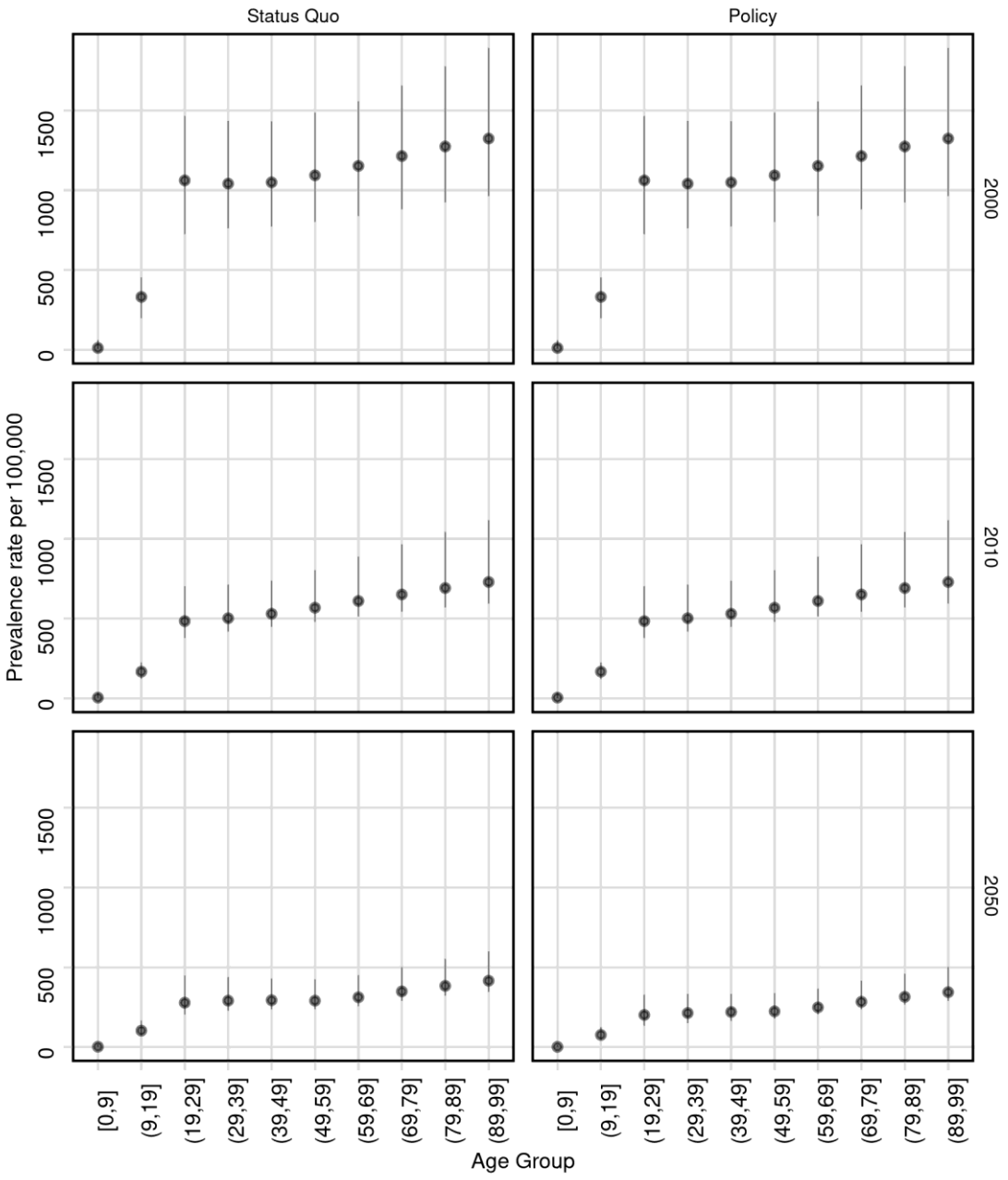

Figure S4: Prevalence rate of tuberculosis in India in 2000, 2010 and 2050. Points represent median model estimates, bars represent uncertainty.

1.3 Policy scenario

The estimated maximum total costs of the vaccination programme and estimated maximum total costs per vaccine course in the "Policy" scenario are presented in Figure S5, Figure S6 and Table S2. For both all age and targeted vaccination strategies, across all levels of coverage, estimated maximum total vaccine programme costs and maximum total costs per vaccine course were lower than in the converse baseline scenario without scale up of TB programme. Correspondingly, estimated averted DALYs per vaccine given (Figure S7) were found to be slightly lower. Total maximum undiscounted costs for the vaccine programme and per vaccine course in the Policy scenario are presented in Figure S8, Figure S9 and Table S3.

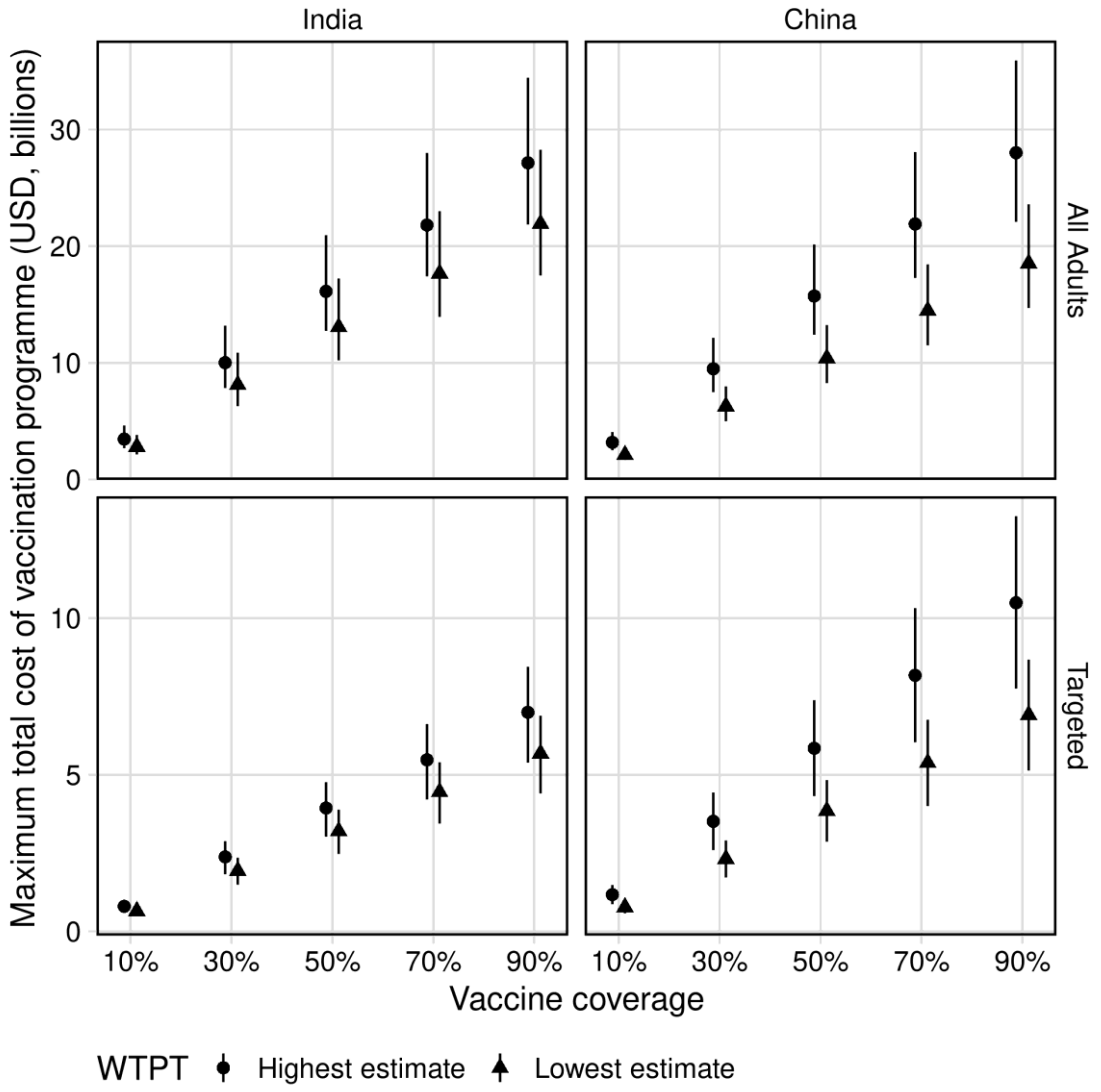

Figure S5: Maximum total vaccine programme cost in the Policy scenario. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs discounted to 2018 values.

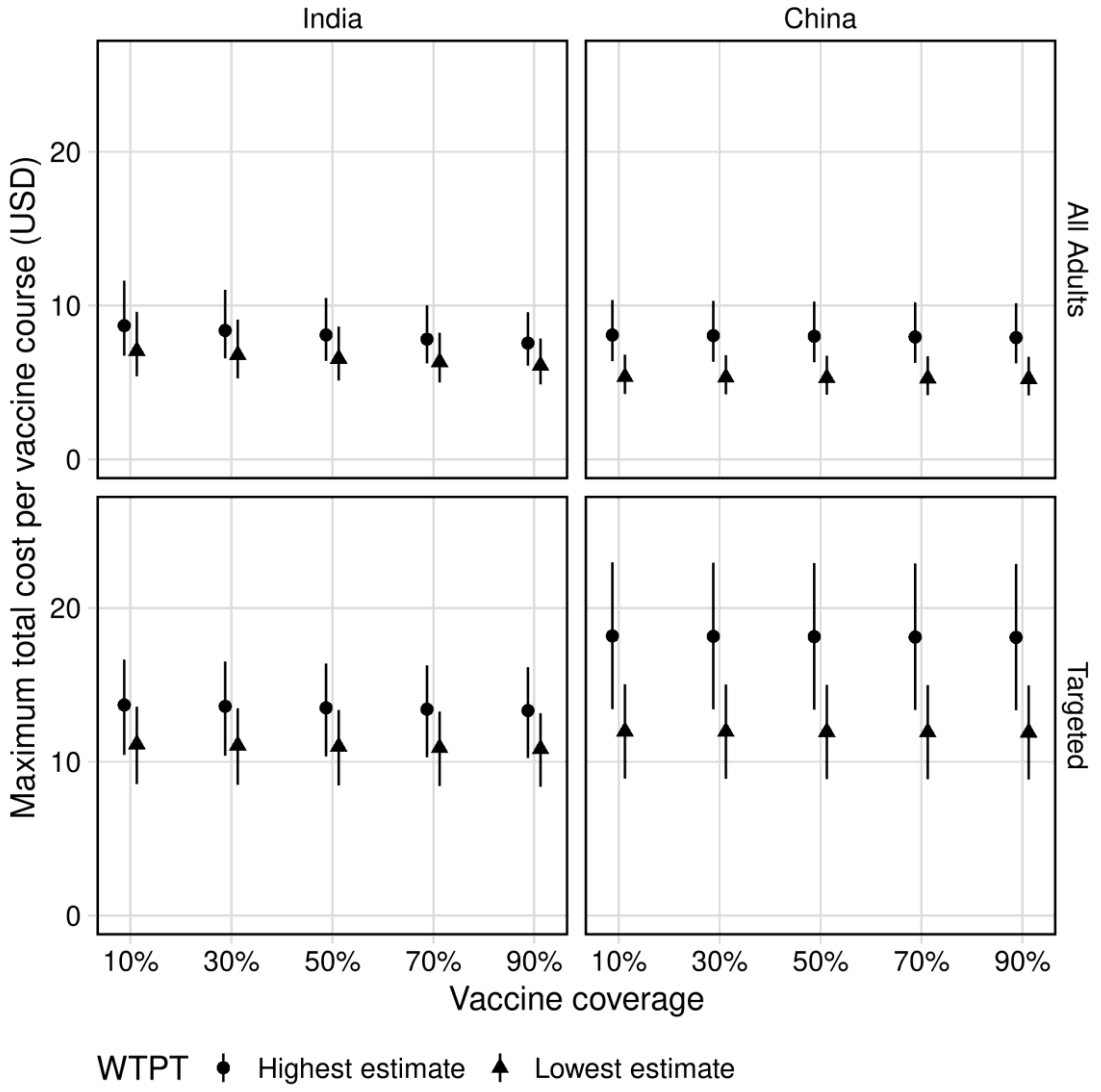

Figure S6: Maximum total cost per vaccine course in the Policy scenario. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = country-specific willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs discounted to 2018 values.

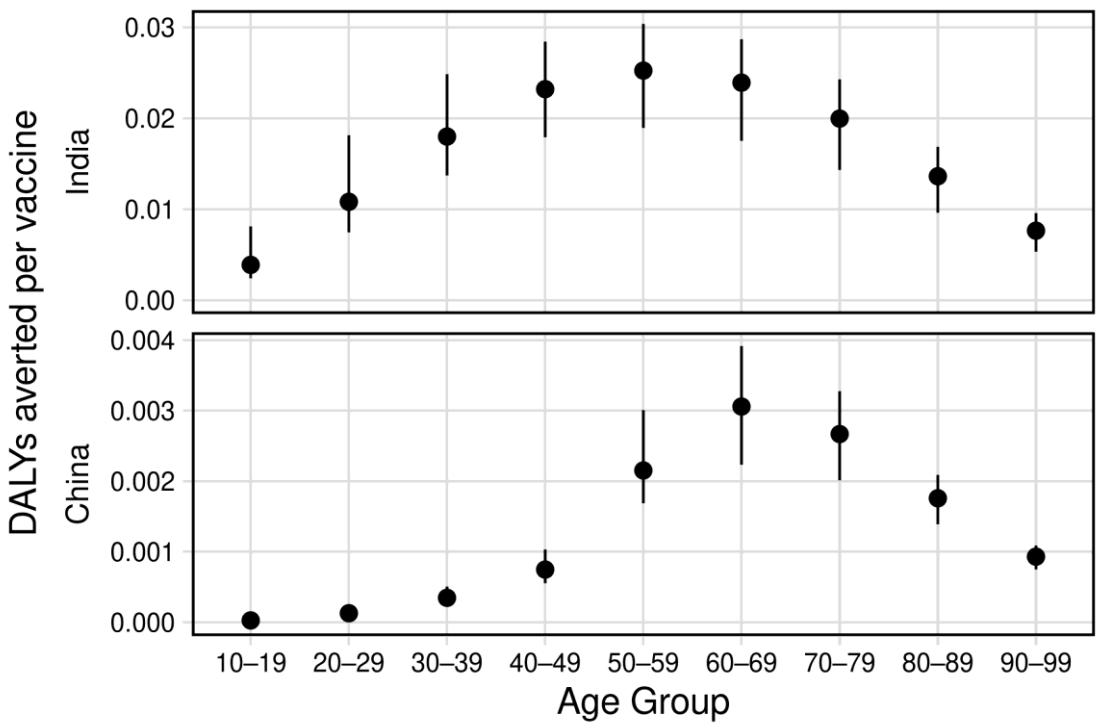

Figure S7: Vaccination efficiency by target age group in the Policy scenario. Efficiency is defined as the number of DALYs averted per vaccine delivered. Mass vaccine campaigns were deployed at 70% coverage to each age group.

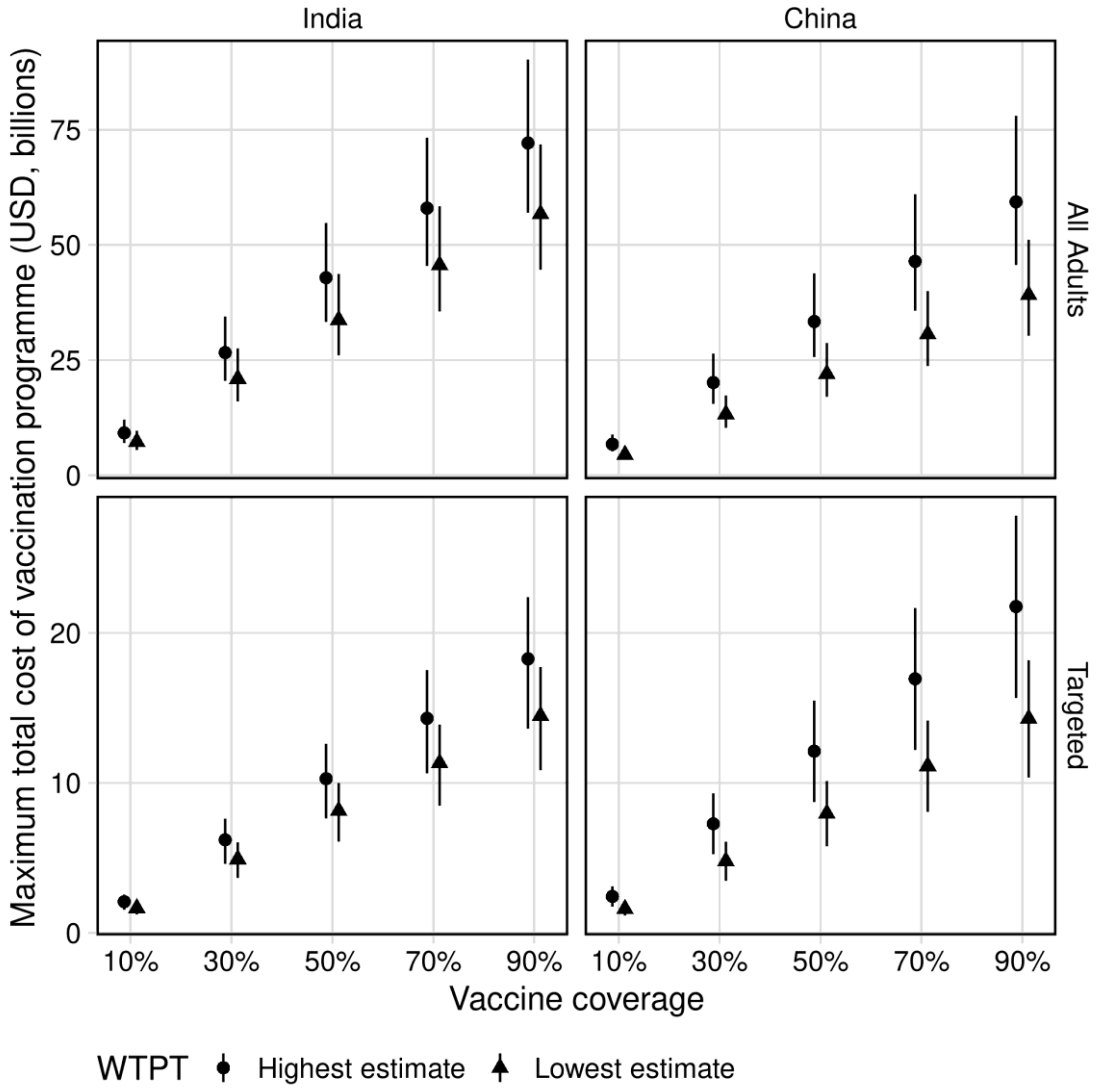

Figure S8: Maximum total vaccine programme cost in the Policy scenario. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs undiscounted.

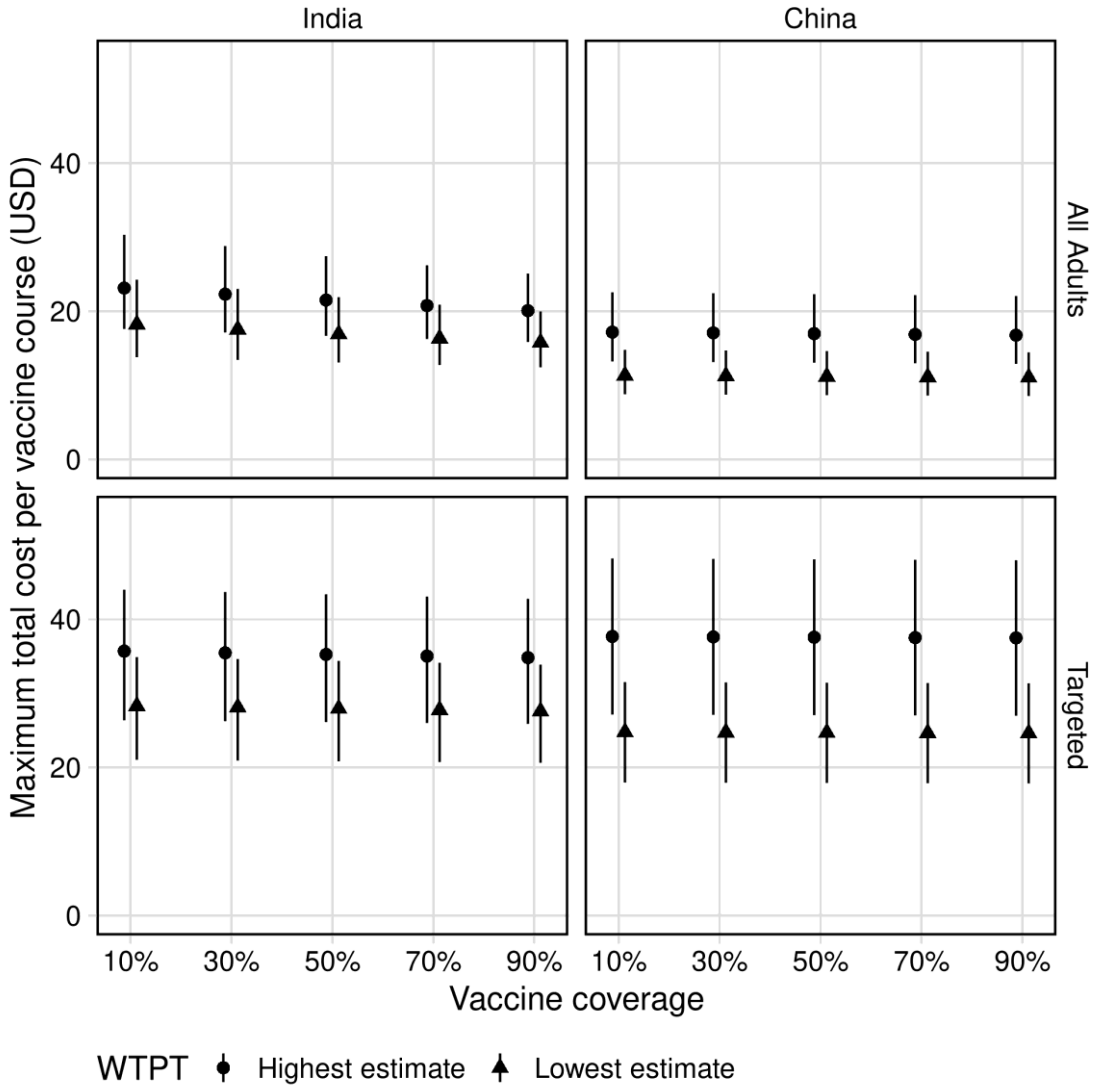

Figure S9: Maximum total cost per vaccine course in the Policy scenario. Top panels represent all-age vaccination (adults≥10 years); bottom panels represent targeted vaccination (ages 50–59 in India and ages 60–69 in China). WTPT = country-specific willingness to pay thresholds per Ochalek et al., estimated at $264 and $363 per DALY averted in India (lowest and highest estimates, respectively) and $3650 and $5669 per DALY averted in China (lowest and highest estimates, respectively). Costs undiscounted.

Table S2: Mass vaccine campaigns in the Policy scenario. Targeted vaccination in India was delivered to ages 50–59 and in China to ages 60–69. Results are aggregated over three campaigns delivered in 2027, 2037 and 2047. Averted DALYs and estimated net vaccine implementation costs are discounted to 2018 values at 3% per year. WTP: willingness to pay

Country	Campaign	Averted DALYs (total)[a]	Averted DALYs (per vaccine)	Vaccinations Delivered[b]	WTP	Maximum Total Cost of Vaccination Programme[b]	Maximum Total Cost per Vaccine Course
India	All Ages	42.23M (33.24–52.36)	0.015 (0.012–0.019)	2.79B (2.78–2.80)	264	$18B (14–23)	$6 (5–8)
					363	$22B (17–28)	$8 (6–10)
	Targeted	10.31M (7.75–12.36)	0.025 (0.019–0.030)	0.41B (0.41–0.41)	264	$4B (3–5)	$11 (8–13)
					363	$5B (4–7)	$13 (10–16)
China	All Ages	3.67M (2.86–4.77)	0.001 (0.001–0.002)	2.75B (2.75–2.75)	3,650	$14B (11–18)	$5 (4–7)
					5,669	$22B (17–28)	$8 (6–10)
	Targeted	1.38M (1.01–1.77)	0.003 (0.002–0.004)	0.45B (0.45–0.45)	3,650	$5B (4–7)	$12 (9–15)
					5,669	$8B (6–10)	$18 (13–23)

[a]M=millions

[b]B=billions

Table S3: Mass vaccine campaigns in the Policy scenario. Targeted vaccination in India was delivered to ages 50–59 and in China to ages 60–69. Results are aggregated over three campaigns delivered in 2027, 2037 and 2047. Averted DALYs and estimated net vaccine implementation costs are undiscounted. WTP: willingness to pay

Country	Campaign	Averted DALYs (total)[a]	Averted DALYs (per vaccine)	Vaccinations Delivered[b]	WTP	Maximum Total Cost of Vaccination Programme[b]	Maximum Total Cost per Vaccine Course
India	All Ages	125.21M (95.84–155.63)	0.045 (0.034–0.056)	2.79B (2.78–2.80)	264	$46B (36–58)	$16 (13–21)
					363	$58B (45–73)	$21 (16–26)
	Targeted	30.03M (21.80–37.18)	0.074 (0.053–0.091)	0.41B (0.41–0.41)	264	$11B (8–14)	$28 (21–34)
					363	$14B (11–18)	$35 (26–43)
China	All Ages	7.82M (5.95–10.42)	0.003 (0.002–0.004)	2.75B (2.75–2.75)	3,650	$31B (24–40)	$11 (9–15)
					5,669	$46B (36–61)	$17 (13–22)
	Targeted	2.87M (2.05–3.72)	0.006 (0.005–0.008)	0.45B (0.45–0.45)	3,650	$11B (8–14)	$25 (18–31)
					5,669	$17B (12–22)	$38 (27–48)

[a]M=millions

[b]B=billions

4.4 Implications for TB vaccines

At thresholds of $264/DALY averted and $3650/DALY averted, adult and adolescent TB vaccine programmes over 2027 to 2050 in India and China, discounted to 2018 US dollars, were estimated to cost $21 billion (uncertainty interval 16–27) and $15 billion (UI: 12–19), respectively, at maximum.

As TB vaccination may be unaffordable at these costs, cost-effectiveness will be an incomplete signal of financial feasibility and decision makers should explicitly consider budgetary implications when considering whether to adopt TB vaccines. It may be useful to consider experience with other health interventions that are highly cost-effective but entail a large total cost.

The prototypical example of a cost-effective but unaffordable health intervention is directly acting antiviral drugs (DAAs) for Hepatitis C. DAAs are highly effective and achieve 90–100% cure rates. They were also found to be cost-effective in England in 2015 by the National Institute for Health and Care Excellence (NICE) at the "standard" threshold of £20,000–30,000 per Quality Adjusted Life Year gained[23]. However, the projected budget impact of providing DAAs to all eligible patients was large enough to compel NICE and NHS England to introduce a 'budget impact test', delaying DAA introduction and allowing time for NHS England to negotiate further with manufacturers[24]. In this situation, costs were driven by the moderately-high prevalence of Hepatitis C and the very high drug prices ($84,000 initial list price per course[25]). TB vaccines are unlikely to be priced at comparable levels. However, countries will need to achieve at least moderate coverage[14] among adults and adolescents to achieve desired TB control goals; thus, the eligible population in India and China will be very large. As such, similar total cost considerations will apply. Even if TB vaccines are listed at prices predicted to render them cost-effective, decision makers in India may need to further negotiate with manufacturers to mitigate total cost.

The total cost estimates from section §4.2 are *a priori* more similar to the scenarios in figure 4.1C or figure 4.1C F than figure 4.1B or figure 4.1D. Given its expected scale, it may be inappropriate to appraise all-adult mass TB vaccination against a single CET based on the opportunity cost of marginal healthcare spending. The results from Research Paper 3 may overestimate the total maximum cost at which vaccination is truly cost-effective.

Using a lower threshold, or varying the threshold with expected budget impact may improve the estimates of total maximum cost and cost-effectiveness. The former approach was adopted by the Australian Pharmaceutical Benefits Advisory committee when faced with reimbursing Hepatitis C drugs (estimated cost >$1 billion AUD; ~2% of annual federal pharmaceutical budget)[26]. Theoretical models to continuously adapt CETs to increasing budget impact, that incentivise manufacturers to provide drugs at lower prices, have also been developed[1,4]. However, while these approaches may reduce the total cost of TB vaccines, they face at least two major obstacles in practice. First, as with the "league table" method, it will be difficult to empirically determine either a lower CET or a

function to continuously adjust the CET with increasing budget impact. Second, setting a lower CET for TB (or any specific health condition) may be ethically contentious. The implication that life-years lost due to TB are "worth less" than other diseases, particularly given the stark socioeconomic gradient of TB, is likely unacceptable to patients, health systems, and wider society. Valuing TB mortality and morbidity less may also exacerbate existing funding shortages faced by global TB control efforts[27].

Finally, decision makers should consider how the large total cost of TB vaccines will affect the interpretability of studies that find TB vaccines to be cost-effective. If a study uses an opportunity cost-based CET and assumes a fixed healthcare budget, a positive cost-effectiveness result should be interpreted with caution as the expected total cost of vaccines increases.

4.4.1 Limitations

Similar to a formal cost-effective analysis, this study collapsed temporally distributed costs into a single summary statistic discounted to the date of analysis. In contrast, a formal budget impact analysis would show costs over time, allowing decision makers to better estimate the short-medium term demands on health budgets. However, an accurate budget impact analysis requires that vaccine price, vaccine delivery costs, and a mass campaign scale up strategy based on the known or planned capacity of the health system, are known. This information is currently not available for TB vaccination in India nor China. Moreover, the analysis in section §4.2 aimed to estimate the *maximum* cost, which is not the outcome of a budget impact analysis with a fixed vaccine price.

A factor that limits the interpretation of section §4.2 (and many health economic evaluations) is that health intervention costs are often incurred substantially before health benefits. Many theoretical frameworks, e.g. relating cost-effectiveness thresholds to budget impact as in section 4.1.1, assume that costs and benefits occur in the same budget cycle. For TB vaccines in particular, costs and benefits are years-decades apart. This complicates the comparison of ICERs for TB vaccines against other interventions.

The total cost estimates in section §4.2 are also biased downwards by discounting. In general, discounting disadvantages vaccines in CEA as costs are incurred much sooner than benefits realised. However, in this analysis, the monetary value was attached to DALYs at the time they are averted. Consequently, these monetary values were discounted more than their corresponding amounts would have been in a formal cost-effectiveness analysis.

A new TB vaccine is likely to be one component of a wider comprehensive TB prevention and control strategy. It will not completely displace existing TB programmes. In fact, per the Policy scenarios for both India and China, both national TB programmes anticipate substantial further scale up to meet End TB goals. Assuming that current and planned non-vaccine programmatic TB management is cost-effective, these may exert downward

pressure on the CET for TB vaccines in the future. Similarly, advances that improve the treatment success rate and reduce the duration of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) regimens will reduce the ICER for MDR/RR-TB treatment.

***

If and when a new TB vaccine becomes available and countries elect to deploy it, country decision makers will be committing to a long term investment that will incur costs and benefits over years-decades. When the decision to proceed is made, they must incorporate the best available, but nonetheless incomplete, information about the future into their deliberations. Some key uncertainties they are likely to face include how health budgets will change, and whether cost-effectiveness thresholds will change in tandem.

The results in section §4.2 provide a preliminary approximation of the *maximum* cost that the health system would incur, *if* that system valued TB vaccine derived health benefit at prevailing cost-effectiveness thresholds. These estimates are substantial, but can be factored into planning vaccine financing or price negotiations. The analysis could be repeated with different implementation scenarios as information on feasibility becomes available. Finally, the study also approximates the impact of changing CETs through the use of both the minimum and maximum thresholds for each country.

4.5 Summary

This chapter attempted to satisfy objective three of this thesis. I have attempted to assess the affordability of large scale adult TB vaccination. The two main outputs of this chapter are these total cost estimates and considerations around their interpretation. Together, these outputs lead to four key takeaways from this chapter.

First, if we value the health benefits of large scale adult and adolescent mass vaccination at exogenously determined CETs, we find that the maximum costs that those health systems would have to pay would be substantial. Cost-effectiveness analysis provides an incomplete signal of financial feasibility and decision makers may need to employ specific processes to reduce the total cost of TB vaccination.

Second, unsurprisingly, targeting a smaller population for vaccination reduces the total estimated cost of vaccination. However, the impact of vaccine, in terms of DALYs averted per recipient is heterogeneous among age groups. The total price at which vaccination is cost-effective is highest among 50–59-year olds in India and 60–69-years in China, reflecting both age group size and the efficiency of targeting these groups. If the price of vaccination is independent of targeting strategy, then a health system could allocate more funds towards programmatic aspects of vaccination rather than dose cost.

Third, because scale up in programmatic management of TB reduced baseline future TB burden and therefore the burden averted by vaccination, this in turn reduced the total

maximum cost at which the vaccine programme remained cost-effective. In order to maintain cost-effectiveness, health systems may need to negotiate lower prices for vaccines depending on the planned strategy for national tuberculosis programmes (NTPs).

Fourth, we may need to factor the scale of proposed TB vaccination when selecting appropriate CETs during cost-effectiveness analysis and total cost-estimation.

The work in this chapter provides preliminary estimates of TB vaccine programme costs to substantiate decision making around vaccine introduction. Decision makers should consider the implications of the CETs they use, how they might change over the course of a TB vaccine programme, and consider sensitivity analyses of thresholds when considering the financial feasibility of said programmes.

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5 Contact Matrices, Evolving Demography, and Vaccine Impact

In this chapter, I investigated whether different methods of updating modelled social contact structures to match secular demographic trends affected estimates of TB vaccine impact.

It is only recently that TB vaccine models began to include heterogeneous age-dependent social contact matrices to better reflect age-specific burden and transmission dynamics[1–5]. Social contact structures are typically derived from (real or synthetic) source populations with specific demographic compositions. However, the demographic structure of relevant populations in TB models—and especially TB vaccine models—is unlikely to remain fixed, as they typically project over multi-decade time horizons. Arregui et al.[6] have recently described methods to continuously update contact structures to match evolving demography. However, whether or not such adaptation affects model-based estimates of TB vaccine impact is unknown.

Here, I hypothesized that different methods of updating social contact structures to match evolving demography might alter transmission dynamics between age groups. These differential transmission dynamics would then interact with, and propagate through, the direct and indirect effects of vaccination, giving rise to differential vaccine impact estimates between different update methods. To examine this hypothesis, I simulated an M72/AS01$_E$-like vaccine in an age-stratified dynamic transmission model of *Mycobacterium tuberculosis* (*Mtb*) in an India-like epidemiologic setting, updating social contact as described by Arregui et al.[6] This model was structured and parameterised similarly to previous work in chapters 3 and 4, and work by Harris et al[1,2].

5.1 Research Paper 4

Reprint Note Research Paper 4 was submitted to *PLoS Computational Biology* in August 2021. It has completed one round of review and is currently undergoing revisions. The original submission is reprinted in this section.

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Thesis Title	ADVANCING MATHEMATICAL MODELS OF MYCOBACTERIUM TRANSMISSION TO SUPPORT VACCINE INTRODUCTION		
Primary Supervisor	PROFESSOR RICHARD G WHITE		

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study and designed the research question. I designed the epidemiologic model, collected relevant epidemiologic and demographic data, adapted the base contact structures, programmed the model in R and Julia, calibrated the model, simulated vaccination, and analysed and visualised the results. I wrote the first full draft of the manuscript and technical appendix and submitted to the journal, including all correspondence with the editorial team. I am currently making revisions to the manuscript and responding to comments from reviewers per editorial request.

SECTION E

Student Signature	
Date	12 DECEMBER 2021

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Date	14 DECEMBER 2021

Updating Contact Structures to Match Evolving Demography in a Dynamic Mathematical Model of Tuberculosis Vaccination

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Abstract

We investigated the effects of updating age-specific social contact matrices to match evolving demography on vaccine impact estimates. We used a dynamic transmission model of tuberculosis in India as a case study.

We modelled four incremental methods to update contact matrices over time, where each method incorporated its predecessor: fixed contact matrix (M0), preserved contact reciprocity (M1), preserved contact assortativity (M2), and preserved average contacts per individual (M3).

We updated the contact matrices of a deterministic compartmental model of tuberculosis transmission, calibrated to epidemiologic data between 2000 and 2019 derived from India. We additionally calibrated the M0, M2, and M3 models to the 2050 TB incidence rate projected by the calibrated M1 model. We stratified age into three groups, children (<15y), adults (≥15y, <65y), and the elderly (≥65y), using World Population Prospects demographic data, between which we applied POLYMOD-derived social contact matrices.

We simulated an M72AS01E-like tuberculosis vaccine delivered from 2027 and estimated the per cent TB incidence rate reduction (IRR) in 2050 under each update method.

We found that vaccine impact estimates in all age groups remained relatively stable between the M0–M3 models, irrespective of vaccine-targeting by age group.

The maximum difference in impact, observed following adult-targeted vaccination, was 7% in the elderly, in whom we observed IRRs of 19% (uncertainty range 13–32), 20% (UR 13–31), 22% (UR 14–37), and 26% (UR 18–38) following M0, M1, M2 and M3 updates, respectively.

We found that model-based TB vaccine impact estimates were relatively insensitive to demography-matched contact matrix updates in an India-like demographic and epidemiologic scenario. Current model-based TB vaccine impact estimates may be reasonably robust to the lack of contact matrix updates, but further research is needed to confirm and generalise this finding.

Introduction

Social contact patterns are a crucial driver of communicable disease transmission. Contacts can be grouped by various criteria, including age groups or gender, behavioural characteristics (e.g., high- or low-risk behaviours), or location (e.g., at home, school, or workplace). Intrinsic biological and behavioural factors drive age-specific burden in many infectious diseases (e.g., measles, mumps, or tuberculosis). Dynamic infectious disease models increasingly use age-specific contact matrices to reflect behavioural factors that contribute to age-specific burden. Multiple recent studies have attempted to characterise such age-specific contact patterns. For example, the POLYMOD study by Mossong et al.[1] provides comprehensive empirical nationally-representative estimates of age-dependent contact rates (expressed as contact matrices) in eight European countries based upon contact diaries. Prem et al.[2] have estimated synthetic contact matrices for a wide range of countries using results from POLYMOD, Demographic and Health Surveys, demographic data, and other sources. Estimates of subnational or localised contact rates and mixing patterns have also been published for China[3], India[4], Zimbabwe[5] and Kenya[6], among others.

Contact matrices reflect a snapshot of contact patterns at a particular time. The time point corresponds to contact survey dates for empirical estimates or some appropriate mid-point for data included in synthetic matrices. Each contact matrix is co-determined by the intrinsic preferences of groups for contact with other groups ("assortativity") and the demographic composition of its source population. Moreover, matrices should demonstrate 'reciprocity of contacts', where the total number of contacts between all members of some age group *i* with another age group *j* equals the total number of contacts between all of group *j* with group *i*. In infectious disease models with a short time horizon, we can reasonably assume that the contribution of demographic composition to age-specific contact patterns remains relatively constant. However, this assumption is violated when the demographic structure is expected to change, as is the case when modelling diseases with long latency periods (e.g., tuberculosis and syphilis) or interventions where impact is expected to be long term (e.g., vaccines). As demography changes, total contacts between age groups become unbalanced, leading to an error in the computed age-specific force of infection parameters within the model.

Arregui et al.[7] describe methods to project a contact matrix estimated from any particular population to a population with an arbitrarily different demographic structure. They identified three properties of a contact matrix that change when it is projected to a different demographic structure: reciprocity, assortativity (the relative preference of one group for contact with another), and overall average contact rate. They presented projection methods that variably preserved these properties.

Despite this development, we are aware of only one study[8] investigating whether such contact matrix updates affect model-based predictions of disease burden. This study of Mycobacterium tuberculosis transmission suggested that a lack of demographically matched contact matrix updates might underestimate future TB burden. In addition, no studies have investigated if contact matrix updates affect dynamic model-based impact estimates infectious disease control interventions.

We hypothesised that changing age-dependent contact rates through different contact matrix update methods in an evolving demographic context would lead to differential transmission dynamics between age groups in a disease with age-specific burden patterns. Furthermore, these differential transmission dynamics would propagate through the direct and indirect (transmission dependent) effects of vaccination, leading to differential vaccine impact estimates.

We investigated the effects of updating age-specific social contact matrices to match evolving demography on dynamic transmission model-based vaccine impact estimates, using tuberculosis in India as a case study.

Methods

Transmission Model

We developed a six-compartment dynamic model of Mycobacterium tuberculosis (M. tb) transmission in the R[9] and Julia[10] programming languages, building on previous studies[11–15]. A full description of model structure, parameterisation and calibration are provided in the appendix.

In brief, the model represented six states: (1) naive to and susceptible to infection; (2) latently infected; (3) active infectious TB disease (bacteriologically positive); (4) non-infectious active TB disease (bacteriologically negative); (5) TB disease on-treatment and (6) recovered from disease through successful treatment or natural cure. In addition, we stratified all states by vaccination status.

Flows between states represented changes in TB natural history state or treatment status. Natural history flows included infection by M. tb followed either 'fast progression' to active disease or 'slow progression' to latent infection, conversion from non-infectious active disease to infectious active disease, natural cure from active disease to the recovered state,

reactivation from latency, and relapse from recovered. Treatment-related flows included detection and initiation on treatment, treatment success and recovery, and treatment failure leading to re-entry into non-infectious active disease.

We modelled ages 0–99, stratified into children (<15y), adults (15–64y) and elderly (≥65y). Annual historical and projected future birth rates and all-cause mortality rates were obtained from the United Nations World Population Prospects 2019 India country profile[16]. New births entered the children group in the first time step of each year. Age-group specific annual all-cause mortality, adjusted to remove TB mortality (appendix §1.1), was applied at the beginning of each time step.

We ran the model over 1950–2050 using a six-month timestep, calibrated to historical epidemiologic data over 2000–2019 and projected over 2020–2050.

We obtained prior ranges for natural history parameters from the literature, applying age-group specific ranges where possible. Rates of fast progression, reactivation from latency and TB mortality were constrained to be greater in children than adults. Rates of relapse from the recovered state and fast progression were constrained to be greater in the elderly than adults. Conversely, we constrained the natural cure rate and proportion of fast-progressors entering non-infectious disease to be lower in the elderly than adults.

Social Contact Matrices

Empirical social contact data from India is limited to a study from one rural setting in Haryana[4]. These data were not nationally representative, and raw contact data were not published at the time of writing. As such, we used the SOCIALMIXR R package [17] to generate a base social contact matrix derived from the POLYMOD study[1], which aggregated empirical social contact survey data across 7,290 respondents and 97,904 contacts across eight European countries. We aggregated the raw POLYMOD contact data and used the demographic structure of the constituent countries to generate a three age-group base matrix (figure 1A) that corresponded to a snapshot of social contact at the time of the survey (2005–2006). This matrix reflected a source population that comprised approximately 16% children, 67% adults, and 17% elderly.

Arregui et al.[7] describe four methods to update contact matrices to match evolving demography, labelled M0–M3. We briefly describe the properties of each method below; detailed calculations and formulae are presented in the appendix §2.2. We adopted the same naming convention, referring to each independently calibrated model by its respective update method.

M0 represented the identity transformation, where contact rates remained invariant with changing demographics. The M1–M3 updates were incremental, such that M3 included the properties of M2, which included the properties of M1.

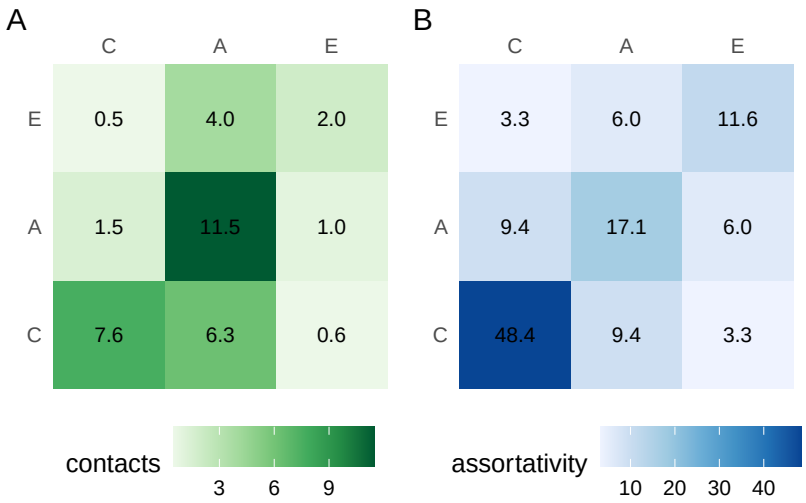

Figure 1: Base contact and assortativity matrices. **A**: contact matrix derived from the POLYMOD study, based on surveys conducted in 2005–2006, used without further transformation in the M0 model and with reciprocity correction in the M1 model. **B**: assortativity matrix derived from POLYMOD matrix, by decoupling the POLYMOD demographic structure from base contact matrix. Numbers within cells represent contact rates between the column-row age-group pairs.

The M1 update method preserved reciprocity. Contact rates were adjusted to ensure that the total number of contacts between any age group i and group j was equal to total contacts between j with i as group sizes changed over time.

The M2 update method preserved assortativity in addition to reciprocity. Assortativity is the relative preference of some age group *i* for contact with another group *j*, over that expected by homogeneous mixing between *i* and *j*. For every contact matrix Q with n age classes, we can compute a corresponding assortativity matrix R. The entries of R are the contact rates expected in a population where the n classes are equally sized and where the relative preferences for contact between groups are the same as in Q, multiplied by n. We derived such an "assortativity matrix" from the M0 matrix (figure 1B) by decoupling it from the original demographic structure of the POLYMOD survey. We then regenerated a contact matrix during each step of model run time by applying the demographic structure of that step to the assortativity matrix.

The M3 update method preserved the average contact rate in addition to reciprocity and assortativity. The M2 matrix was first used to calculate the average population-wide daily contact rate per individual and then normalised by this value.

Each of the methods described above implies different consequences on contact patterns due to demographic change. For example, as total contact volume remains constant with population size in M1, an ageing population would lead to more contacts between each child and older adults. In M2, the overall average contact rate may increase (or decrease) depending on the assortativity pattern and changes in the size of specific age classes,

implying that more (or less) contact occurs between members in general. Finally, M3 implies the opposite: the total volume of contacts would grow in proportion to the total population. Which of the aforementioned update methods best reflects the true change in contact patterns is not known empirically; however, in this study, we use M1 as the intuitively "natural" base case against which other methods were compared.

We present the scaled per-capita effective contact rate (β)—where an effective contact was defined as sufficient to lead to infection, were it to occur between a susceptible and an infectious individual[18]—between each age-group pair to demonstrate evolving contact over time. In each contact matrix update scenario, we sampled an independent scaled probability of transmission per infectious contact, which we transformed and multiplied into the contact rate to compute β. Therefore, in all calibrated models,

$$\beta \propto \kappa$$

where kappa (κ) represented the contact rate. Because each transformation scenario was calibrated independently (see below), β parameters were difficult to compare across scenarios; we examine differences in β parameter trends rather than magnitude.

Calibration

We calibrated four transmission models, labelled M0–3, using each of the contact matrix update methods. Each baseline (unvaccinated) scenario was fitted to overall rates of TB prevalence in 2015[19], incidence in 2010 and 2019[20,21], notifications in 2019[20,21], and mortality in 2019[20,21]. Age-specific incidence rates were not published at the time of writing. Therefore, we estimated incidence rates for <15, 15–99, and 65–99 year age groups using raw incidence estimates from WHO[20,21] and population estimates from World Population Prospects[16].

We captured historical programmatic control of TB by fitting treatment initiation rate to notification rate data, with treatment outcome rates per the WHO TB database[20].

We assumed M1 to be the "natural" base case against which to measure the other update methods. Further, to ensure that the baseline (unvaccinated) TB burden projected using all update methods remained comparable, allowing any differences in vaccine impact to be attributed to differential contact matrix updates, we calibrated models M0, M2, and M3 to the 2050 incidence rate projected by the fully calibrated M1 model.

Model calibration was performed in two stages. First, we used box-constrained optimisation to find initial parameter sets that fit all calibration targets. Second, we used these initial parameter sets to initialise an Approximate Bayesian Computation Markov chain Monte-Carlo (ABC-MCMC) sampler to fully characterise the parameter space compatible with the uncertainty ranges of the calibration targets. We extracted a final subsample of 1000 parameter sets from the ABC-MCMC chains for each contact matrix update method,

with which the model was run to project baseline TB burden. We present median values as a measure of central tendency and minimum and maximum trajectories as uncertainty ranges. Posterior distributions for parameters and other calibration results are presented in appendix §3 and §4.

Vaccine Implementation

We simulated a 50% efficacy prevention of disease vaccine, effective in individuals with a prior history of TB infection (post-infection; PSI) that conferred 10-years of protection. Vaccination was delivered to populations without active disease and who were not receiving treatment.

We simulated vaccine delivery targeted to children, adults, or the elderly via 10-yearly mass campaigns that began in 2027 and achieved 70% coverage. Vaccine protection was modelled through a reduction (proportional to vaccine efficacy) in the rates of fast progression, reactivation from latency, and relapse from the recovered state. Vaccine waning was modelled as instantaneous at the end of protection. Details of the vaccine implementation are given in appendix §2.5.

We measured vaccine impact as the per cent incidence rate reduction in 2050 in vaccinated model runs compared to no-new-vaccine baseline runs.

We conducted sensitivity analysis by varying the host-infection status required for vaccine efficacy to include vaccines effective in individuals with no prior history of infection (pre-infection; PRI) and vaccines effective in individuals irrespective of TB infection history (pre- and post-infection; P&PI).

Results

Calibration and Baseline Trajectory

We calibrated to TB prevalence, incidence, notification, and mortality rates. The M1 model projected an overall 2015 prevalence rate of 217 (Uncertainty range (UR): 195–312) per 100,000, and incidence, mortality, and notification rates of 244 (UR: 205–265) per 100,000, 32 (UR: 30–35) per 100,000, and 167 (UR: 152–213) per 100,000, respectively, in 2019. The M1 model also projected an overall incidence of 234 (UR: 190–271) per 100,000 in 2050.

Overall TB incidence rates in the M0, M2, and M3 models were projected at 244 (UR: 206–265) per 100,000, 242 (UR: 209–266) per 100,000, and 225 (UR: 206–263) per 100,000, respectively in 2019. As expected, the projected incidence in 2050 for M0, M2, and M3 models remained within the envelope of the M1 projection. Projected 2050 incidence rates in M0 and M2, at 239 (UR: 195–271) per 100,000 and 258 (UR: 213–271)

per 100,000, respectively, remained relatively stable compared to 2019. The 2050 projected median incidence rate in M3 rose slightly, with a narrowed uncertainty interval to 266 (UR: 237–271) per 100,000.

Age-specific incidence calibration for M1 and full calibration results for M0, M2, and M3 are presented in appendix §4.3. In general, we found a substantially lower TB burden in children than adults or the elderly (appendix §4.3). TB burden was comparable between adults and elderly (appendix §4.3). In addition, we found similar proportions of incident TB due to relapse, reactivation, or new infection followed by transmission across M0–M3 (appendix §4.3.2).

Evolution of Contacts

The temporal evolution of the median per capita effective contact rates (β) for all age-group pairs are presented in figure 2. The subscripts indicate the age classes of the individual and their contactee (A = adults; C = children; E = elderly). In addition, measures of reciprocity error, assortativity, and average contact rate differences between the update methods are presented in appendix §2.2.

In the M0 scenario, as expected, β values for all age-group pairs remain constant over time.

In the M1 model, the reciprocity correction ensured that within age-group β values remained constant over time and demographic change. Broadly, β_{AC}, β_{AE}, and β_{EC} also remained relatively constant. β_{EA} demonstrated the most marked decline, reflecting the distribution of a fixed total volume of contacts over a growing proportion of elderly. The opposite effect, albeit less marked, was seen in β_{CA},

In the M2 model, values for β_{AA}, β_{CA}, β_{CC}, and β_{EA} were higher than in the M0 or M1 models, reflecting the higher proportion of adults and children in India than in POLYMOD countries. Accordingly, values of β_{CC} and β_{AC} declined over 2025–2050, mirroring the declining proportion of children in the population, suggesting fewer contacts between children and between each adult with children. We found the opposite effect in β_{EE}, β_{AE}, and β_{CE}: as the proportion of elderly in the population rose, the number of contacts with the elderly also rose.

β values and trends were similar between the M2 and M3 models. However, as the average contact rate declined in the M2 model over time (appendix §2.2) we found increasing trends in counterpart β values projected by the M3 model.

Vaccine Impact

A summary of vaccine impact, for a vaccine with 50% efficacy, conferring 10-years of protection, effective in individuals with a previous history of disease, and which prevented disease but not infection, is presented in figure 3.

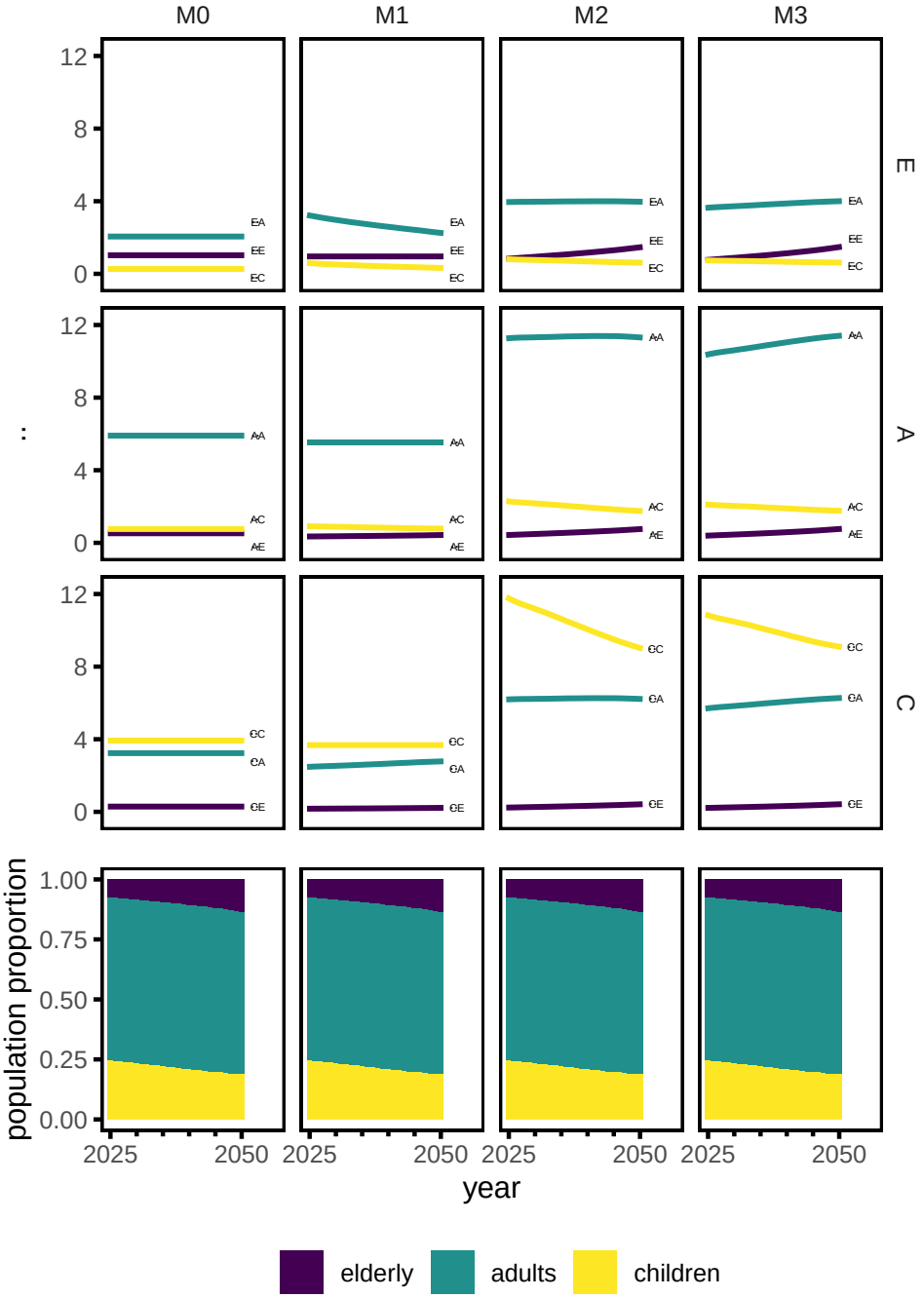

Figure 2: Beta parameter change with time between all age group pairs. Beta represents the effective contact rate between two age groups (subscripts) per six-month time step. Horizontal panels represent the age group making contacts; lines represent the beta parameter values corresponding to the number of contacts with the contactee group. A=adult, C=children, E=elderly.

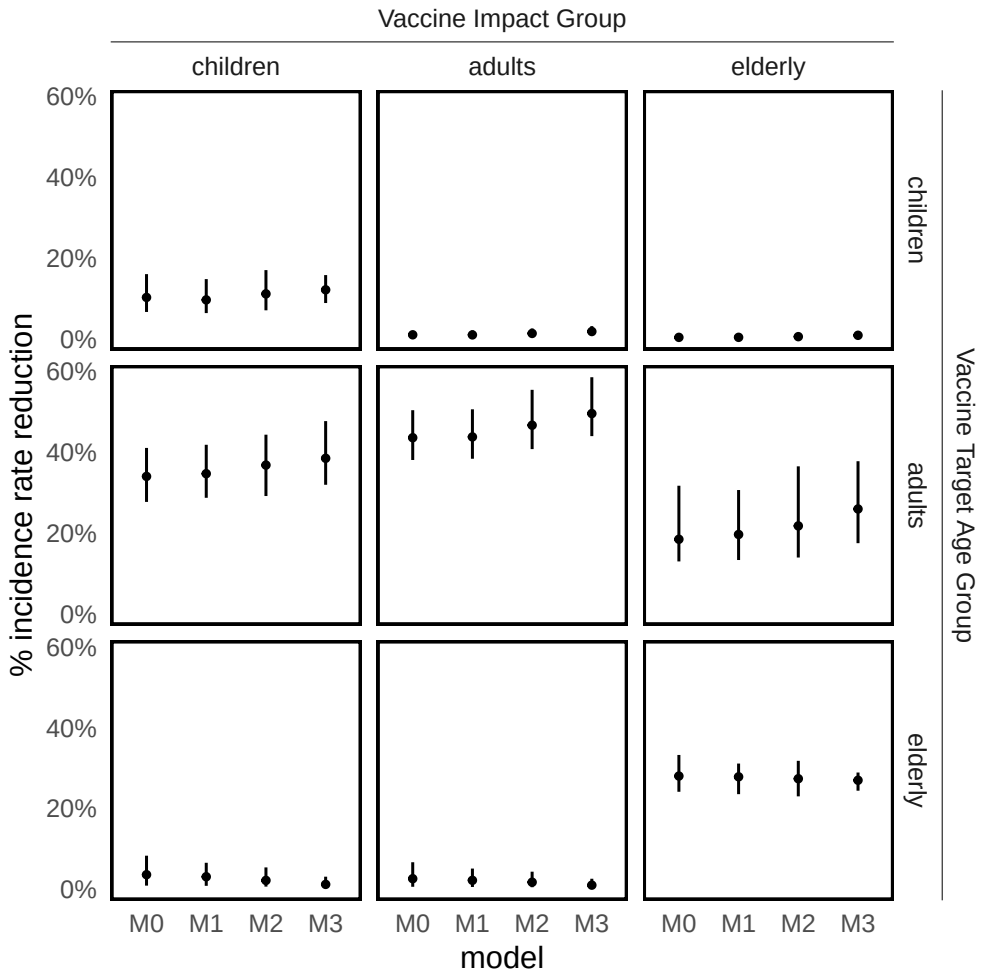

Figure 3: Per cent TB incidence rate reduction in 2050 compared to no-vaccine baseline. Rows indicate age group to which vaccine was targeted. Columns indicate in which age group impact was measured. Points indicate median estimate, bars indicate uncertainty range.

We found that vaccine impact estimates in all age groups remained relatively stable between the M0–M3 models, irrespective of vaccine targeting by age group. The maximum difference in impact, observed following adult-targeted vaccination, was 7% in the elderly, in whom we observed IRRs of 19% (uncertainty range 13–32), 20% (UR 13–31), 22% (UR 14–37), and 26% (UR 18–38) following M0, M1, M2 and M3 updates, respectively.

When the vaccine was delivered to adults, we observed an increasing vaccine impact in M0 through M3 models in all age groups. A similar across-model trend was seen in vaccine impact when vaccinating children, albeit of a smaller magnitude. A decreasing trend in vaccine impact from M0 to M3 was found in all age groups when vaccinating the elderly. However, we found substantial overlap in the uncertainty ranges of vaccine impact estimates across M0–M3 for all vaccine targeting and outcome combinations.

Overall findings were robust to variation in host-infection status required for efficacy; we found similarly stable vaccine impacts between M0–M3 for pre-infection or pre-and post-infection vaccines (appendix §5).

Discussion

We found that model-based estimates of TB vaccine impact in India remained stable over a range of simulated changes that matched contact structures to evolving demography.

Vaccine impact estimates in all age groups remained relatively stable between contact matrix update methods, irrespective of vaccine targeting by age group. The maximum difference in incidence rate reduction in 2050, observed following adult-targeted vaccination, was 7% in the elderly, in whom we observed IRRs of 19% (uncertainty range 13–32), 20% (UR 13–31), 22% (UR 14–37), and 26% (UR 18–38) following M0, M1, M2, and M3 updates, respectively.

Adult-targeted PSI vaccination led to the greatest vaccine impact in all age groups. In contrast, child- or elderly-targeted vaccination reduced TB burden within those groups with minimal indirect impact on others. This pattern suggests relatively low transmission of infection from children or the elderly to outside their age groups in the modelled epidemic.

The effective contact rate between children (β_{CC}) declined markedly over time in the M2 and M3 models, while in M0 and M1 it remained relatively constant. We found that targeting vaccines to children did not yield different vaccine impacts between M0–M3 despite this difference. This is likely because the burden of TB in children was very low in all models (appendix §4.3), leading to a correspondingly low force of infection originating from this group. Thus, the disease and transmission avertible by targeting vaccination to children was limited in all models, minimising differential impact. We note that, although TB vaccine impact is unchanged, differential contact matrix updates may substantially affect models of other more prevalent or more infectious childhood diseases.

In contrast to children, we found that disease burden in the elderly was greater than or comparable to adults. However, the elderly had lower contact rates with all age groups, with low and stable β_{E^*} and β_{*E} values across M0–M3. This may also have contributed to lower avertible disease and transmission levels, reducing differential impact across the update methods.

Our findings may reflect the dominant contribution of intrinsic biological factors (represented in the model as constrained parameterisation and age-specific parameter values) over behavioural factors (i.e., age-specific contact patterns) to age-specific disease burden in TB. This would reduce the sensitivity of the force of infection to changes in contact rates, contributing to the stability of vaccine impacts across M0–M3. However, this balance may differ in other diseases, warranting investigation on a per disease basis.

Finally, numerically, it can be shown that only the M2 and M3 transformations satisfy the frequency dependence assumption commonly used when calculating force of infection parameters in human dynamic transmission models. However, even in the M2 and M3 models, frequency dependence is only maintained if the population grows while maintaining a constant age composition, which is unlikely.

Our findings must be interpreted considering several limitations of this study.

Firstly, we used large age strata. Although granular contact data from the POLYMOD study were available, we were limited to stratifying the model into three relatively broad age groups by the resolution of available calibration data in India. As a result, subtle interactions of contact rates with evolving demography may have been obscured, especially within the wide adult age group. It is difficult to estimate the direction of bias this limitation might impose. However, most previous TB vaccine models have considered these age groups in aggregate, as we have done, as they are of interest from an epidemiologic and vaccine implementation strategy perspective[11,13,14].

Secondly, our case study of India was limited by the scarcity of granular, nationally representative TB epidemiologic data. India has not yet published a national survey of TB prevalence; nationally representative empirical estimates of age-specific prevalence are unavailable. In general, TB notification data are known to have age-specific biases, which may underestimate the burden of disease in children and older people[22,23]. Additionally, our use of a generic POLYMOD contact matrix rather than an India-specific matrix may reduce the accuracy of our findings. We know of two previous studies which estimated social contact patterns in India. Prem et al.[2] combined Demographic and Health Survey results, POLYMOD data, and other household-level data to generate synthetic age-specific contact matrices for India. Kumar et al.[4] reported a social contact survey limited to Haryana, North India. At the time of writing, raw data from neither study was available in the form needed to generate matrices for our model. However, similarly to the POLYMOD matrix, both studies found strong assortativity for in-age-group contacts, with additional assortativity between younger adults and children. Therefore, we speculate

that differential impact across update methods is likely to remain stable, despite possible different magnitudes of vaccine impact and age-specific impact patterns.

Finally, we calibrated the M0, M2, and M3 models to fit the baseline predicted overall TB incidence rate in 2050 of the M1 model. This likely reduced the parameter space available to calibrate the M0, M2, and M3 models. However, this deliberate constraint allowed us to isolate the effects of differential contact matrix updates on vaccine impact by maintaining comparable baseline trajectories between the four models. Thus, we assumed that relative differences in vaccine impact between M0–M3 were preserved at the cost of an error in absolute magnitudes. Further, we assumed a constant probability of infection per infectious contact in all age groups. Children are believed to be less infectious than adults or the elderly[24]. Thus, independently calibrating this parameter for each age group may magnify the effects of changes to the contact matrix; however, as the contribution to transmission from children is very small, this is unlikely to affect our findings substantially.

Our findings also likely reflect characteristics of tuberculosis' natural history. TB disease can recur through either reactivation from latency or relapse from the recovered state; thus, some fraction of disease remains resistant to contact and transmission changes. Both latency and recovered state may persist for many years, introducing lag time between changes in transmission dynamics and changes in disease burden. It would be interesting to carry out similar experiments with other long-duration infections.

Further work is necessary to test the generalisability of our findings, in particular in settings with more significant changes to demographic composition, with different patterns of age-specific disease burden, and with diseases with shorter time courses.

Conclusions

We found that model-based TB vaccine impact estimates were relatively insensitive to demography-matched contact matrix updates in an India-like demographic and epidemiologic scenario. Current model-based TB vaccine impact estimates may be reasonably robust to the lack of contact matrix updates, but further research is needed to confirm and generalise this finding. Further work is also required to investigate whether this result can be generalised to other epidemiologic and demographic contexts and other diseases.

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5.2 Technical Appendix

Reprint Note This Technical Appendix was submitted with Research Paper 4 was submitted to *PLoS Computational Biology* in August 2021. It has completed one round of review and is currently undergoing revisions. The original submission is reprinted in this section.

Updating Contact Structures to Match Evolving Demography in a Dynamic Mathematical Model of Tuberculosis Vaccination

Technical Appendix

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Supplementary Methods

1 Natural History Model

We constructed a difference equation-based compartmental dynamic transmission model of *Mycobacterium tuberculosis* (Mtb) , with a timestep of 6 months and a time horizon of 1950-2050. The model was an evolution of previous compartmental models developed and used by Knight et al. [1] , Harris et al. [2, 3], and Weerasuriya et al. [4, 5]. The model had the following compartments:

1. Susceptible (S; never infected by Mtb);
2. Latently infected (L; infected with Mtb, but without active disease);
3. Infectious active disease (I; bacteriologically positive TB disease capable of transmission);
4. Non-infectious active disease (N; bacteriologically negative TB and incapable of transmission);
5. On-treatment for tuberculosis (T) and;
6. Resolved (R; recovered from active disease, either via treatment or through natural cure).

A diagram of model compartments and flows between compartments is presented in Figure 1.

Susceptible (naive) populations infected by Mtb could either become latently infected or directly progress to active disease. Individuals in the active disease state could either: (1) be detected and move to treatment; (2) cure TB disease naturally; or (3) die from tuberculosis or other causes. Those who experienced natural cure moved to the resolved compartment. Those starting treatments entered the treatment state where they could experience either treatment success (and move to the resolved state) or treatment failure (and return to noninfectious active disease). Latently infected and resolved populations could reactivate and relapse, respectively, back into the active disease state. Alternatively, these populations could be reinfected and experience rapid progression to active disease. We applied background age-specific mortality to all compartments.

1.1 Demography

The model was structured into three age classes: children (C; < 15 years), adults (A; ≥ 15 and < 65 years) and elderly (E; ≥ 65 and ≤ 99 years). New births entered the chidren S compartment at the beginning of each year. Annual mortality and ageing rates out of each age class were derived from the United Nations World Population Prospects [6] for India, using the medium estimates of projected population from 2019–2050. UN population estimates and projections of all-cause mortality include TB mortality. During model calibration (section §3), we removed model-estimated TB deaths from background mortality and recalculated cause-deleted background mortality. Cause-deleted background mortality was stored for each calibrated parameter set and used as the model input during vaccine simulation (section 2.5).

2 Parameterisation

Prior ranges, references, and constraints for model parameters are presented in Table 1. Mtb transmission was modelled using the force of infection parameter λ section 2.1. Following

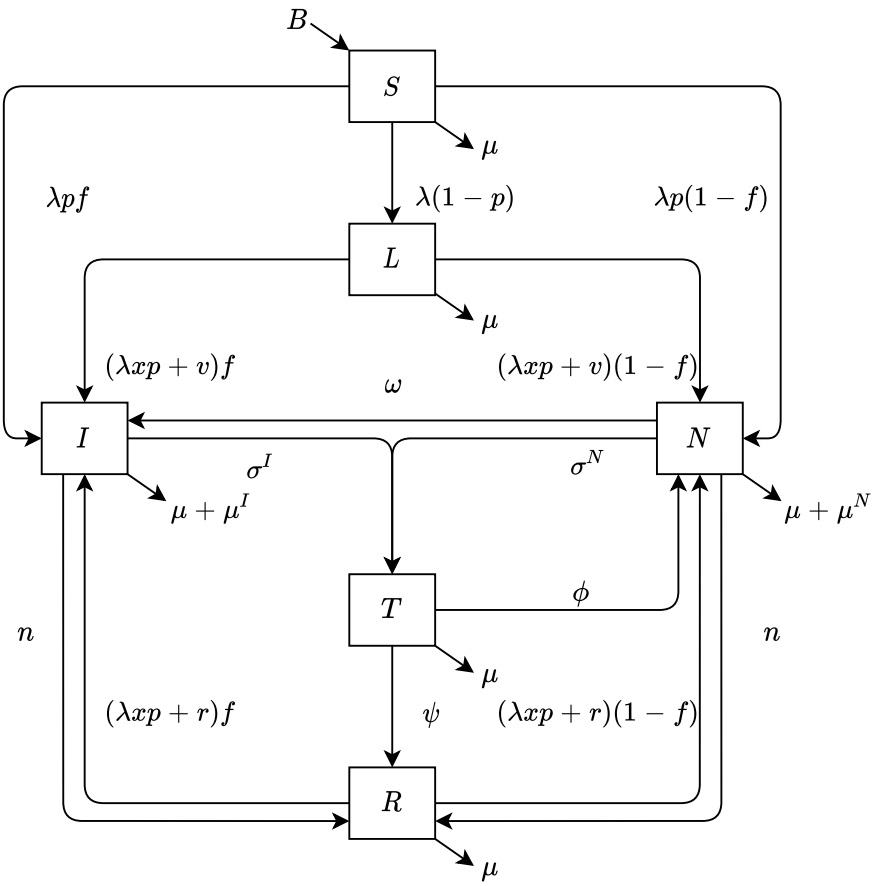

Figure 1: Model diagram. Key for symbols given in Table 1. Boxes represent model compartments, arrows represent transitions. Transitions B and μ represent births into the model and non-TB background mortality, respectively.

infection by Mtb, susceptible individuals transitioned directly to active disease ("fast-progression") or latency with age-specific risk p and $1-p$ respectively. Fast-progressors were divided into infectious vs noninfectious active disease via age-specific parameters f and $1-f$, respectively. Individuals in the L and R compartments could reactivate or relapse, respectively, per age-specific risk parameters v and r. Latently infected individuals and individuals in the recovered compartment could be reinfected and progress to active disease. However current or previous infection was assumed to confer protection against fast-progression to disease: risk of disease following reinfection was reduced per parameter x (where $1-x$ equaled the relative degree of protection). Reinfected latently infected individuals who did not fast-progress remained in the L compartment. However, as relapse rates from recovered are higher than reactivation rates from latency [7–9], reinfected recovered individuals who did not fast-progress did not become latently infected. This would have implied that reinfection would reduce the risk of active disease (from r to v) in recovered individuals, which we considered implausible.

2.1 Transmission

We adapted the formation for age-specific force of infection (λ_i) from Keeling and Rohani [10] to a difference equation (discrete time) model.

Continuous time The standard formulation for force of infection over continuous time derives δq, the probability of infection in some small time interval δt, given some probability π of infection following an infectious contact, average daily contact rate κ, and *proportion* $I(t)$ of infectious individuals in the population at time t. Assuming each contact is an independent event, the probability that an individual avoids infection in some interval δt is

$$1-\delta q = (1-\pi)^{\kappa I(t)\delta t},$$

leading to the expression for the probability of infection in time period δt,

$$\delta q = 1-(1-\pi)^{\kappa I(t)\delta t}.$$

Defining $\beta = -\kappa \cdot \ln(1-\pi)$, taking $\exp(\kappa \ln(1-\pi)) = \exp(-\beta)$ and substituting gives

$$\delta q = 1-\exp(-\beta)^{I(t)\delta t} = 1-\exp(-\beta I(t)\delta t).$$

At the limit of $\frac{\delta q}{\delta t}$ as $\delta t \to 0$,

$$\frac{dq}{dt} = \lambda(t) = -\beta I(t),$$

where λ represents the force of infection and β represents the effective daily contact rate.

Discrete time To adapt the formulation to discrete time, we first multiplied the contact rate κ by 180 to adjust for a six-month time step, leading to the scaled six-monthly effective contact rate:

$$\beta = -180\kappa \ln(1-\pi)$$

We adapted expression $\delta q = 1-\exp(-\beta I(t)\delta t)$ to derive the risk of infection in time step t:

$$\lambda_t = 1-\exp(-\beta I_{t-1})$$

To calculate age-specific force of infection ($\lambda_{i,t}$), we first constructed a pairwise matrix B containing β terms for all combinations of children (c), adults (a) and the elderly (e):

$$B = \begin{bmatrix} \beta_{c,c} & \beta_{c,a} & \beta_{c,e} \\ \beta_{a,c} & \beta_{a,a} & \beta_{a,e} \\ \beta_{e,c} & \beta_{e,a} & \beta_{e,e} \end{bmatrix} = -180 \cdot \ln(1-\pi) \cdot \begin{bmatrix} \kappa_{c,c} & \kappa_{c,a} & \kappa_{c,e} \\ \kappa_{a,c} & \kappa_{a,a} & \kappa_{a,e} \\ \kappa_{e,c} & \kappa_{e,a} & \kappa_{e,e} \end{bmatrix}$$

We assumed that π was constant across all age groups. Thus, differential transmission between age classes was driven solely by heterogeneity in contact rates, represented by the matrix containing κ terms. Each constituent term, $\kappa_{i,j}$ represented the number of contacts each member of i made with group j per day, normalised to give an overall population-wide average contact rate of one per day.

Using matrix B, we derived the final following expression for age-specific force of infection for age group i at time t:

$$\lambda_{i,t} = 1 - \exp(-\sum_{j \in \{c,a,e\}} \beta_{i,j} I_{j,t-1})$$

As this study normalised the contact matrix κ to have a population-wide average contact rate of 1 day^{-1}, π represented an aggregate transmission scaling factor comprising a correction for contact rate and transmission probability.

2.2 Contact Matrix Update Methods

We adapted contact matrix transformation methods from Arregui et al. [11]. We first derived the base contact matrix from aggregated POLYMOD [12] data (Fig 1A in the main text). Then, we divided each contact rate by the overall average contact rate of the source population (approximately 12.79 contacts per day) to provide a normalised matrix $\kappa_{i,j}$.

Here we describe the methods to generate a new contact matrix $\kappa'_{i,j}$, matching the demographic specific composition of population N', containing age groups i and j of magnitude N'_i and N'_j, from some initial matrix $\kappa_{i,j}$, originating from a population N, where age groups i and j have magnitudes N_i and N_j, respectively.

M0

The contact matrix was constant at each time step in the model, applying no corrections to match demography. Median reciprocity error—defined as the fraction of non-reciprocal contacts among all contacts between non-self age-group pairs [11]—is presented in Fig crossref. There was substantial reciprocity error over the model time horizon figure 2A, including over the vaccine simulation period of 2025 (56%) to 2050 (21%).

The M0 method is computationally simple but fails to preserve reciprocity. This may not introduce substantial error, for example, when modelling annual viral epidemics, or in populations where the demographic composition is stable. However, tuberculosis models routinely project over decades, very likely encountering substantial demographic change.

The effect of unadapted, unbalanced matrices are highlighted by considering a different hypothetical population containing age groups l and m, of magnitude N_l and N_m respectively, with contact rates $\kappa_{l,m}$ between each member of l and group m, and $\kappa_{m,l}$ between each member of m and group l. If N_l is increased to N'_l, holding $\kappa_{l,m}$, $\kappa_{m,l}$, and N_m constant, the total contacts with l, by all members of m, $N_m \kappa_{m,l}$ would be fewer than the total new number of contacts with m by l, $N'_l \kappa_{l,m}$, thus underestimating the force of infection experienced by members of m.

M1

The M1 method avoids the reciprocity error inherent to M0, as $\kappa_{i,j}$ and $\kappa_{j,i}$ are recalculated taking the total contacts as the mean of $N_i'\kappa_{i,j}$ and $N_j'\kappa_{j,i}$. This update was applied at each time step, formulated as:

$$\kappa'_{i,j} = \frac{1}{2N'_i}\left(\kappa_{i,j}N'_i + \kappa_{j,i}N'_j\right)$$

By definition, the contact rate of an age-group with itself does not change.

M2

The contact rate between age groups i and j is a function of both intrinsic preference for contact with j by i, relative to contact with other i (i.e., *assortativity*), and the relative *density* of N_j (i.e., $\frac{N_j}{N_i+N_j}$) in the total population. For every contact matrix Q with n age classes, we can compute a corresponding *assortativity matrix* R. The entries of R are the contact rates between i and j, multiplied by a constant factor n, that would be expected in a population where the n classes are equally sized and where the relative preferences for contact between groups are the same as in Q. We derived the base assortativity matrix, A, from the original POLYMOD matrix as:

$$A_{i,j} = \kappa_{i,j}\frac{N}{N_j}.$$

We then recalculated the updated contact matrix during each time step of the model run,

$$\kappa'_{i,j} = A_{i,j}\frac{N'_j}{N'}.$$

In both M0 and M1, despite the changing density of l from of $\frac{N_l}{N}$ to $\frac{N'_l}{N'}$, the contact rate $\kappa_{l,l}$ remains unchanged, implying a counterbalancing change in assortativity.

To provide a summary measure of assortativity in a given mixing matrix, Newman [13] defines an *assortativity coefficient*, which we have adapted as follows.

First, a matrix E is constructed where each entry ϵ_{ij} (with row indices i and column indices j) represents the *fraction* of all contacts made by its associated pair of age groups (children, c, adults, a, and elderly, e in our study)

$$E = \begin{bmatrix} \epsilon_{cc} & \epsilon_{ca} & \epsilon_{ce} \\ \epsilon_{ac} & \epsilon_{aa} & \epsilon_{ae} \\ \epsilon_{ec} & \epsilon_{ea} & \epsilon_{ee} \end{bmatrix}, \sum_{ij}\epsilon_{ij} = 1.$$

.

The row-wise and column-wise sums of contact fractions are defined as

$$\sum_i \epsilon_{ji} = \gamma_j, \sum_j \epsilon_{ij} = a_i.$$

The *assortativity coefficient* [13], ρ, is then given by

$$\rho = \frac{(\epsilon_{cc}+\epsilon_{aa}+\epsilon_{ee}) - (\alpha_c\gamma_c + \alpha_a\gamma_a + \alpha_e\gamma_e)}{1 - (\alpha_c\gamma_c + \alpha_a\gamma_a + \alpha_e\gamma_e)}.$$

In a balanced contact matrix, $\alpha_i = \gamma_i$.

This coefficient ranges from −1 to +1, where +1 represents completely assortative mixing (where each group mixes exclusively within itself), 0 represents random (homogeneous) mixing, and a value $\geq -1, < 0$ for completely disassortative mixing. We observed increasing assortativity in

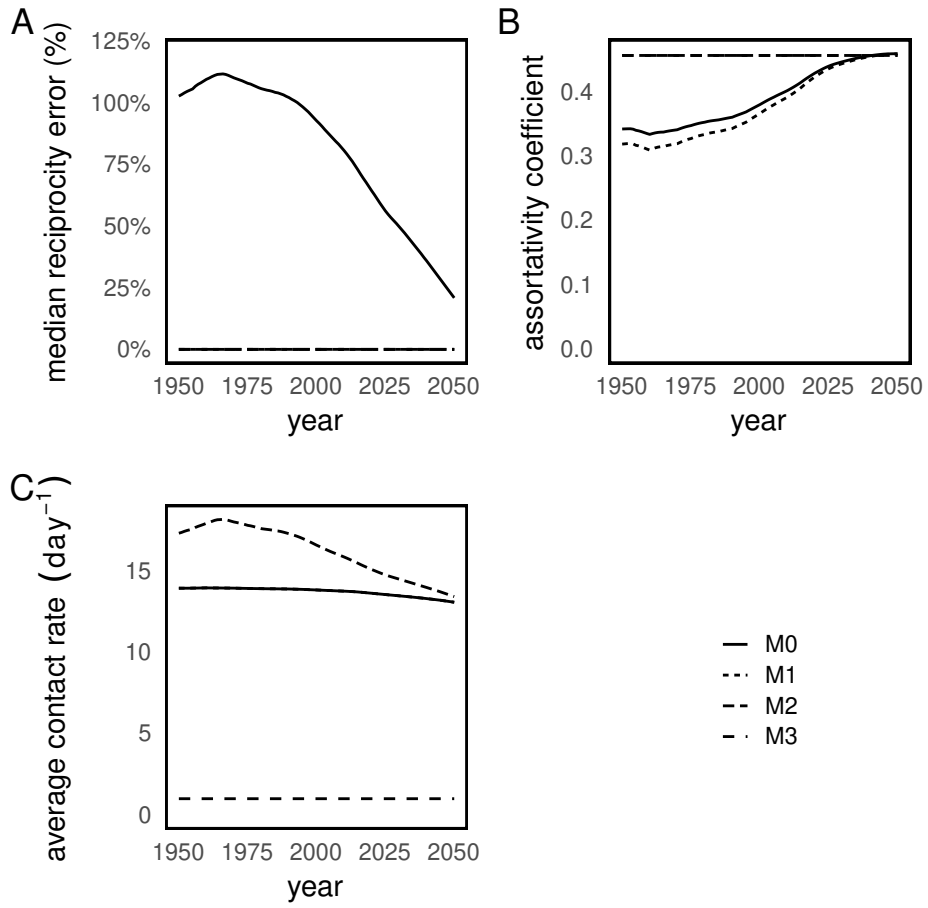

Figure 2: Contact matrix update analysis. **A** Median reciprocity error. Lines for M0–M2 are overlaid on one another. **B** Median assortativity coefficient, ρ. Lines for M2 and M3 are overlaid on one another. **C** Median value for average contact rate per day.

the M0 and M1 models over the model time horizon, with ρ between approximately 0.3 and 0.45 figure 2B. Assortativity remained constant at approximately 0.45 for both M2 and M3 models.

M3

In the M3 update method, we normalised the assortativity matrix derived from the M2 model (denoted here as $\hat{\kappa}$) to have a population-wide average contact of one, as:

$$\hat{\kappa}_{i,j} = \kappa_{i,j} \frac{N N'_j}{N_j N'}$$

$$d = \frac{\sum_{i,j} \hat{\kappa}_{i,j} N'_i}{N'}$$

$$\kappa'_{i,j} = \frac{\hat{\kappa}_{i,j}}{d}$$

We found that average contact rate was higher in the M2 than the M1 model over the model time horizon. Average contact in M1 remained stable at approximately 14.5 contacts per day figure 2**C**.

2.3 Model Parameterisation

Natural history parameters with prior ranges and references are presented in table 1.

We stratified parameters for rates of fast progression following infection (p), progression to infectious vs. non-infectious disease (f), reactivation from latency (v), relapse from the recovered state (r), and TB mortality (separately for infectious [μ^{I}] vs non-infectious disease [μ^{N}]) by age for children, adults, and the elderly, independently sampling each from age-specific priors during calibration (table 1). There is no empirical data to substantiate the upper bound for fast-progression rate in the elderly; therefore, we used progression rates in HIV+ populations for this value, assuming that immunocompromise was a reasonable proxy for immunosenescence. Where age-specific prior ranges overlapped, we constrained the sampling process to retain values for progression rate, reactivation from latency, and TB mortality, in children and the elderly only if greater than in adults. Similarly, natural cure rate was constrained to be lower in the elderly than adults. We fitted treatment initiation rate ($c2020$) in 2020, interpolating from zero in 1960 to the fitted value in 2020. Treatment outcomes were taken from WHO [14] data. Both treatment initiation rates and outcomes were held constant after 2020.

2.4 Model Equations

Equations describing transitions between model compartments are given in this section. In the following equations, subscript t represents the current time step and j represents a generic age class. Symbol definitions are presented in table 1. Where indicated, subscripts c, a, and e specifically refer to child, adult, and elderly specific states, respectively. As the model time-step was defined as six months (the duration of first-line therapy for active tuberculosis), outflow from the treatment compartment (T) is the entire content of that compartment in step $t-1$.

Susceptible (S) compartment

$$S_{t,j} = (1 - \lambda_{t-1,j})S_{t-1,j}$$

Latent Infection (L) compartment

$$\begin{aligned} L_{t,j} = &(1 - v_j - \lambda_{t-1,j}xp_j - \mu_{t-1,j})L_{t-1,j} \\ &+ (1 - p_j)\lambda_{t-1,j}S_{t-1,j} \end{aligned}$$

Active infectious disease (I) compartment

$$\begin{aligned} I_{t,j} = &(1 - n_j - \sigma^{\mathrm{I}}_{t-1} - \mu^{\mathrm{I}}_j - \mu_{t-1,j})I_{t-1,j} \\ &+ \lambda_{t-1,j}p_j f_j S_{t-1,j} \\ &+ (\lambda_{t-1,j}xp_j + v_j)f_j L_{t-1,j} \\ &+ N_{t-1,j}\omega \\ &+ (\lambda_{t-1,j}xp_j + r_j)f_j R_{t-1,j} \end{aligned}$$

Active noninfectious (N) compartment

$$\begin{aligned} N_{t,j} = &(1 - n_j - \sigma^{\mathrm{N}}_{t-1} - \mu^{\mathrm{N}}_j - \mu_{t-1,j} - \omega)N_{t-1,j} \\ &+ \lambda_{t-1,j}p_j(1 - f_j)S_{t-1,j} \\ &+ (\lambda_{t-1,j}xp_j + v_j)(1 - f_j)L_{t-1,j} \\ &+ (\lambda_{t-1,j}xp_j + r_j)(1 - f_j)R_{t-1,j} \\ &+ (1 - \mu_{t-1,j})\phi_{t-1}T_{t-1,j} \end{aligned}$$

Table 1: Model Parameters. Subscript j indicates the parameter was age-stratified, with subscripts c, a, and e representing child, adult, and elderly age groups respectively. We assumed uniform prior ranges for all sampled parameters.

Parameter and symbols	**Prior ranges and constraints**	**References**
NATURAL HISTORY PARAMETERS		
Risk of progressing directly to active TB following (re-)infection p_j	$0.01 \leq p_c \leq 0.06$ $0.08 \leq p_a \leq 0.2$ $p_a \leq p_e \leq 0.36$	[1, 7, 8, 15]
Protection from re-infection or developing active TB due to latent infection or recovered state x	$0.25 \leq x \leq 0.4$	[7, 8, 16, 17]
Risk of reactivation from latent infection or recovered state v_j	$0.0001 \leq v_c \leq 0.0003$ $0.0001 \leq v_a \leq 0.0003$ $v_a \leq v_e \leq 0.04$	[1, 15, 17–19]
Proportion of new active cases becoming infectious f_j	$0 \leq f_c \leq 0.15$ $0.25 \leq f_a \leq 0.75$ $0.19 \leq f_e \leq f_a$	[7, 15, 18, 20–22]
Risk of converting from noninfectious to infectious active disease ω	$0.007 \leq \omega \leq 0.02$	[23]
Risk of natural cure n_j	$0.1 \leq n_c \leq 0.25$ $n_c = n_a$ $0.1 \leq n_e \leq n_a$	[7, 15]
Risk of relapse from recovered r_j	$0.005 \leq r_c \leq 0.015$ $0.005 \leq r_a \leq 0.015$ $r_a \leq r_e \leq 0.015$	[24]
Risk of mortality with active infectious TB μ^{I}	$0 \leq \mu_a^{\mathrm{I}} \leq 0.178$ $\mu_a^{\mathrm{I}} \leq \mu_c^{\mathrm{I}} \leq 0.178$ $\mu_a^{\mathrm{I}} \leq \mu_e^{\mathrm{I}} \leq 0.178$	[25]
Risk of mortality with active noninfectious TB μ^{N}	$0 \leq \mu_a^{\mathrm{N}} \leq 0.034$ $\mu_a^{\mathrm{N}} \leq \mu_c^{\mathrm{N}} \leq 0.034$ $\mu_a^{\mathrm{N}} \leq \mu_e^{\mathrm{N}} \leq 0.034$	[25]
Transmission calibration factor π	$0 \leq -\log_{10}(\pi) \leq 2$	Fitted.
TREATMENT AND DIAGNOSIS PARAMETERS		
Risk of treatment initiation in 2020 $c2020$	$0 \leq c2020 \leq 1$	Fitted.
Relative detection of non-infectious cases e	$0.4 \leq e \leq 0.8$	Fitted.

Treatment (T) compartment

$$T_{t,j} = \sigma^{\mathrm{I}}_{t-1} I_{t-1,j} + \sigma^{\mathrm{N}}_{t-1} N_{t-1,j}$$

Recovered (R) compartment

$$\begin{aligned} R_{t,j} = {} & (1 - \lambda_{t-1,j} x p_j - r_j - \mu_{t-1,j}) R_{t-1,j} \\ & + (I_{t-1,j} + N_{t-1,j}) n_j \\ & + (1 - \mu_{t-1,j}) \psi_{t-1} T_{t-1,j} \end{aligned}$$

Demography

New births into the model were implemented as new entries into the children age group in the first time step of each calendar year.

$S_{t,c} = S_{t,c} + B_t$

We implemented population aging at every time step as a calendar-time specific risk, calculated from World Population Prospects [6] projections, out of the child compartments into the adult compartments, and out of the adult compartments into the elderly compartments. Individuals aging out of the elderly compartment were assumed to experience 100% mortality. Thus, for any particular compartment Y, aging rates g were applied as:

Ageing out of S, L, and I compartments:

$Y_{j,t} = Y_{j,t} - g_{j,t-1} Y_{j,t-1}$

Ageing out of compartment N:

$N_{j,t} = N_{j,t} - g_{j,t-1}(N_{j,t-1} + T_{j,t-1}\phi_{t-1})$

Ageing out of compartment R:

$R_{j,t} = R_{j,t} - g_{j,t-1}(R_{j,t-1} + T_{j,t-1}\psi_{t-1})$

Aging into compartments S, L, and I:

$Y_{a,t} = Y_{a,t} + g_{c,t-1} Y_{c,t-1}$

$Y_{e,t} = Y_{e,t} + g_{a,t-1} Y_{a,t-1}$

Ageing into compartment N:

$N_{a,t} = N_{a,t} + g_{c,t-1}(N_{c,t-1} + T_{c,t-1}\phi_{t-1})$

$N_{e,t} = N_{e,t} + g_{a,t-1}(N_{a,t-1} + T_{a,t-1}\phi_{t-1})$

Ageing into compartment R:

$R_{a,t} = R_{a,t} + g_{c,t-1}(R_{c,t-1} + T_{c,t-1}\psi_{t-1})$

$R_{e,t} = R_{e,t} + g_{a,t-1}(R_{a,t-1} + T_{a,t-1}\psi_{t-1})$

Aging in and out of the N and R compartments had additional terms to represent aging which occurred to those exiting the T compartment. The foregoing demographic transitions were replicated during vaccine simulation in the vaccinated stratum.

2.5 Vaccine Implementation

We implemented vaccination in the model as described elsewhere [2–5].

We categorised vaccines qualitatively into two dimensions: by host-infection required for efficacy and by preventive effect. We stratified vaccine by the host-infection status required for efficacy: (1) "preinfection" (PRI) vaccines were only effective in susceptible individuals, with no prior history of infection; (2) "postinfection" (PSI) vaccines were effective in those with latent infection and resolved infection; and (3) "pre- and postinfection" (P&PI) vaccines were effective in all three types of host infection status. We also stratified vaccines to prevent infection (POI), prevent disease (POD), or both (POI/D). To represent the vaccinated population, we replicated each compartment C to create an equivalent vaccinated compartment C_V.

Table 2: Calibration Targets. Target values and ranges are specified as per 100,000 population.

Target	Year	Age group	Value		References
			midpoint	range	
Incidence	2010	All	247	(128–405)	[14, 26]
	2019	Children ($<$ 15y)	90	(55–126)	
		All	193	(132–266)	
		All Adults ($\geq$ 15y)	230	(140–321)	
		Elderly ($\geq$ 65y)	277	(0–622)	
	2050[1]	All	234	(190–271)	M1 model projection.
Mortality	2019	All	33	(30–35)	[14, 26]
Notification	2019	All	190	(152–228)	[14, 26]
Prevalence	2015	All	253	(195–312)	[27]

Vaccination at coverage q was represented by transition from the unvaccinated compartment to its corresponding vaccinated equivalent ($C \rightarrow C_V$) and waning of protection at rate omega as transition in the opposite direction ($C_V \rightarrow C$).

3 Calibration

3.1 Targets

The common calibration targets for all models M0–M3 are presented in table 2. We calibrated all models to a minimum of eight calibration targets, including prevalence, mortality, incidence and notification rates [14, 26]. As India has not yet reported a nationally representative tuberculosis prevalence survey, we used estimates of bacteriologically-positive prevalence rate derived through pooling subnational estimates as a calibration target for all TB prevalence rate [27]. We derived age-stratified incidence *rates* from overall incidence estimates published by WHO and population estimates from World Population Prospects [6]. Overall mortality rates were obtained form the WHO Tubeculosis Database [14].

We assumed that treatment initiation rate within the model corresponded to published notification rates. We assumed a 20% uncertainty interval around point estimates of notification rate to adjust for potential private sector (unreported) treatment of TB and for loss to follow up between diagnosis and treatment initiation and calibrated rates of treatment initiation (σ) to this range. As described in the main text, we also calibrated models M0, M2, and M3 to all-age TB incidence rate projected by model M1.

3.2 Methods

We calibrated the model independently for each update method (M0–M3).

We calculated a normalised distance ratio, o, using model output t that required calibration to target t_{mid} within range t_{low}–t_{high} as:

$$o = \begin{cases} \frac{t - t_{\text{mid}}}{t_{\text{high}} - t_{\text{mid}}} & \text{if } t \geq t_{\text{mid}} \\ \frac{t_{\text{mid}} - t}{t_{\text{mid}} - t_{\text{low}}} & \text{if } t < t_{\text{mid}} \end{cases}$$

We applied a penalty for model outputs which fell outside the uncertainty bounds as

[1] For models M0, M2, and M3 only

$$\hat{o} = \begin{cases} o \cdot n & \text{if } o > 1 \\ o & \text{if } o \leq 1 \end{cases},$$

where n equaled the total number of targets to fit.

We then sampled the parameter space consistent with calibration targets using an Approximate Bayesian Computation Markov Chain Monte Carlo (ABC-MCMC) [28–31]. We used (random) ABC rejection sampling to initialise the MCMC chains. Where random sampling failed to find an adequate parameter set to initiate an MCMC chain, we used box-constrained optimisation to minimise the sum of $\hat{o}$. MCMC chains were then seeded with these optimised parameter sets to fully characterise the compatible parameter space.

The sampler tolerance, ϵ, was set equal to n, representing the maximum Euclidean distance of the normalised model outputs at which the ABC-MCMC sampler would accept parameter samples. Each MCMC chain was run for 10 million iterations, thinning accepted samples at a ratio of 100:1. Of the resulting 100,000 samples we randomly subsampled 1000 parameter sets to generate final results.

Supplementary Results

4 Calibration and Baseline Projections

4.1 ABC-MCMC Sampler Performance

Broadly, we achieved good mixing of MCMC chains over all models calibrated to all updated methods. The posterior parameter space compatible with model fit to all calibration targets was most constrained in the M3 model, as evidenced in the posterior density plots Figure 7, leading to comparatively reduced mixing compared to M0–2. MCMC chains for the 100,000 retained final samples for each calibrated model are presented in figures 3–6.

4.2 Posterior Distributions

The posterior distributions for all parameters across calibrated models for M0–M3 are presented in Figure 7. We found that the posterior parameter space compatible with full fit to calibration targets was consistently reduced in the M3 model compared to M0–M2.

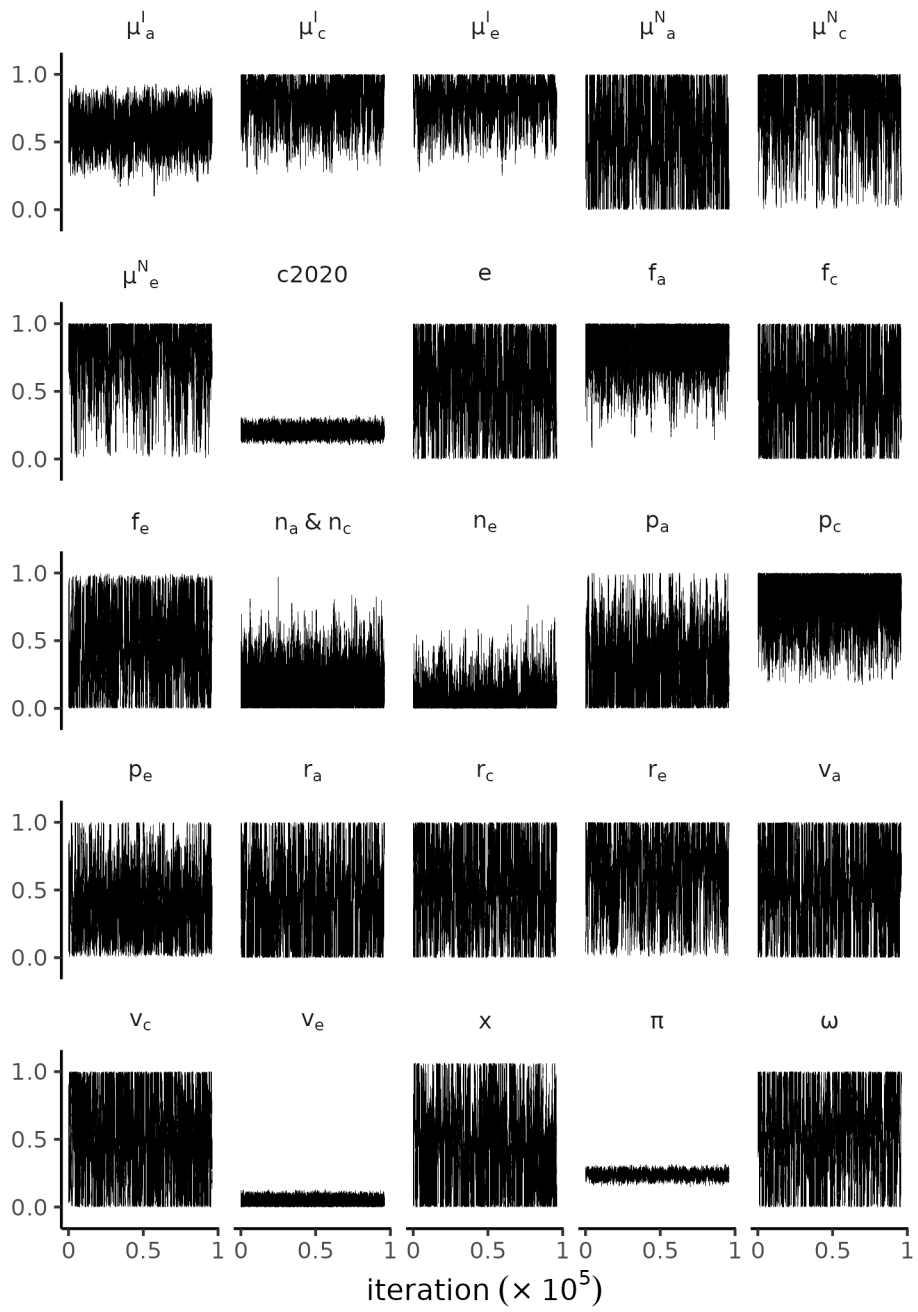

Figure 3: MCMC chains generated during calibration of M0 model. 100,000 samples were retained per chain. Y-axes display parameter values normalised against their respective prior ranges.

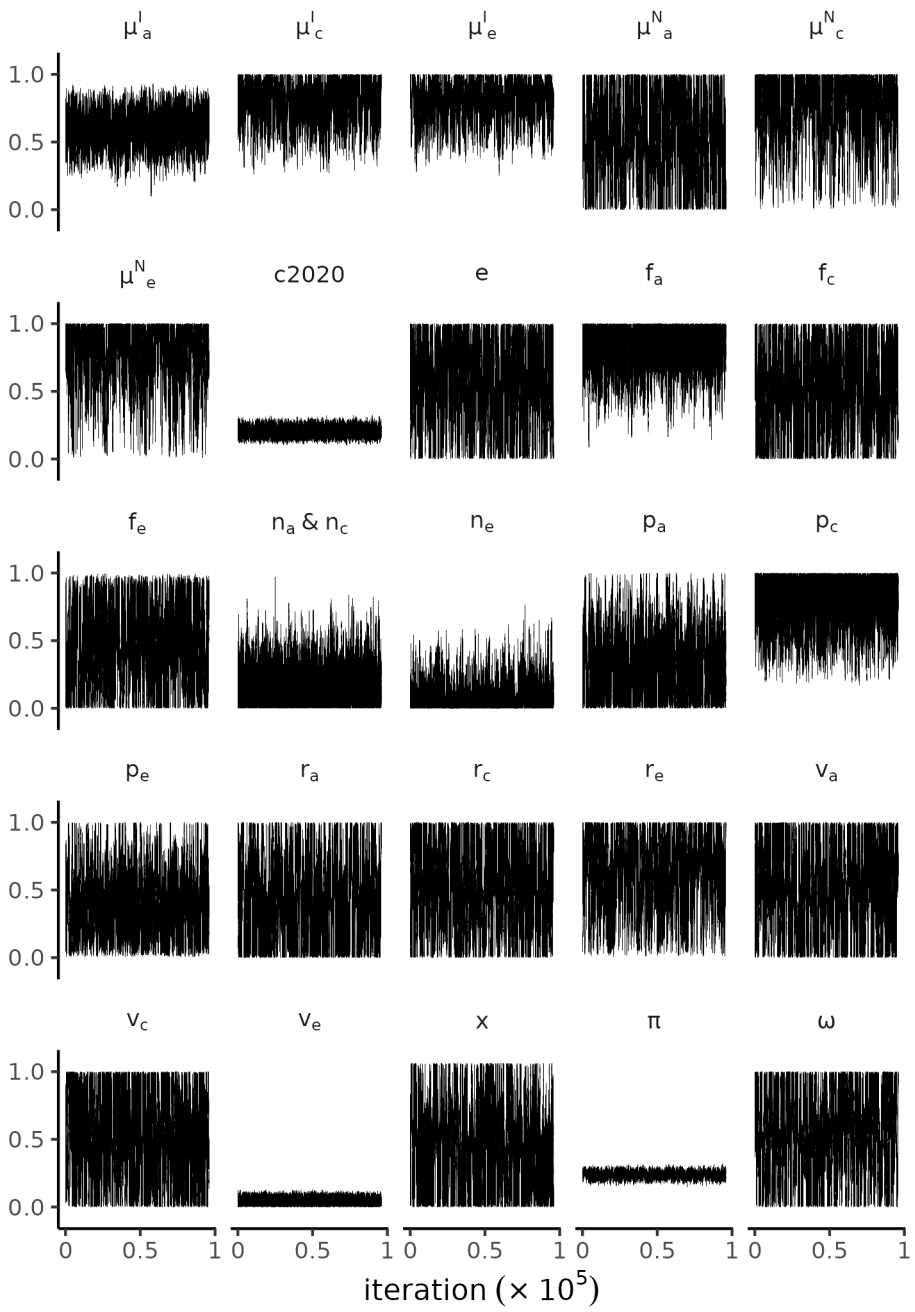

Figure 4: MCMC chains generated during calibration of M1 model. 100,000 samples were retained per chain. Y-axes display parameter values normalised against their respective prior ranges.

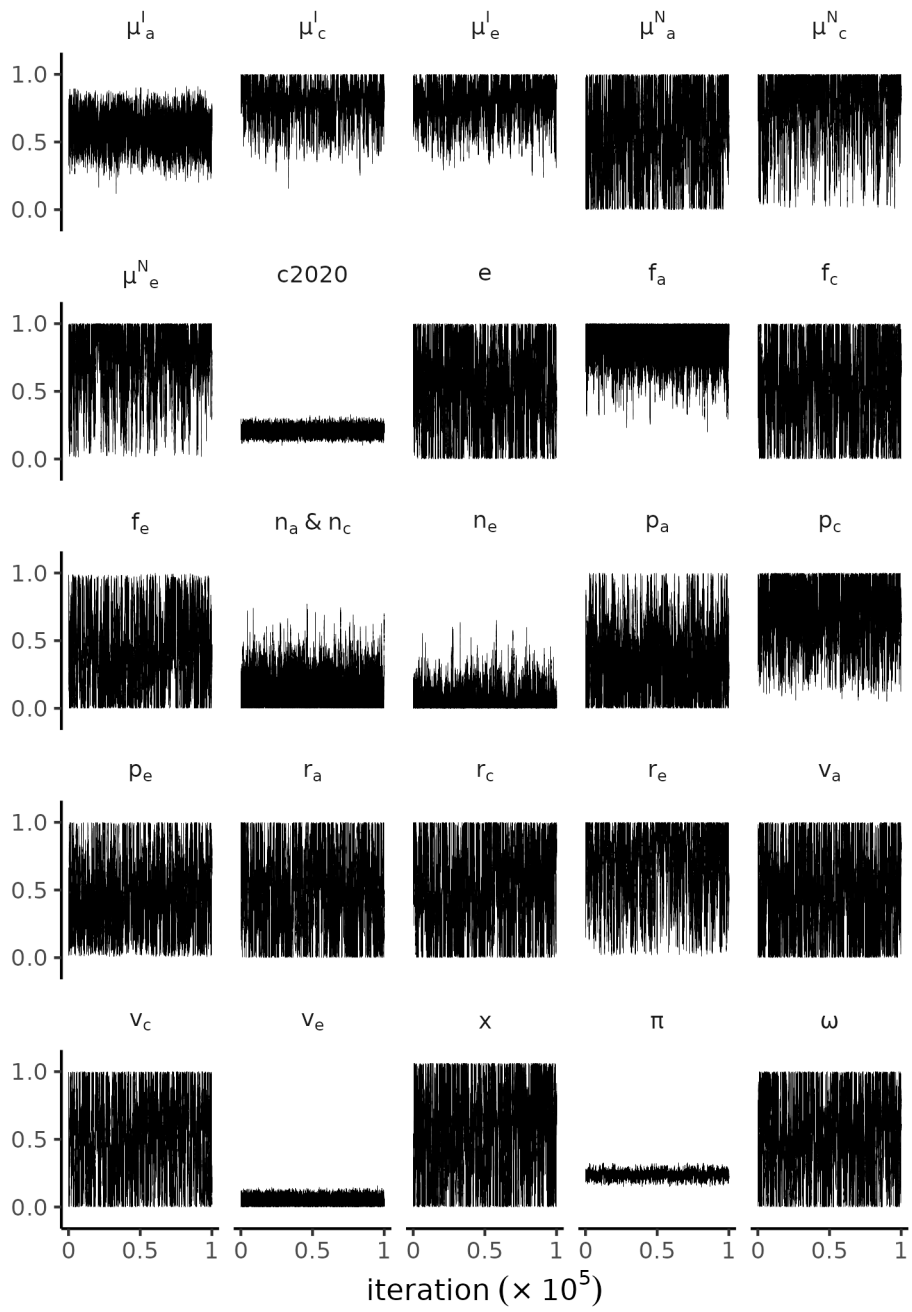

Figure 5: MCMC chains generated during calibration of M2 model. 100,000 samples were retained per chain. Y-axes display parameter values normalised against their respective prior ranges.

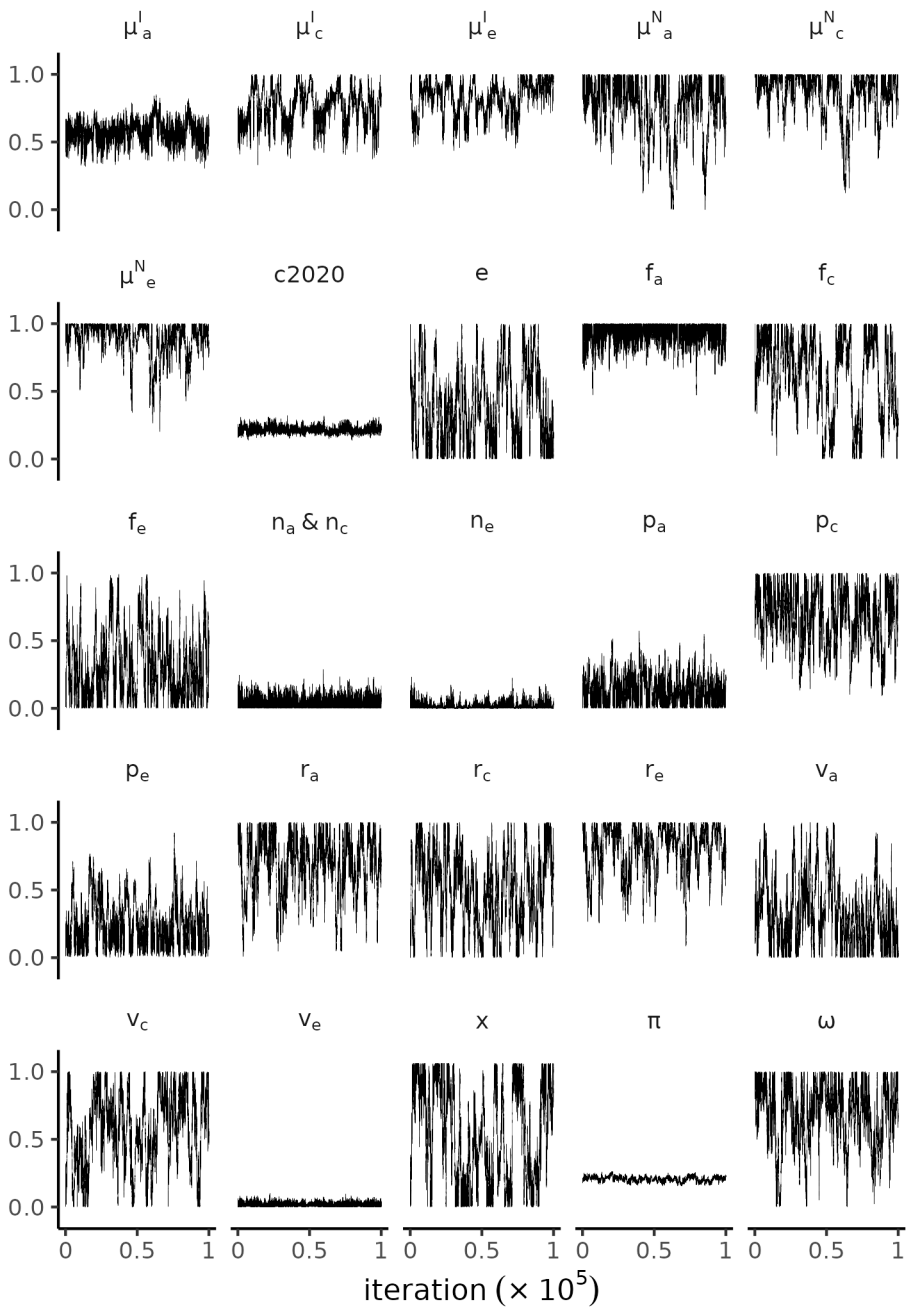

Figure 6: MCMC chains generated during calibration of M3 model. 100,000 samples were retained per chain. Y-axes display parameter values normalised against their respective prior ranges.

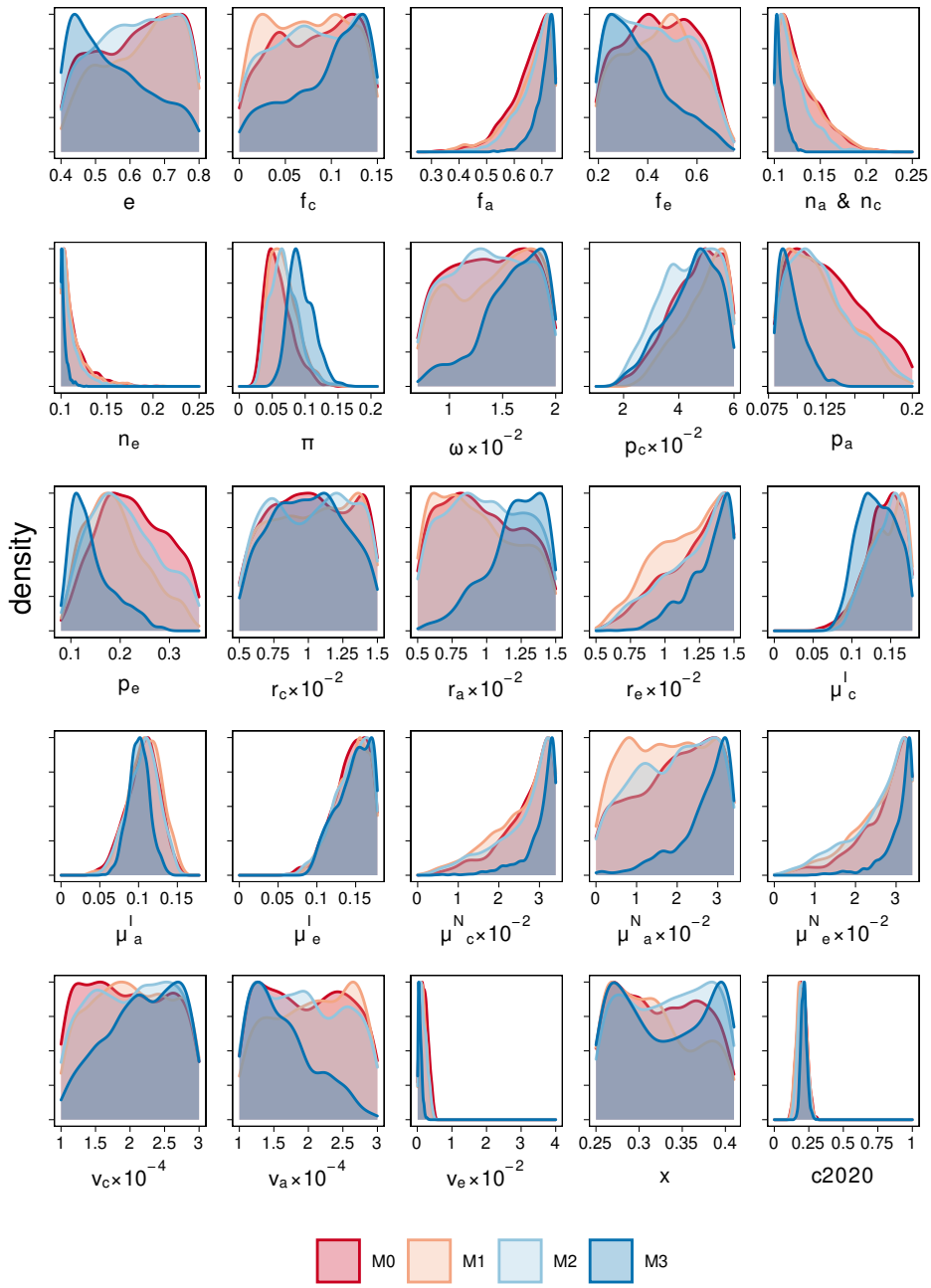

Figure 7: Posterior distributions of model parameters. Y-axis values are normalised to a maximum value of one. X-axis limits represent the prior ranges of each parameter.

4.3 Baseline Projections

Calibration results for the M1 model and baseline incidence projections to 2050 are presented in Figure 8.

In the M1 model, prevalence rate was predicted to be 217 (uncertainty range: 195–312) per 100,000 in 2015, mortality rate was predicted to be 32 (UR: 30–35) per 100,000 and notification rate was predicted to be 167 (UR: 152–213) per 100,000 in 2019, respectively. Overall incidence rate was predicted to be 248 (UR: 206–293) per 100,000, 244 (UR: 205–265) per 100,000, and 234 (UR: 190–271) per 100,000 in 2010, 2019, and 2050 respectively.

As described in the main text, we applied the M0 2050 incidence rate value as a calibration target for the M0, M2, and M3 models.

Calibration results and baseline incidence projections to 2050 for the M0, M2, and M3 models are presented in Figures 9, 10 and 11 respectively.

In the M0 model, prevalence rate was predicted to be 217 (UR: 195–310) per 100,000 in 2015, mortality rate was predicted to be 32 (UR: 30–35) per 100,000 and notification rate was predicted to be 168 (UR: 152–217) per 100,000 in 2019, respectively. Overall incidence rate was predicted to be 249 (UR: 205–288) per 100,000, 244 (UR: 206–265) per 100,000, and 239 (UR: 195–271) per 100,000 in 2010, 2019, and 2050 respectively.

In the M2 model, prevalence rate was predicted to be 213 (UR: 195–312) per 100,000 in 2015, mortality rate was predicted to be 32 (UR: 30–35) per 100,000 and notification rate was predicted to be 167 (UR: 152–221) per 100,000 in 2019, respectively. Overall incidence rate was predicted to be 234 (UR: 195–275) per 100,000, 242 (UR: 209–266) per 100,000, and 258 (UR: 213–271) per 100,000 in 2010, 2019, and 2050 respectively.

In the M3 model, prevalence rate was predicted to be 204 (UR: 195–273) per 100,000 in 2015, mortality rate was predicted to be 31 (UR: 30–35) per 100,000 and notification rate was predicted to be 161 (UR: 152–214) per 100,000 in 2019, respectively. Overall incidence rate was predicted to be 210 (UR: 180–263) per 100,000, 225 (UR: 206–263) per 100,000, and 266 (UR: 237–271) per 100,000 in 2010, 2019, and 2050 respectively.

4.3.1 Model Demography

Demographic projections for India from World Population Prospects for 2025–2050 are shown in figure 12A for the population overall and for the three age-groups of interest. Assuming υ_{U} as the World Population Prospected projected population value, and υ_{M} as the population estimate predicted by the M0–M3 models, we defined the relative error as:

$$\text{relative error} = \log_{10}\left(\frac{\upsilon_{\mathrm{U}} - \upsilon_{\mathrm{M}}}{\upsilon_{\mathrm{U}}}\right).$$

We found low relative error across all models, suggesting good concordance between projected demography and the underlying UN data figure 12B–E. Error was smallest in the M3 model, likely reflecting the smaller fitted parameter space and ensuing reduced variability in model projections.

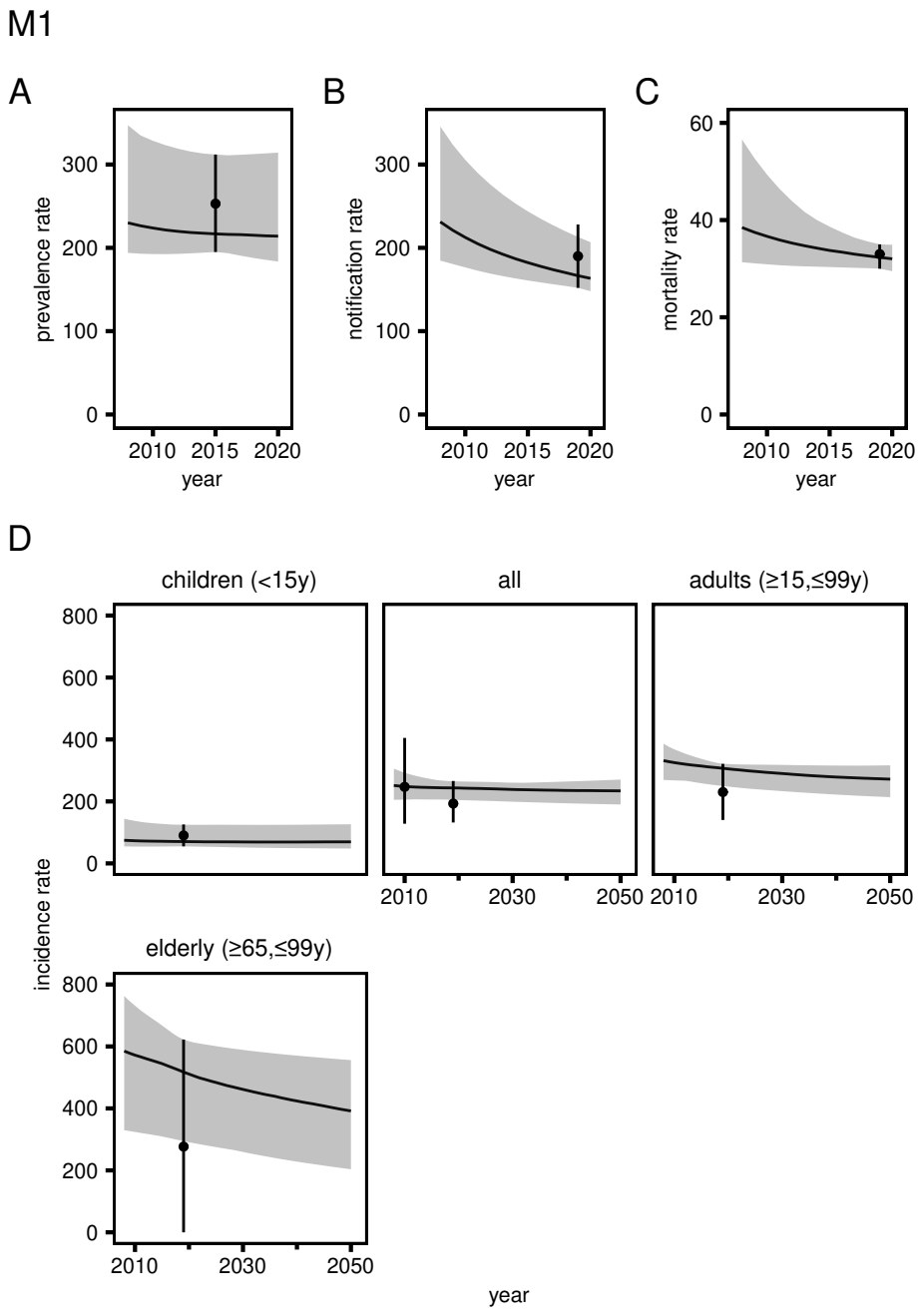

Figure 8: Calibration and Baseline Projections—M1. Rates are specified per 100,000 population. Lines represent median estimates, ribbons represent uncertainty range. Points and bars represent calibration target and range, respectively. **A:** overall prevalence rate. **B:** overall notification rate. **C:** overall mortality rate. **D:** incidence rate, overall and disaggregated by age group, projected to 2050.

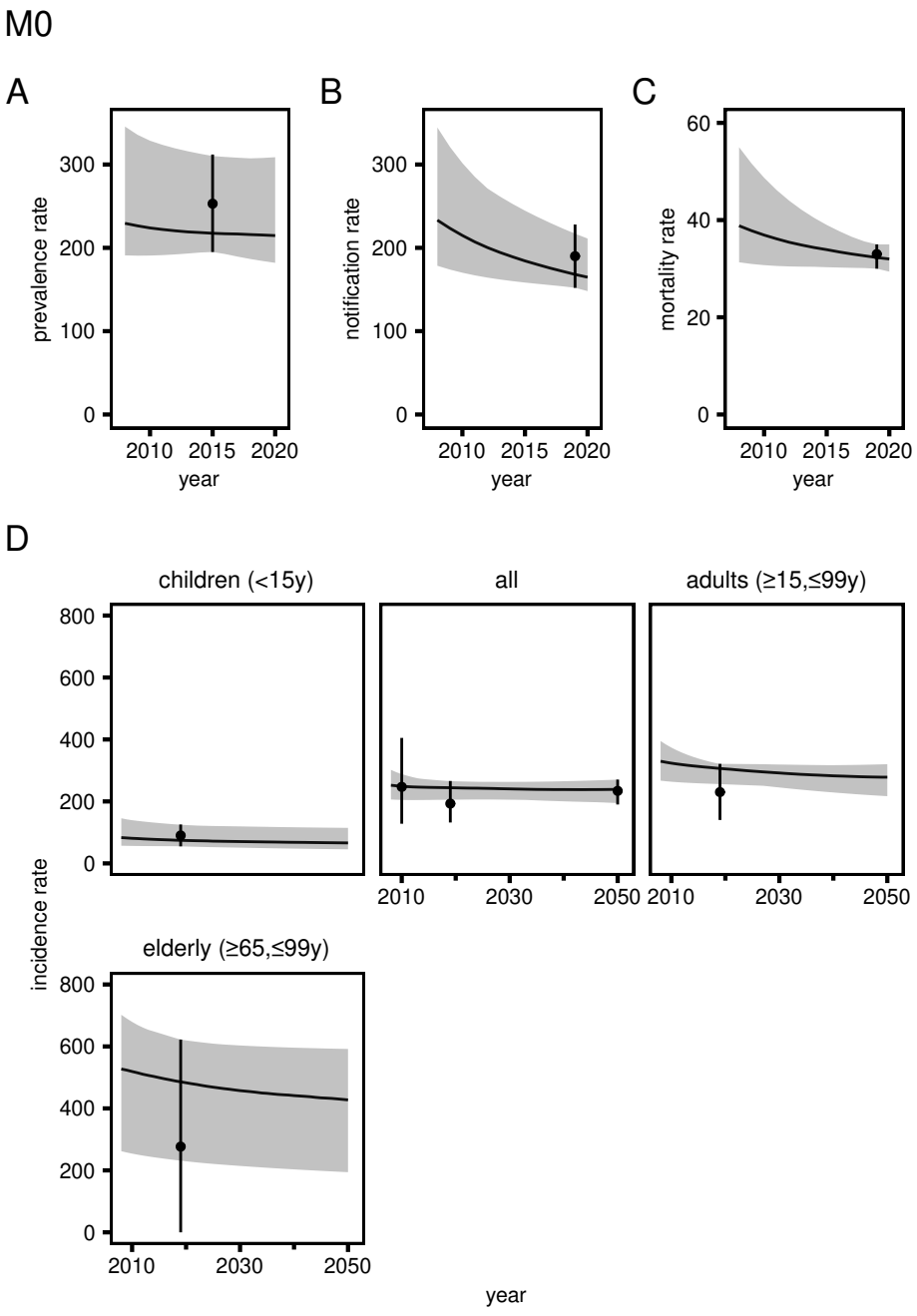

Figure 9: Calibration and Baseline Projections—M0. Rates are specified per 100,000 population. Lines represent median estimates, ribbons represent uncertainty range. Points and bars represent calibration target and range, respectively. **A:** overall prevalence rate. **B:** overall notification rate. **C:** overall mortality rate. **D:** incidence rate, overall and disaggregated by age group, projected to 2050, including calibration target derived from model M1.

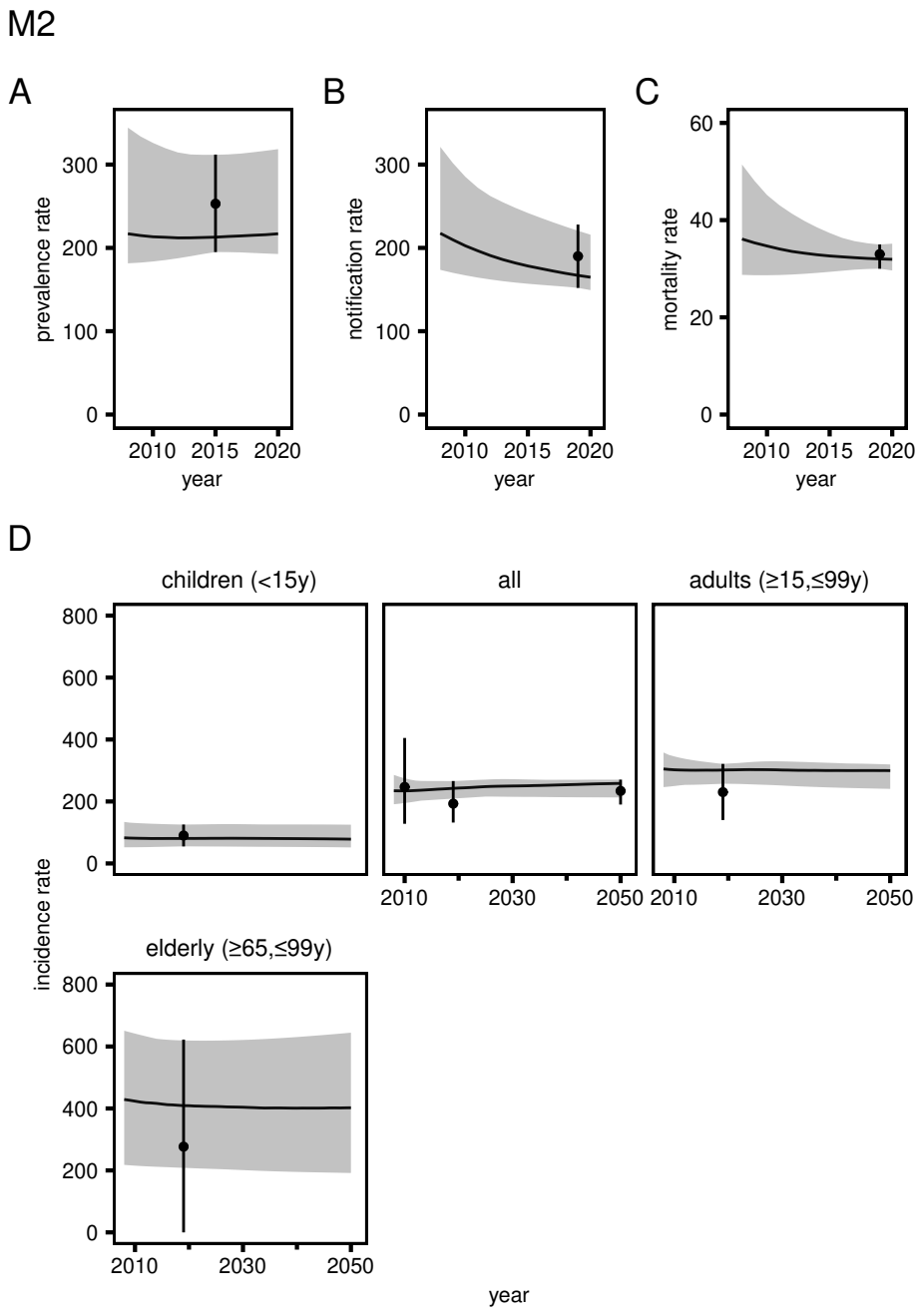

Figure 10: Calibration and Baseline Projections—M2. Rates are specified per 100,000 population. Lines represent median estimates, ribbons represent uncertainty range. Points and bars represent calibration target and range, respectively. **A:** overall prevalence rate. **B:** overall notification rate. **C:** overall mortality rate. **D:** incidence rate, overall and disaggregated by age group, projected to 2050, including calibration target derived from model M1.

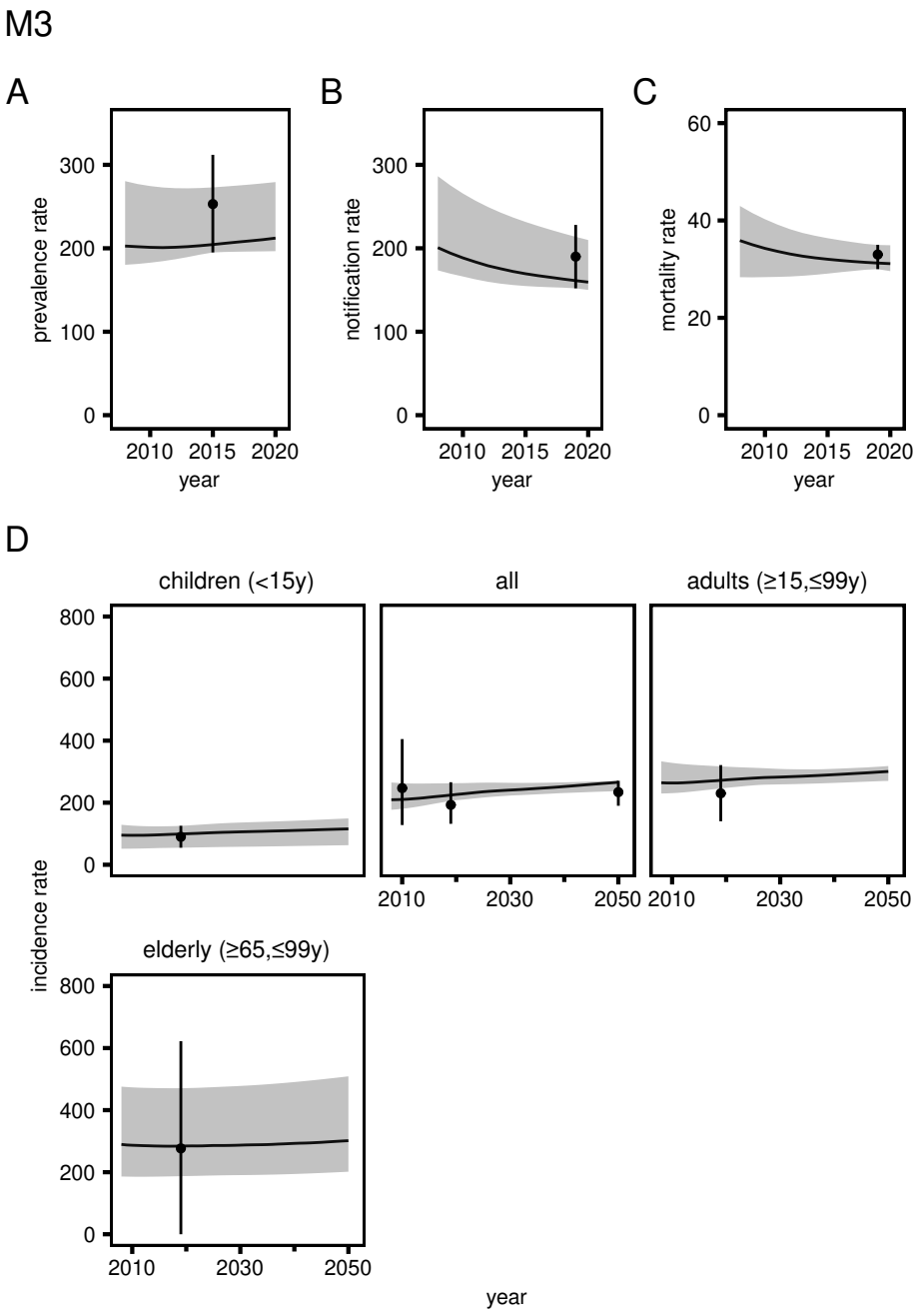

Figure 11: Calibration and Baseline Projections—M3. Rates are specified per 100,000 population. Lines represent median estimates, ribbons represent uncertainty range. Points and bars represent calibration target and range, respectively. **A:** overall prevalence rate. **B:** overall notification rate. **C:** overall mortality rate. **D:** incidence rate, overall and disaggregated by age group, projected to 2050, including calibration target derived from model M1.

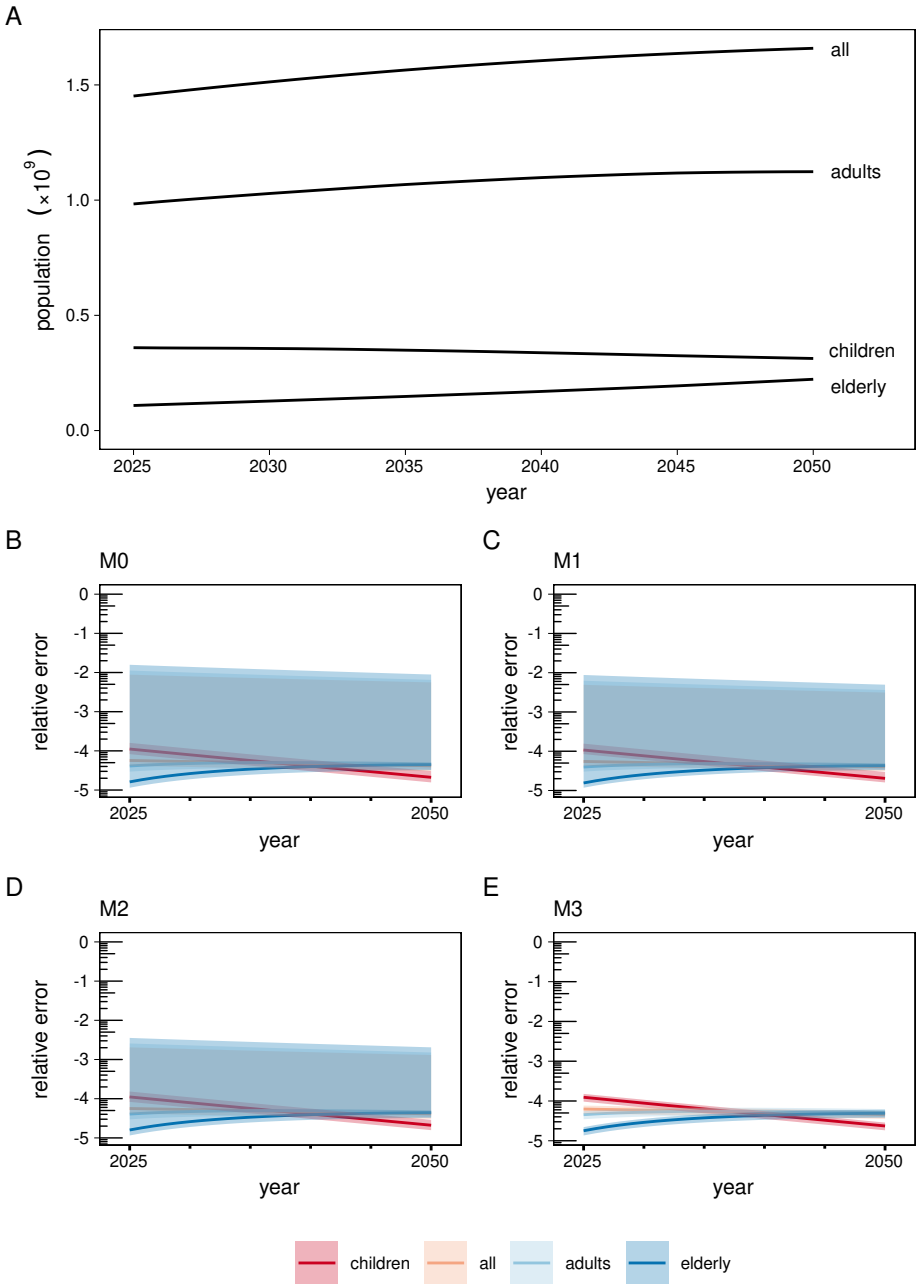

Figure 12: Model demography. **A:** UN World Population Prospects (WPP) [6] medium projection—India country profile. **B–E:** Model relative error in update methods M0–M3. Less negative relative error values indicate a higher discrepancy between the model projected demography and WPP demography.

4.3.2 Epidemic Analysis

Figure 13 shows TB incidence disaggregated by source. We find that the epidemic structure is broadly similar across M0–M3 models, largely driven by new infection followed by fast progression in naive individuals and recovered individuals, with a comparatively minor contribution from either reactivation or reinfection of latently infected individuals.

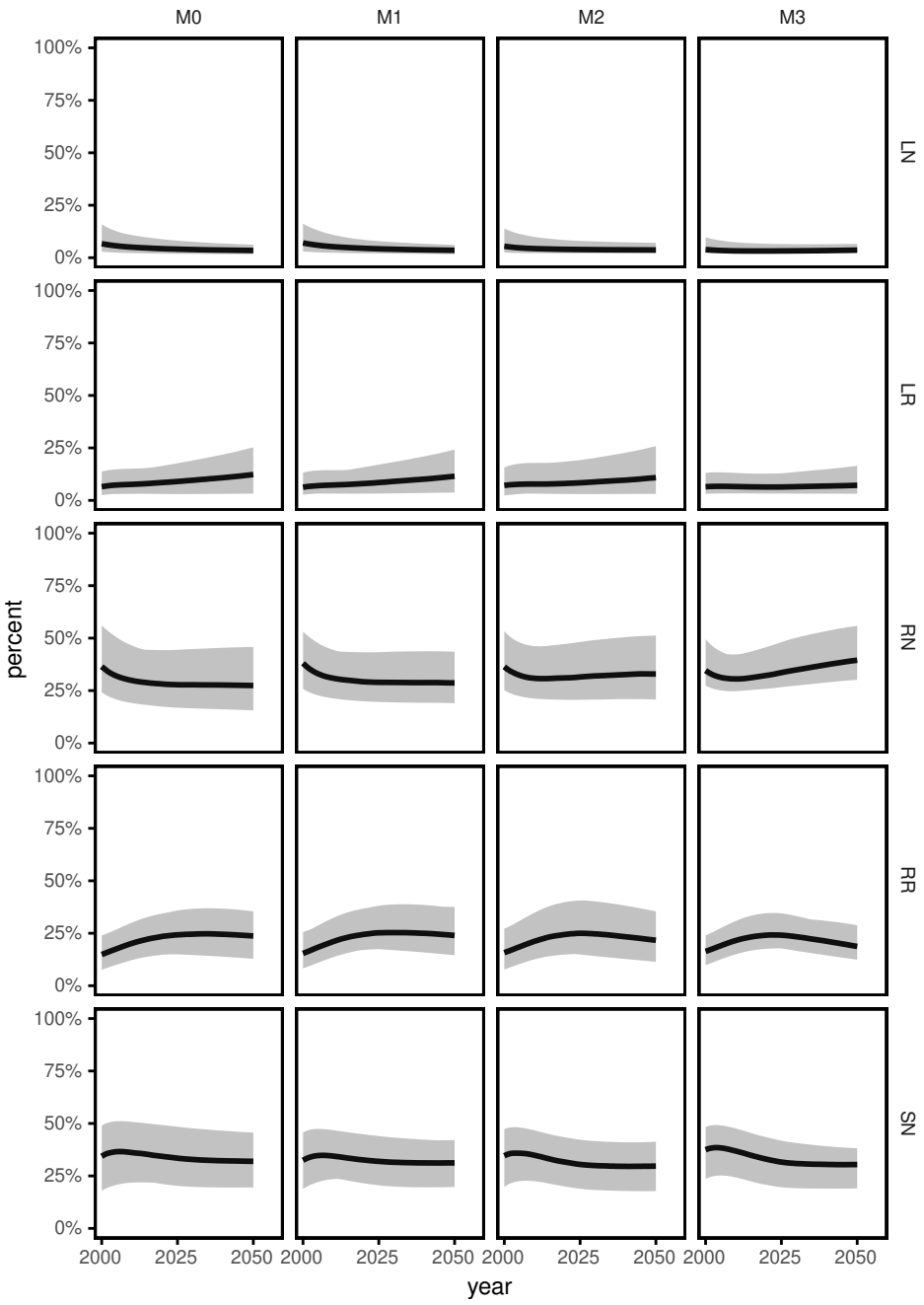

Figure 13: Proportion of incident TB due to each transition-type. Rows represent the proportion of incident TB due to new infection and fastprogression of latently infected individuals (LN); reactivation in latent individuals (LR); new infection and fastprogression in recovered individuals (RN); relapse in recovered individuals (RR); and new infection followed by fastprogression in susceptible individuals (SN). Columns represent M0–M3 updated models. Lines represent median estimates, ribbons represent uncertainty ranges.

5 Vaccine Impact

Vaccine impact across models M0–M3 is summarised in table 3, including a sensitivity analysis for host infection status required for efficacy. We find that differential vaccine impact across update methods remains insensitive to host-infection status required for efficacy. Similar to PSI vaccines, the maximum difference in impact in the elderly following adult-targeted vaccination at 8% between M0 and M3 scenarios.

Table 3: Percent TB incidence rate reduction due to vaccine compared to no-vaccine in 2050, over four contact matrix update scenarios. The vaccine is assumed to have been delivered at 70% coverage and 10-yearly mass campaigns beginning in 2027. Values represent median (uncertainty interval).

Host Status	Target Group	Update Method	Outcome Group		
			children	adults	elderly
P&PI	children	M0	33% (30–35)	5% (4–7)	2% (1–4)
		M1	33% (30–35)	5% (4–8)	2% (1–4)
		M2	33% (30–36)	6% (4–8)	2% (1–5)
		M3	33% (30–35)	6% (5–8)	3% (2–5)
	adults	M0	43% (34–53)	55% (49–63)	23% (15–38)
		M1	45% (35–55)	55% (50–63)	25% (15–38)
		M2	46% (36–57)	58% (51–66)	27% (16–43)
		M3	47% (39–56)	59% (55–67)	31% (20–45)
	elderly	M0	4% (1–9)	3% (1–7)	31% (29–36)
		M1	3% (1–7)	2% (1–6)	31% (29–35)
		M2	2% (1–6)	2% (1–5)	30% (28–35)
		M3	1% (1–3)	1% (0–3)	29% (28–32)
PRI	children	M0	24% (17–27)	4% (3–6)	1% (1–3)
		M1	24% (19–28)	4% (3–6)	2% (1–3)
		M2	23% (17–27)	4% (3–7)	2% (1–4)
		M3	22% (17–26)	5% (4–6)	2% (1–4)
	adults	M0	12% (5–23)	17% (8–28)	6% (2–14)
		M1	12% (5–25)	17% (9–32)	6% (2–16)
		M2	12% (4–24)	16% (7–29)	7% (2–16)
		M3	9% (5–19)	13% (8–25)	6% (3–15)
	elderly	M0	0% (0–1)	0% (0–1)	3% (1–8)
		M1	0% (0–1)	0% (0–1)	3% (1–8)
		M2	0% (0–1)	0% (0–1)	3% (1–7)
		M3	0% (0–0)	0% (0–0)	2% (1–6)
PSI	children	M0	10% (7–16)	1% (1–2)	0% (0–1)
		M1	10% (6–15)	1% (1–2)	0% (0–1)
		M2	11% (7–17)	1% (1–3)	1% (0–1)
		M3	12% (9–16)	2% (1–3)	1% (1–2)
	adults	M0	34% (28–41)	44% (38–50)	19% (13–32)
		M1	35% (29–42)	44% (38–51)	20% (13–31)
		M2	37% (29–44)	47% (41–55)	22% (14–37)
		M3	39% (32–48)	50% (44–59)	26% (18–38)
	elderly	M0	4% (1–8)	3% (1–7)	28% (24–33)
		M1	3% (1–7)	2% (1–5)	28% (24–31)
		M2	2% (1–5)	2% (1–4)	27% (23–32)
		M3	1% (0–3)	1% (0–3)	27% (24–29)

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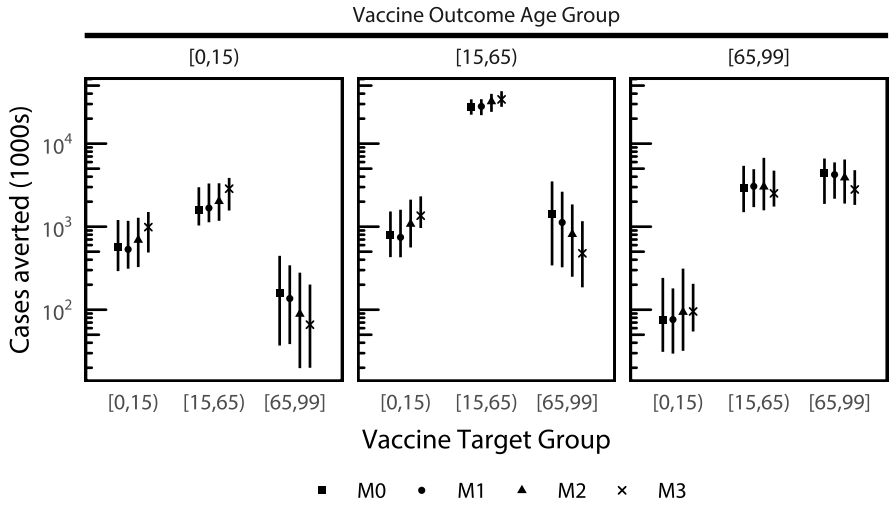

Figure 5.1: Cumulative vaccine impact across update methods M0–M3

5.3 Further Analysis: Cumulative Outcomes

In section §5.1, I found that vaccine impact—measured in relative terms as per cent incidence rate reduction (%IRR) compared to unvaccinated baseline—in an India-like setting was relatively unaffected across the various scenarios of no updates to contact matrices (M0), reciprocity-preserving updates (M1), reciprocity- and assortativity-preserving updates (M2), and reciprocity-, assortativity-, and average contact rate-preserving updates (M3).

These findings are somewhat reassuring for those analyses that aimed to estimate the *trajectory* of the TB epidemic (in relative terms) after vaccine introduction. However, it is possible that different contact update methods lead to differential *cumulative* vaccine outcomes and downstream calculations (e.g. cases averted and cost-effectiveness calculations).

To explore this, figure 5.1 presents a plot of cumulative TB cases averted 2027–2050 (log scale) of the same 50% efficacy, prevention of disease, post-infection (post-infection efficacy (PSI)) efficacy vaccine modelled in section §5.1, delivered at 70% coverage to children, adults, or the elderly, using models with M0–M3 updates.

Broadly, the results in figure 5.1 suggest a similar conclusion to that in section §5.1. The cumulative cases averted by vaccination remained reasonably stable over M0–M3. As in Research Paper 3, the largest impact was predicted in adults after adult-targeted vaccination. Unlike Research Paper 3, however, the largest difference in vaccine impact was predicted in cases averted among adults: over the 24 year time horizon, approximately 6 million more cases were averted in M3 (34.1 million [uncertainty range 27.8–42.8]) compared to M0 (28.0 million [UR: 22.3–34.1]). In contrast, the largest difference in point-estimate vaccine impact (%IRR) was observed in the elderly, following adult-targeted

vaccination (~7%).

I posit that the elevated number of averted cases among adults seen in the M2 and M3 models, compared to M0 and M1, can be attributed to two factors. First, baseline 2027–2050 TB incidence was slightly higher in M2 and M3 compared to M0 and M1, as evidenced by plots of projected incidence rate (Figs 8–11 supplementary material).

The 2050 TB incidence rates in M0, M2, and M3 were constrained to lie within the bounds predicted by M1. However, I found a slight upward trajectory in incidence in M2 and M3, with their final projections in 2050 concentrated towards the upper bound of the M1 projection. Second, as this is a cumulative outcome measure, small differences accumulated over 2027 to 2050: thus, the slightly higher incidence rates of M2 and M3 over M0 and M1 likely resulted in small increases in absolute vaccine impact, which in turn accumulated to give rise to the observed differences.

The generalisability of this finding beyond similarly structured and parameterised models set in India is unknown, much like that for point estimates of vaccine impact.

5.4 Summary

In this chapter, I have attempted to address the second aim of this thesis: investigating the robustness of TB vaccine impact estimates to structural uncertainty in TB vaccine models.

I found that point estimates of TB vaccine impact in India in 2050 remained relatively stable over different methods of updating social contact structures to match evolving demography, across different age targeting scenarios and when measured across a range of age groups.

In general, this finding was also true for cumulative cases averted by TB vaccination over this time horizon. The differences in cumulative cases averted, while ostensibly slightly greater, were likely due to small differences in baseline (unvaccinated) trajectories in M2 & M3 over M0 & M1 and the accumulation of the resulting slightly greater absolute vaccine impacts.

Finally, the summary measures of interaction between social contact adaptation and demography (supplementary materials Figs 2A–C)—median reciprocity error, the assortativity coefficient, and average daily contact rate—showed reasonable stability over the period of vaccine impact (2027–2050).

The India-models in the studies in chapters 3 and 4 and historical studies by Harris et al.[1,2] did not adapt contact matrices to match demography over their respective time horizons. These models were similarly structured and parameterised to Research Paper 4, projected over the same time horizon, and used the same underlying demographic projections (World Population Prospects[7]). The findings of section §5.1 suggest that

estimates of vaccine impact reported by these studies are unlikely to be substantially biased by this choice.

However, the generalisability of this study is unknown. Two future research priorities immediately follow from it.

First, it may be useful to investigate the effect of contact update methods on other demographic and epidemiologic settings (e.g. in China, with an ageing population in whom TB burden is concentrated), contact patterns, model parameterisation, and vaccine implementations.

Second, we should develop *a priori* methods to determine if contact update methods are likely to bias future modelling efforts. It is impractical to conduct a comparative analysis as above for each future modelling exercise, particularly for complex computationally expensive models. One potential avenue might be the summary measures of demographic-contact interaction described above—e.g. predicted reciprocity error, assortativity coefficients, or average contact rates. If these or similar measures are validated as reliable predictors of the bias introduced by (lack of) contact updates, model builders may be better informed in selecting appropriate update methods based on data or *a priori* assumptions relevant to their specific model context.

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6 Discussion

This thesis set out to advance mathematical modelling evidence to support decision making around TB vaccine introduction.

In this chapter, I first restate my principal findings. I then assess these findings against the aims and objectives of the thesis and delineate their novel contributions to the TB vaccine modelling literature. I move on to review how the strengths and limitations of my work might affect the interpretation of its findings. Finally, I discuss implications for decision makers, research implications, avenues for future work and my overall conclusions.

6.1 Key Findings

- An M72/AS01$_E$-like vaccine could substantially reduce the incidence and mortality of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), both in relative and absolute terms (chapter 3).
- Periodic adult and adolescent (age ≥10) with routine child (aged 9) vaccination with a pre- and post-infection efficacy (P&PI) vaccine could be cost-effective in India and China when MDR/RR-TB costs were included (chapter 3).
- Investing in scaling up and improving programmatic (non-vaccine) management of (MDR-)TB reduced absolute vaccine impact and decreased vaccine cost-effectiveness (chapter 3).
- The estimated total maximum costs for untargeted adult mass vaccination in India and China were found to be substantial when vaccine health benefits were valued at prevailing cost-effectiveness thresholds, and cost-effective age-targeted vaccination was found to be more affordable (chapter 4).
- Relative and cumulative vaccine impact over 2027 to 2050 may be robust to different methods of updating model social contact matrices to match evolving demography in an India-like demographic and epidemiologic scenario (chapter 5).

This thesis had two broad aims, corresponding to two important research needs that should be met to advance models to support vaccine introduction:

1. Estimate the epidemiologic impact, cost-effectiveness and affordability of new TB vaccines in India and China, incorporating drug-resistance transmission and acquisition. This aim reflects the need to adapt models to include locally important features of, and uncertainty in, TB epidemiology and health systems (research gaps 1–3).

2. Describe how different assumptions of adapting social contact structures to long-term demographic trends in India—as a country undergoing the demographic transition—might affect vaccine impact estimates. This aim reflects the need to establish whether vaccine impact estimates are robust to structural decisions in model design (research gap 4).

As vaccine development continues to progress, addressing these needs and aims has become more urgent. With a vaccine in the foreseeable future, decision makers may need to begin planning vaccine deployment. Modelling evidence to substantiate these deliberations needs to be locally adapted and robust.

I sought to achieve the aims of this thesis by fulfilling the four core objectives described in chapter 1. In the next section, I summarise how these results address these objectives and their relationship to the literature.

6.1.1 Vaccine epidemiologic impact and cost-effectiveness

In chapter 3, I sought to address two objectives:

- Develop a transmission model of *Mycobacterium tuberculosis* (*Mtb*) that included drug resistance acquisition and transmission, including country-specific cost models of TB programmatic control and vaccination.
- Assess the epidemiologic impact and cost-effectiveness of TB vaccines under future country-specific scale-up scenarios for (non-vaccine) programmatic TB management.

Epidemiologic Impact When this PhD was conceived, no published study had explicitly included primary and secondary drug resistance in a mathematical model of new TB vaccination.

To fill this gap, I constructed an age-, treatment history- and drug-resistance-stratified compartmental dynamic transmission model of *Mtb* transmission calibrated to historical epidemiologic data from India and China (chapter 3; Research Paper 2). I simulated a range of vaccines using this model, focusing on the impact of an M72/AS01$_E$-like, 50% efficacy, prevention of disease (POD) vaccine, effective irrespective of *Mtb* infection status, conferring 10-years of protection, delivered through mass campaigns to 70% adults and adolescents (aged ≥10 years), and annually to 80% of 9-year-olds.

Overall, Research Paper 2 found that adult and adolescent vaccination could substantially reduce MDR/RR-TB burden between 2027 and 2050. Where future programmatic TB management was unchanged after 2018 ("Status Quo scenario"), a P&PI M72/AS01$_E$-like vaccine was found to reduce the 2050 MDR/RR-TB incidence rate by 73% (uncertainly interval: 66–76) and 72% (UI: 65–77) in China and India, respectively. Cumulatively, vaccination averted 2.1 (UI: 1.1–2.7) and 2.0 (UI: 1.4–4.1) million MDR/RR-TB cases in China and India respectively, corresponding to 0.8 (UI: 0.5–1.4) and 1.0 (UI: 0.6–1.3) million averted second-line treatment regimens.

Where programmatic TB management was scaled up ("Policy scenario"), relative vaccine impact (e.g. per cent incidence rate reduction) was maintained. However, because baseline TB burden was lower than in "Status Quo", absolute vaccine impact was reduced.

In previous studies, differences in underlying drug susceptible TB (DSTB) epidemic dynamics across settings have led to different levels of vaccine impact by host infection status required for vaccine efficacy. Evidence from DSTB vaccine models[1,2] suggests that pre-infection efficacy (PRI) vaccines reduce burden more than post-infection efficacy (PSI) vaccines in settings where TB burden is primarily due to *Mtb* transmission among uninfected individuals (typically where disease burden is concentrated in younger adults). Post-infection (PSI) vaccines reduce burden more than PRI vaccines where TB is driven more by reinfection, reactivation and relapse (typically where disease burden is in the elderly).

In chapter 3, differences in MDR/RR-TB epidemic dynamics interacted similarly with host-infection status required for vaccine efficacy. PRI vaccines had a greater impact on MDR/RR-TB in China, where transmission to uninfected individuals drove the MDR/RR-TB epidemic. In India PSI and PRI vaccine impact were more evenly balanced because a greater proportion of MDR/RR-TB was due to recurrence (from latency or the resolved state) or reinfection.

In contrast to MDR/RR-TB , the DSTB TB epidemic in China in chapter 3 was dominated by recurrence. Since MDR/RR-TB constituted a minority of all TB, PSI vaccines had a greater overall impact in China than India. This result is also consistent with prior work by Harris et al.[1,3], who reported greater impact of PSI POD vaccines in China compared to PRI POD vaccines.

Optimal vaccine characteristics for the control of DSTB and drug-resistant TB may therefore differ depending on the context. More accurate estimates of MDR/RR-TB burden and empirical characterisation of the underlying epidemic dynamics will enable future models to more accurately quantify the contribution of a vaccine to MDR/RR-TB control in specific settings. This is important for decision makers to correctly assess the specific role of vaccines as an MDR/RR-TB control measure.

Since this study was conceived, Fu et al.[4] have published a dynamic modelling study investigating the impact of new vaccines on rifampicin-resistant tuberculosis (RR-TB) burden in 30 countries, including India and China. Importantly, Fu et al. directly extended

current TB trends into the future, modelling an intrinsically declining baseline burden of TB until 2035 (cf. chapter 3, where future TB burden was driven only by programmatic control and transmission dynamics). Fu et al. predicted that vaccines would avert a substantial burden of RR-TB . By extending the range of future TB burden scenarios in which vaccines have been modelled this work may lend support to my findings overall.

Cost-effectiveness Previous cost-effectiveness analyses of TB vaccination (section 2.5.2) suggest that adult and adolescent vaccination is likely to be cost-effective even where vaccine efficacy is low. However, when this thesis was conceived, only two studies that modelled new TB vaccines integrated cost-effectiveness analyses into dynamic transmission models. Neither included a dynamic representation of drug resistance nor integrated cost uncertainty into the their results and neither investigated cost-effectiveness at thresholds other than gross domestic product (GDP)-based thresholds.

My study in chapter 3 incorporated a cost-model of TB diagnosis, treatment, and vaccination based on country-level data. Uncertainty in costs for DSTB and MDR/RR-TB diagnosis, drug susceptibility testing (DST), drug treatment, and vaccine delivery costs was incorporated by sampling unit cost values from data driven prior distributions. I estimated vaccine cost-effectiveness at three cost-effectiveness thresholds (CETs) per country: 1× GDP per capita[5] and maximum and minimum country-specific thresholds based on healthcare opportunity costs estimated by Ochalek et al .[6] This study concurred with prior work[7,8] in finding TB vaccines generally cost-effective. P&PI and PSI vaccines priced at $10 were uniformly cost-effective at the 1×GDP per capita threshold in the main analysis. As expected, PSI vaccines were less cost-effective than P&PI vaccines. Vaccines were highly likely to be cost-effective in India with both P&PI and PSI vaccines cost-effective at the upper healthcare opportunity cost (HCOC) threshold.

Novel contributions to the literature The study in chapter 3 is one of only two dynamic models to measure the epidemiologic impact of new TB vaccines on MDR/RR-TB. It is the only study to incorporate both a dynamic drug resistance and country-specific alternative future baseline scenario into estimates of vaccine cost-effectiveness to date and is the first to include cost-effectiveness thresholds based on healthcare costs in its analysis.

6.1.2 Total Cost and Affordability of TB Vaccination

Chapter 4 addressed objective 3:

- Given country-specific cost-effectiveness thresholds, estimate the total maximum cost of TB vaccination programmes that are considered cost-effective based on the value they provide to the health systems in India and China.

Modelling evidence from chapter 3 and previous studies[7,8] suggests that adult and adolescent mass vaccination is likely to be cost-effective at hypothesized prices and cost-effectiveness thresholds defined by GDP per capita and healthcare opportunity costs. However these cost-effectiveness thresholds do not specifically reflect budget constraints in their respective settings.

Using the model introduced in chapter 3, the study in chapter 4 estimated the maximum cost at which the vaccine programme would remain cost-effective if the disability adjusted life years (DALYs) averted by vaccination were valued at country-specific CETs based on healthcare opportunity costs. These estimates of total cost serve to indicate the affordability (or lack thereof) of large scale adult mass vaccination under these cost-effectiveness assumptions.

Given the scale of the current and projected TB burden in India and China, even a modestly effective vaccine was predicted to avert a large volume of TB-associated DALYs. Unsurprisingly, the total value of these DALYs, and therefore the maximum cost of a vaccine programme that averted them, was predicted to be substantial. Assuming cost-effectiveness thresholds \$264 and \$3650 per DALY averted, mass vaccination of individuals aged ≥ 10 at 70% coverage with an M72/AS01$_E$-like vaccine could cost, at maximum, \$21 (UI: 16–27) billion and \$15 (UI: 12–19) billion in India and China over 2027–50, respectively.

Targeting vaccination to 50–59-year olds and 60–69-year olds in India and China was found to avert the most DALYs per vaccinated individual, with associated predicted costs \$5 billion and \$6 billion, respectively. In prior work, Harris et al.[3] predicted that targeted vaccination of the elderly (aged ≥65) in China would maximise population-level impact. This study did not investigate cost-effectiveness, nor measure DALYs averted. I corroborated this finding by identifying 60–69-year olds as the most epidemiologically efficient age group to target. In addition, I confirmed that this age group was likely to be the most cost-effective to target, based on the number of DALYs averted per vaccine delivered. A younger optimal age band in India than China is consistent with current estimates that disease in India is concentrated in younger adults[9].

In this study, as in chapter 3, scaling up programmatic TB management reduced the future burden of disease averted by a new vaccine. In chapter 4, the total maximum cost at which the targeted vaccine programme remained cost-effective was reduced to \$4 billion and \$5 billion in India (50–59-year olds) and China (60–69-year olds), respectively. In chapter 3 vaccine price was fixed, leading to an increase in the incremental cost-effectiveness ratio (ICER). As expected, this study found the complementary effect: for a vaccine to remain cost-effective in the face of concurrent programmatic scale up, its unit price must decrease. These twin effects suggest that decision makers should integrate planned or anticipated changes in programmatic TB control into negotiations with vaccine manufacturers, to ensure that vaccines remain cost-effective and affordable over a range of future scenarios.

Novel contributions to the literature This is the only study to date which estimates the total cost of a TB vaccination programme by valuing DALYs averted at prevailing cost-effectiveness thresholds. It makes no assumptions around vaccine price, nor the programmatic costs of vaccine delivery. It provides evidence for decision makers to use when considering the financial feasibility of new TB vaccines and provides evidence on the implications of using CETs based on healthcare opportunity costs.

6.1.3 Contact structures, evolving demography, and vaccine impact

In chapter 5, I addressed objective four:

- Investigate whether model-based vaccine impact estimates in an India-like epidemiologic context are robust to different methods of updating model social contact structures to match evolving demography.

An investment into TB vaccine programmes is a long term commitment. If we choose to inform such an investment with model evidence, we must ensure that the evidence is robust to equally long term structural uncertainties in the model. Motivated by this need, the study in chapter 5 investigated whether updating social contact structures to match evolving demography in an *Mtb* transmission model affected vaccine impact. Demography was stratified into three age groups: children (aged ≤14), adults (aged ≥15, ≤64) and elderly (aged ≥65). Four contact matrix update methods were investigated: fixed contact matrix (M0), reciprocity corrected (M1), reciprocity and assortativity corrected (M2), and reciprocity, assortativity, and mean contact rate corrected (M3). I estimated the impact of vaccinating 70% of children, the adults, or the elderly, with a 50% efficacy, PSI POD vaccine conferring 10-years of protection.

Vaccine impact estimates in all age groups remained relatively stable between the M0–M3 models irrespective of vaccine-targeting by age group. The maximum difference in 2050 incidence rate was 7% in the elderly age group, observed following adult-targeted vaccination. The incidence rate in the elderly declined by 19% (uncertainty range 13–32), 20% (UR: 13–31), 22% (UR: 14–37), and 26% (UR: 18–38) using M0, M1, M2 and M3 updates, respectively. In an additional analysis, I also confirmed that estimates of cumulative vaccine impact remained similarly stable over this time horizon.

Only five studies (including those in chapters 3 and 4)[1,3,4] have incorporated age-specific contact structures into TB vaccine models. Three of these included a model set in India and none updated their respective contact structures over time. The findings of this thesis suggest that this particular modelling decision is unlikely to have impacted the India-specific results of TB vaccine impact substantially.

Novel contributions to the literature This is the only study to date which has systematically investigated whether (and if so how) updating contact matrices to match demography affects the impact of an age targeted intervention (vaccine) for TB control. It has improved the reliability of similarly structured and parameterised[1,3,10,11] models that preceded it.

6.2 Synthesis, Strengths, and Limitations

In this section, I briefly highlight recent developments in our understanding of TB natural history and review any common threads, particularly concerning strengths and limitations, in the results of chapters 3, 4, and 5. I also briefly restate any major study-specific strengths and limitations important for interpreting the results summarised in section §6.1.

6.2.1 New advances in TB natural history

Recent work by Behr et al.[12,13] argues that most incident TB disease in high endemicity settings occurs within two years of infection by *Mtb*. They propose that disease that occurs more than two years after infection is the minority, reflecting a long asymptomatic period rather than a pathophysiologically distinct "reactivation" event from a distinct latent bacterial state. They also suggest that most, if not all, recurrent disease after curative treatment is due to reinfection. Finally, they posit that a substantial fraction of people self-clear *Mtb* infection while retaining immunological evidence of it[14].

This hypothesis is based on reanalysis of data from the pre-chemotherapeutic era of TB and from special patient cohorts (e.g. solid organ transplant or tumour necrosis factor-α antagonist recipients, both representing immunosuppressed states that predispose to TB).

Among other arguments, Behr et al. assert that

1. studies that follow up individuals after a known exposure to *Mtb* show that most disease in this individuals occurs within 2 years[15] ; and
2. rates of disease in the placebo arms of isoniazid prophylaxis trials (given for 12 months to persons with immunological evidence of TB infection) converge with the investigational arms after one year, suggesting that "late disease" in both arms was due to reinfection[16]; and
3. post-mortem histopathologic analyses from the pre-chemotherapeutic era of TB of calcified TB lung lesions in individuals who died of non-TB causes failed to demonstrate viable mycobacteria, suggesting bacterial clearance[17]; and
4. estimates of the prevalence of latent tuberculosis infection (LTBI) are based on assays that indicate immunologic exposure to *Mtb*, rather than persistent infection[16].

Critics of this hypothesis point to contradictory data: individuals with a long history of LTBI but no new recent exposure develop active disease soon after gaining new immunosuppressive medical comorbidities[18–20]; in immigrant cohorts, although risk declines shortly after arrival, more than 50% of disease still occurs after two years[21]; and statistical evidence[22], transmission models[23] and molecular epidemiology[24] suggest that approximately half of cases in native populations in various settings are due to reactivation.

Nevertheless, if this hypothesis were confirmed, it would necessitate a paradigm shift in our understanding of TB natural history, with significant implications for TB vaccines and TB vaccine models. I speculate at least three consequences:

1. We would be compelled to revisit the host-infection status required for efficacy (P&PI, PSI, and PRI) in the taxonomy of TB vaccines and reevaluate those results where PSI efficacy exceeds PRI. As the pool of infected-but-asymptomatic individuals shrinks, PSI efficacy may decrease.

2. How self-cure affects vaccine impact will likely depend on what we assume about residual immunity in self-cured individuals (e.g. as compared to latently infected individuals).

3. Results from TB vaccine trials may become more directly transferable to vaccine models, as trial timescales will better reflect the time course of disease in most individuals .

6.2.2 Strengths and Limitations

The main strengths and limitations of each study are discussed in their respective chapters. Here, I briefly restate those that span multiple studies and which are particularly important for the overall conclusions of this thesis.

Drug resistance Compared to previous TB vaccine models[7], the studies in chapter 3 and chapter 4 implemented a more complete representation of drug resistance in TB. The key strengths of my model include the integration of both primary and secondary resistance, differential rates of diagnosis, treatment, treatment outcomes, and stratification by treatment history.

What is the value of these features? Firstly, previous evidence suggests that preventing onward transmission (by averting disease) is responsible for a substantial proportion of TB vaccine impact. For example, using a model set in Cape Town, South Africa, Dye[8] suggested that approximately half of all vaccine averted TB was due to transmission effects. Secondly, MDR/RR-TB is increasingly due to primary resistance; in some settings this is the dominant mode of resistance[25–27]. By incorporating dynamic drug resistance, the model could better reflect evolving MDR/RR-TB epidemic dynamics and provide better estimates of vaccine impact (for example, variation by host infection status necessary for

vaccine efficacy). For decision makers, this model could better reflect how changes to DSTB management might affect vaccine impact on MDR/RR-TB (for example, through improvements in DSTB diagnosis and treatment on secondary resistance).

Nevertheless, the drug resistance implementation had some key limitations. MDR/RR-TB was represented as a monolith. In reality, circulating drug-resistant *Mtb* strains are diverse, with myriad resistance profiles[28,29]. As there is inadequate data to parameterise this heterogeneity (or the consequences thereof) it was not included in the model. However, the uncertainty introduced by these phenomena are likely small compared to prominent unknowns in TB natural history itself or in country health systems; therefore, I speculate that these limitations do not negate the general conclusions that I drew from this work.

Data availability A model strength was that MDR/RR-TB epidemiology was calibrated to the best available empirical and nationally representative data from China and India. In China, there are two robust MDR/RR-TB data points—one from a published drug resistance survey[30], the other from unpublished but national estimates from the Chinese Centres for Disease Control (CCDC) (chapter 3). In India, the first national drug resistance survey was reported in 2017, in time for model calibration[31]. Calibrating the model to these estimates of incidence and proportion resistant among notifications likely improved overall MDR/RR-TB burden projections and underlying dynamics (e.g. new infections vs reinfections).

The accuracy of the baseline TB projection in India was hampered by the lack of high quality nationally-representative empirical estimates of TB prevalence and incidence. The first national tuberculosis prevalence survey of India is currently on hold due to the COVID-19 pandemic. Therefore, as in previous studies[1], I calibrated TB prevalence in India to values derived by aggregating subnational estimates[32–34]. The biases of these data are not well characterised. The model was calibrated to World Health Organization (WHO) estimates of overall TB incidence rate to capture time trends in TB burden. These estimates are derived from notification data (which have known biases), expert opinion, and from subnational surveys[35], using assumptions about the distribution of the duration of TB disease. Additionally, to capture age-specific burden (chapter 5), I calibrated the model to WHO estimates of age-specific incidence. However, for India, these estimates are imprecise as they are model-based, interpolated using age-specific TB burden distributions from neighbouring countries. Finally, data are limited to substantiate the extent and outcomes of private-sector TB management, though there is consensus that the former is generally large and the latter generally poor[36–38]. Given the uncertainties in the data, relatively wide prior bounds (for inputs) and target bounds (for calibration) are used in the India MDR/RR-TB model, reducing the precision of model results.

Because age-specific data from India is limited, the model investigating vaccine impact, social contact change, and demography was stratified into three broad age groups (children, adults, and elderly). It is possible these wide groups obscured subtle interactions between changing inter-group contact rates, evolving demography, and vaccine impact, leading to

underestimation of the differential impact of contact update methods M0–M3. However, this error was likely mitigated by the decreased contribution by contact between any given age group pair to total contact in the population as the number of age groups increases. Thus, even if contact between that pair was more sensitive to a particular contact matrix update method, the impact on total infectious contact is decreased. Moreover, these age groups are epidemiologically important, as reflected by their use in other studies[1,3,4].

Model Structure To ensure parsimony and focus on the specific research questions of their respective studies, all models omitted some sources of heterogeneity in, and populations at risk for, (MDR)-TB that may be important in India and China.

The spatial epidemiology of TB in India and China is heterogeneous[39,40], varying along axes including urbanisation, social mixing patterns, and migration[41–43]. The models in this thesis did not incorporate these heterogeneities as they are not immediately relevant to the research questions posed the current stage of vaccine development. Integrating these variables is likely to become important when vaccine development has progressed further and models begin to answer more granular implementation questions.

Model populations were not disaggregated by risk strata such as socioeconomic status or comorbidity (e.g. malnutrition and diabetes mellitus—both of which contribute to and modify TB disease in India). The omission of HIV—which is the greatest biological contributor to TB burden worldwide[44]—is unlikely to be a major source of error: in 2020, TB incidence among people living with HIV constituted less than 3% of all incident TB in India and China[44].

The significance of these limitations is likely to vary by chapter. For example, vaccine impact on MDR/RR-TB was likely more sensitive to the omission of comorbidities and socioeconomic stratification, whereas contact-demography-vaccine interaction was likely affected more by the omission of geographic heterogeneity, differential urban-rural mixing, and trends in migration.

Health economic analysis The overall strengths of the economic analyses include (i) use of country-level unit costs and uncertainty for programmatic TB management, (ii) the use of country-specific cost-effectiveness thresholds based on healthcare opportunity costs, (iii) alternative programmatic TB scale up scenarios based on in-country expert opinion and published strategies, and (iv) in India, the inclusion of costs of incentive payments to the private sector. These led to cost-effective estimates that were conservative and grounded in local data. Further, the reliability of the result for decision makers was improved by demonstrating that vaccination remained cost-effective over different scale up scenarios.

However, important data gaps remain. Firstly, the exceptional circumstances around COVID-19 notwithstanding, there is no direct data to substantiate the costs of large scale adult mass vaccine campaigns in India and China delivered by a health system under

routine conditions. Instead, the cost model for vaccine delivery was constructed using the experience of other mass vaccine campaigns (e.g. Hepatitis B catch-up vaccination campaigns in China[45]) and routine childhood immunisation. Periodic adult mass campaigns for TB may incur different and additional costs (e.g. related to community outreach or mobilisation) that were not captured in these estimates. Secondly, as described in chapter 4, the CETs are exogenous. Ochalek et al.[6] use a regression model incorporating published estimates of the expenditure elasticity of health (the elasticity of the effects of government health expenditure on health outcomes) to estimate number of DALYs averted by a 1% change in healthcare expenditure in low- and middle-income countries (LMICs) including India and China. The resulting thresholds are not empirically validated against current health spending in India and China and may be substantially different to the "true" willingness-to-pay. If the estimated thresholds are too high both the probability of vaccine cost-effectiveness and the total cost-effective vaccine programme cost may be overestimated. The total cost estimates are more sensitive to potential errors in the threshold, but this is mitigated by the use of both the maximum and minimum thresholds per country.

Scenario analysis The key strength of the scenario analysis was country stakeholder involvement. The "Policy" baseline scenario—representing the scale-up of programmatic (non-vaccine) management of (MDR)-TB—reflected what is planned, or considered plausible, under the technical capacity, resource constraints, and priorities of the national tuberculosis programmes (NTPs) in India and China. Thus, it represented a combination of "best guess" and aspirational targets for future TB control in these settings.

It is possible that baseline changes that I did not model could substantially alter the impact and cost-effectiveness of new vaccines, particularly a highly effective diagnostic technology or increased treatment efficacy for MDR/RR-TB. However, at the time of model design, such changes were purely speculative. Consequently, MDR/RR-TB treatment success rates were held at approximately ~50% over the model time horizon. In principal, if resistance were to worsen (e.g. increasing prevalence of extensively drug-resistant TB (XDR-TB)), my results may reflect an underestimate; however, such a scenario would also be speculation. However, as discussed in chapter 3, promising new trial results (final results of STREAM[46] and TB-PRACTECAL[47–49]) could substantiate sensitivity analyses in future modelling studies. Finally, as discussed in section 3.3.1, Fu et al.[4] did model vaccine impact in the context of a purely hypothetical highly effective MDR/RR-TB treatment strategy in an "alternative" baseline scenario and showed that while vaccine impact was diminished, it remained substantial. While it is very likely that vaccine cost-effectiveness would decrease in such a scenario, this reduction remains to be quantified.

Vaccines The methodological limitations of the vaccine representation fall into two broad groups: (i) those related to intrinsic characteristics of the vaccine; and (ii) those related to the practical implementation of the vaccine.

The vaccines modelled in this thesis are hypothetical but based on the known characteristics of M72/AS01$_E$. We currently have 3-years of published follow-up data from the M72/AS01$_E$ phase IIb trial[50], demonstrating 48% PSI POD efficacy. In this thesis, I assumed that TB vaccines would confer 50% efficacy for 10-years in the central example. The durability assumption was based on (i) trial data showing a persistent immune response and good clinical outcomes at 3 years and (ii) expert opinion. In sensitivity analyses, vaccine impact varied with changes in durability and efficacy as expected, with changes with host-infection status for efficacy determined by underlying epidemic dynamics.

A limitation in the vaccine characterisation was that protection was modelled as continuous, with waning occurring instantly at the end of the duration of protection. While this limitation had impact at the individual level in the model, it was not expected to substantially affect population estimates of vaccine impact, cost-effectiveness, and affordability.

The coverage, delivery strategy, targeting, and scale up of the vaccine implementation was limited by the lack of data. In this model, I assumed that routine vaccination of 9-year olds would be delivered through schools (e.g. as is planned for HPV vaccination in many settings—although these have not yet been implemented in India nor China). Apart from recent emergency programmes for COVID-19, there is no precedent for large scale mass vaccination of the entire adult and adolescent population. Therefore, coverage estimates for both modes of delivery were derived from vaccine programmes for other diseases, e.g. vaccination against meningitis (MENAFRIVAC)[51] or influenza vaccination in the elderly[52,53]. Mass campaigns were assumed to scale-up instantaneously, achieving full coverage within a single year. In reality, mass vaccination campaigns against TB are more likely to be implemented as a gradual scale-up towards some target coverage, which will likely reduce estimates of vaccine impact (in the short-medium term) and cost-effectiveness.

Our conceptions regarding the plausibility of large scale rapid adult vaccination—previously regarded as impossible due to technological, logistical, and financial limits—have been upended by COVID-19. We now know that with adequate financing and political will, even very large populations can be vaccinated rapidly: both India[54] and China[55] have each administered more than 1 billion doses of COVID-19 vaccine in less than one year. However, whether this experience will translate to, or is appropriate for, TB vaccination remains unknown.

6.3 Research implications and future work

This section situates this thesis within the wider TB vaccine decision-making process informed by mathematical models.

Figure 6.1 shows the schematic of the TB vaccine decision-making pathway from chapter 1, updated to reflect the contributions of this thesis. The "if" and "how" parts of the pathway overlap substantially and serve as question generators for one another (for example, once

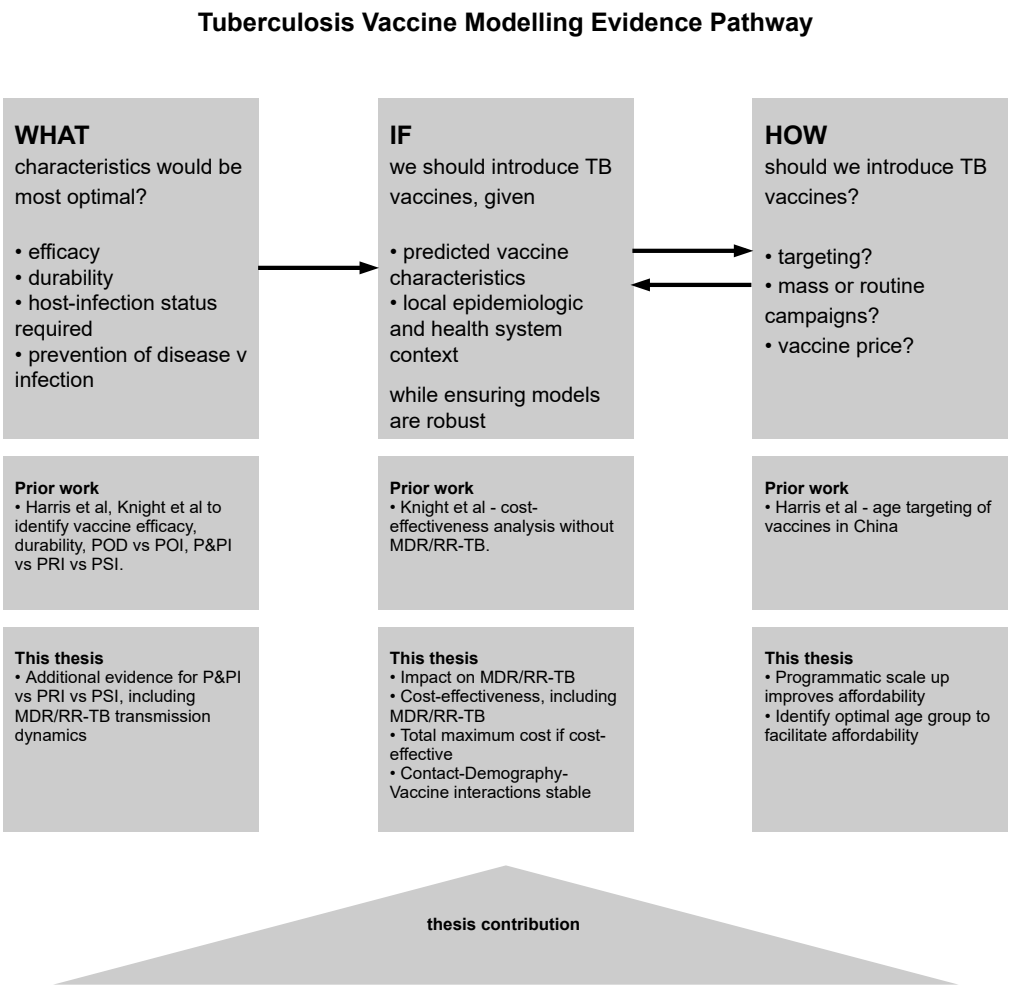

Figure 6.1: TB Vaccine Decision Making Pathway

vaccine impact on MDR/RR-TB is established, should vaccines be targeted to contacts of MDR/RR-TB cases or people at high risk of developing MDR/RR-TB?).

This thesis contributes to the beginning of evidence generation to inform TB vaccine introduction. It primarily informs the macroscopic "if" considerations, producing broad country-level estimates, with secondary contributions to "what" (e.g. the interaction between MDR/RR-TB dynamics and host-infection status required for efficacy) and "how" (e.g. quantifying total cost of untargeted and age-targeted vaccination). It does not purport to recommend specific vaccine implementation strategies. To generate such recommendations will require more granular data on vaccine characteristics (which are pending clinical trials) and more operational data (e.g. logistics, cold chain, human resources, and budget and finance considerations).

Instead, these results inform decision-makers about the feasibility and utility of vaccines and where vaccines might fit within wider TB control efforts. The results also act as a starting point for researchers and decision-makers to subsequently construct more specific questions appropriate for India and China, or develop further methodological approaches to ensure model robustness.

6.3.1 Implications for TB vaccine decision-making

This thesis has identified four important implications for TB vaccine policy- and decision-making, which follow from the core results:

1. New TB vaccines may be an effective MDR/RR-TB control measure in their own right.
2. Probable and possible changes to programmatic TB management must be factored into TB vaccine planning.
3. Decision-makers should begin to identify potential vaccine delivery strategies and their component costs, grounded in local health system capacity, local priorities and budgets.
4. Strategies to improve the affordability of large scale adult vaccination must be investigated.

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New TB vaccines may be a highly effective MDR/RR-TB prevention strategy in their own right

Decision-makers should consider a new TB vaccine as a tool for MDR/RR-TB prevention in its own right.

There are few systematic strategies in use for MDR/RR-TB prevention. Ostensibly, strategies to improve DSTB treatment adherence and treatment of presumed LTBI in close contacts of MDR/RR-TB patients with tuberculosis preventive therapy (TPT) may have a role. However, globally, the provision of preventive therapy for household contacts of TB patients is poor[44]. Further, evidence for the efficacy of TPT in preventing MDR/RR-TB is scant[56–58]. Current evidence originates from small observational studies, although trials to investigate agents such as bedaquiline and levofloxacin are under way[59–61].

However, both strategies have existing or foreseeable limitations. As evidenced by previous studies and shown in chapter 3, MDR/RR-TB is an increasingly transmitted disease. As primary resistance drives more MDR/RR-TB, strategies to improve DSTB treatment adherence will become less effective. Resistance to fluoroquinolones is well described[62,63] and the real-world efficacy of a universal MDR/RR-TB TPT regimen is unknown and may change over time.

Vaccines are less vulnerable to changes in underlying epidemic dynamics than adherence improvement, less toxic and protracted than TPT, and do not require personalisation, resistance profiling nor therapeutic drug monitoring. We have no *a priori* reason to anticipate that vaccine efficacy will be lower against drug-resistant than DSTB. In this work, vaccines substantially reduced MDR/RR-TB burden in two very different epidemic

settings. Decision-makers should explicitly include the anticipated effect of a TB vaccine—should it become available—into the national MDR/RR-TB control strategy. The value of vaccine averted MDR/RR-TB should also be accounted for, as failure to do so will substantially underestimate vaccine cost-effectiveness.

Probable and possible changes to programmatic TB management must be factored into TB vaccine planning.

TB vaccine decision-makers must be vigilant to new diagnostic tools and treatment methods for MDR/RR-TB. As shown here, improvements to programmatic MDR/RR-TB management may reduce the absolute epidemiologic impact and cost-effectiveness of future vaccines. If such new technology arises, the implications for a TB vaccine programme depend at least in part on whether MDR/RR-TB control is a local priority in its own right. If so, then vaccines will likely remain an useful tool for MDR/RR-TB prevention, as the relative burden (e.g. per cent incidence rate reduction) due to vaccination is stable to changes in (non-vaccine) programmatic TB control. However, if the major reason for MDR/RR-TB prevention is to control costs, then decision-makers may need to reevaluate vaccine cost-effectiveness. Targeted interventions for MDR/RR-TB will disproportionately reduce the cost-effectiveness of vaccines.

Decision-makers should begin to identify potential vaccine delivery strategies and their component costs, grounded in local health system capacity, local priorities and budgets.

In this thesis, I have modelled a relatively optimistic vaccine delivery strategy, particularly with respect to how rapidly mass vaccination can be delivered. The unit costs used in the economic evaluation reflect reasonable estimates for programmatic management and those for vaccine delivery a reasonable approximation from other vaccine programmes. However, a range of questions must be answered to build models that can address more localised, granular, implementation related issues, including but not limited to:

- What mode of delivery is possible for adult vaccination? (e.g. periodic mass campaigns or routine campaigns with mass catch up)
- Through what channels would such vaccination be delivered? (e.g. schools, hospitals, workplaces)
- What target coverage is envisaged and over what timeframe should it be attained?
- How will vaccination be financed? How much funding is (or might become) available and when?
- What is the willingness-to-pay for TB vaccination at the required scale?
- Are there other local priorities—for example, social equity?

Work has begun to answer some of these questions. Results from a qualitative study where investigators conducted in-depth semi-structured interviews with key decision makers in India, South Africa, and China to explore potential implementation strategies for M72/AS01$_E$-like and BCG-revaccination-like vaccine candidates, their acceptability and feasibility[64] are upcoming. Finally, country level experts may be able to leverage related experience (e.g. COVID vaccination) or proxy data to narrow the range of probable answers and facilitate more focused modelling.

Strategies to improve affordability of large scale adult vaccination must be investigated.

If we assume that the Indian and Chinese health systems will pay for health at the thresholds proposed by Ochalek et al., the total maximum costs of adult mass vaccination in both settings would be substantial. Decision makers should consider means to improve affordability if mass vaccination is considered a likely deployment strategy.

There are two main points to consider:

- The Ochalek threshold value may be too high for the scale of intervention proposed. This issue is not inherent to TB but is exacerbated by its scale. Decision-makers may be able to review currently funded interventions, both in TB and outside of it, and use established health economics methods to generate endogenous estimates of willingness-to-pay or cost-effectiveness thresholds to use in TB vaccine cost-effectiveness analysis.
- Assuming the CET is correct, strategies to improve affordability must be sought. As shown here, decision-makers may be able to estimate the decline in the cost-effective price of vaccination due to planned scale up in programmatic management. Such estimates may be useful in negotiating pricing with manufacturers. Similarly, assuming that vaccine price is independent of implementation strategy (which may not necessarily be true), identifying highly cost-efficient and epidemiologically-efficient subgroups (e.g. by age) may allow for proportionally more expenditure on vaccine delivery.

6.3.2 Future work

The unknowns regarding the future impact of TB vaccines are numerous, not least because we do not yet have a fully-characterised and licensed vaccine. This is reflected in the limitations and implications described in section 6.2.2 and section 6.3.1, respectively. Model estimates can be further refined as data becomes available from vaccine trials. Moreover, it is likely that model focus will shift further towards the "how"-oriented research questions (figure 6.1).

Two immediate research questions follow directly from this thesis: (i) how will vaccine impact on MDR/RR-TB be affected by higher efficacy new MDR/RR-TB treatment regimens?; and (ii) are vaccine estimates stable to contact matrix update methods in settings other than India?

If the findings from TB-PRACTECAL can be robustly translated to programmatic outcomes[47,48], then there is an urgent need to re-evaluate the expected vaccine impact, including an updated cost-model to quantify the expected impact on vaccine cost-effectiveness.

The impact of updating social contact structures to match evolving demography could be investigated in different demographic and epidemiologic settings. We cannot reliably extrapolate from India to a setting where both the underlying epidemic dynamics and demographic projection differ substantially, e.g. China (where the population is expected to age, further reinforcing a recurrence driven epidemic). More generally, we should aim to develop methods that can determine *a priori* whether updating contact structures for demography will affect vaccine impact. A candidate approach may be to analyse the summary measures of contact change with demography presented in section §5.1 after model calibration but prior to vaccine simulation. Where summary measures suggest a strong effect, additional sensitivity analyses of contact update methods may be necessary. However, summary measures would require validation across a range of demographic settings and contact patterns.

As described in section 2.4.1, section 2.4.2, and section §3.4, the tuberculosis epidemics in both India and China are heterogeneous. TB burden and programmatic outcomes vary with comorbidities, urbanisation, socioeconomic status, and gender, among other factors. These observed differences may be partially attributable to—or amplified by—differential social mixing and contact structures within or between these risk groups. For example, a recent systematic review of sex differences in social contact patterns has identified moderate sex-assortative mixing across a range of settings[65]. Shaweno and colleagues[66] have subsequently estimated that random mixing, as compared to sex-assortative mixing, could reduce male:female prevalence ratios by 12% (95% CrI 0–31%) using a model set in Uganda and Ethiopia. Similar analyses suggest that assortative mixing may amplify TB-related disparities between socioeconomic groups. Andrews et al[67] report an observable prevalence ratio of 2.59 between the poorest 40% against the wealthiest 60% of the population in India. The authors found that this disparity would imply 58% greater duration of infectiousness and contact rate among the poor if random mixing between socioeconomic strata was assumed. In contrast, reproducing the disparity would require only 22% greater duration of infectiousness and contact rates among the poor if 90% within-strata associative mixing was assumed. However, the underlying distribution of these risk factors—and therefore their associated contact patterns—may change over time (e.g., trends in urbanisation, changes in wealth inequalities). By analogy to research paper 4, future work should investigate whether updating contact structures to match such changes might affect estimates of vaccine impact.

6.4 Conclusions

MDR/RR-TB is an expanding threat to global TB control and an important component of the TB epidemics in India and China. Here, it has been integrated as a dynamic component of a *Mtb* transmission model, alongside country-specific estimates of its costs to the health system. This modelling work shows that vaccines are likely to be a substantial and cost-effective contributor to MDR/RR-TB control. As such, decision- and policy-makers should recognise the potential role of vaccines within wider MDR/RR-TB control strategies. However, both the epidemiologic impact of vaccines on MDR/RR-TB and their cost-effectiveness are sensitive to developments in MDR/RR-TB diagnosis and treatment.

Assuming that published cost-effectiveness thresholds reflect marginal health spending in India and China, cost-effective large scale adult mass vaccination for TB will impose a substantial cost on their respective health systems. Decision-makers should fully incorporate the impact of other programmatic TB management strategies into the calculation of vaccine derived value to improve vaccine affordability.

Despite their limitations and given the long time horizons involved in TB disease and TB vaccine impact, mathematical models have an important place in informing vaccine policy. Here, I have shown that, in an India-like epidemic and demographic setting, vaccine impact estimates are robust to structural uncertainty imposed by interactions between social contact, evolving demography, and dynamic effects of vaccination. It is unlikely that previous similarly parameterised and structured models of TB vaccination are biased substantially by these uncertainties.

Overall, I present evidence that supports the introduction of new TB vaccines in India and China. However, we must now urgently consider how to improve affordability, and progress to investigating more detailed country-level vaccine implementation scenarios, based on realistic in-country assessments of health system capacity and financing.

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A Research Paper Appendices

A.1 Research Paper 1: Systematic Review Methods

Appendix to Research Paper 1, containing systematic review methodology, flow diagram, PRISMA checklist and quality appraisal for included publications.

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New tuberculosis vaccines: advances in clinical development and modelling

Supplementary Materials

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Search Strategy

Details of the literature search strategy, inclusion and exclusion criteria and flow diagram are presented here.

We re-ran the search as specified in Harris et al (1) on the 5th of April 2020, restricting the date range to studies published following the 1 January 2016. We searched PubMed, EMBASE and the WHO Global Health Library. The PICOS framework for the research question is specified in Table A1. Search terms used in each database are described in Table A2. We identified 380 new studies. Seventeen duplicates were excluded, and 25 papers remained for abstract review after title screening. Following exclusions, seven (2–8) papers were included (six from original search, one from reference searching). An additional three unpublished studies (9–11) were identified by expert input (Box A1).

The inclusion and exclusion criteria for the search were as in the original review (1) and are listed in Box 1. Studies were omitted if they did not report exact epidemiologic outcomes or were primarily methods based. The earliest paper, Shrestha et al. 2016 (4), was identified post hoc in the previous systematic review and is included here for completeness given it is within the search period of this review. For consistency, the studies were evaluated using the same criteria as the original review (1). Quality appraisal criteria are presented in Table A3.

Table A1: Research question PICOS framework

Limit	Definition	Limit management
Population	Humans, any age any country	Search limit
Intervention	Novel/theoretical/pipeline TB vaccines *Not* single efficacy BCG-only	Search terms and exclusion criteria
Comparator	No intervention, currently available interventions (at current or scaled-up levels), or other theoretical interventions.	No limit applied
Outcome	Tuberculosis epidemiological impact (incidence, prevalence, mortality, number needed to vaccinate, cost effectiveness) Not *Mycobacterium bovis* *Not* within-host impact models	Inclusion/exclusion criteria
Time	No limit	No limit applied
Study Design	Epidemiological mathematical models *Not* reviews/commentaries	Search terms and Inclusion/exclusion criteria

Table A2: Search terms used in literature review

	Search Term Group		
	Modelling	**Tuberculosis**	**Vaccine**
Pubmed	"Models, Theoretical"[Mesh]) OR "mathematical model*"	TB OR tuberculosis OR "Tuberculosis"[Mesh]	vaccin* OR immuniz* OR immunis* OR "Tuberculosis Vaccines"[Mesh]
Embase	("mathematical model$".mp. OR mathematical model.mp. or mathematical model/)	(tuberculosis control/ or exp tuberculosis/ or Mycobacterium tuberculosis/ or tb.mp. or tuberculosis.mp.)	(exp vaccine/ or (vaccin$ or immunis$ or immuniz$).mp.)
WHO Global Health Library	("computer models" OR "epidemiologic models" OR "mathematical models")	TB OR tuberculosis OR "tuberculosis"	Not required as very few hits with first two search terms

Table A3: Risk of bias tool for assessment of epidemiological modelling studies

	Criterion (adapted from Fone *et al.* and Caro *et al.)*	Considerations (adapted from Fone et al. and Caro et al.)	Score considerations (0, poor to 2, good)	
1	**Are the aims and objectives clear?**	Are the research questions and modelling objectives clearly defined?	0 Not stated 1 Stated but vague 2 Stated and focussed	Definitions: max 8 points
2	**Is the setting and population clearly defined?**	Does the paper clearly state the setting (e.g. geographical location, high/low TB burden)?	0 Not stated 1 Stated but vague or details missing 2 Stated and focussed	
		In health economics models, has the perspective been stated?		
		Does the paper clearly state the modelled population? (e.g. patient or population group characteristics)		
		Have sub-populations necessary for the research question and setting been modelled?		
3	**Are the intervention and comparators adequately defined?**	Does the paper clearly state the population(s) targeted for vaccination?	0 Not stated or very unclear 1 Stated but details missing 2 Stated and all necessary details stated	
		Does the paper clearly define the vaccine characteristics (e.g. vaccine efficacy, duration of protection, number of doses, waning, timing)?		
		If there is a comparator (no vaccine, baseline or alternative intervention scenario), is it clearly defined?		
4	**Are the outcome measures defined and answer the research question?**	Does the paper clearly define the outcomes of interest?	0 Not stated, very unclear or not suited to research question 1 Stated but details missing or not directly aligned with research question 2 Stated, all necessary details stated, and aligned with research question	
		Do the outcomes correspond to the research question?		
5	**Are the model structure and time horizon clearly described and appropriate for the research question?**	Is the model structure clearly reported and appropriate for the research question?	0 Not appropriate model structure, or poor/no description of model 1 Incomplete description, and/or appropriate in part for research question	Model methods: max 4 points
		Does the model reflect current knowledge of disease natural history?		

		Is the time horizon and time step of the model clearly stated and appropriate to the research question (i.e. is it long enough to capture health effects)?	2 Complete and reproducible, appropriate structure and time horizon	
6	**Are the modelling methods appropriate for the research question and adequately described?**	Were the modelling methods clearly described, and suited to the research question?	0 Not appropriate model structure, or poor/no description of methods 1 Incomplete description, and/or appropriate in part for research question 2 Complete and reproducible, appropriate method	
7	**Are the parameters, ranges and data sources specified?**	Are all parameters and their ranges reported? Are the data sources for parameters reported?	0 Poorly reported 1 Some information missing 2 Complete reporting of parameters, ranges and data sources	Model inputs: max 6 points
8	**Are any assumptions explicit and justified?**	Are all assumptions explicit and justified?	0 Not reported 1 Explicit 2 Explicit and justified	
9	**Is the quality of data considered and is uncertainty explored through uncertainty and/or sensitivity analyses?**	Are data limitations discussed? Are any of the sources known to the reviewer to be inappropriate (e.g. do not match the parameter, are outdated, or known to be poor quality)? Is uncertainty in model structure, parameters and/or assumptions explored through uncertainty and/or sensitivity analyses?	0 No sources or uncertainty 1 Partially addressed, and/or some data inappropriate 2 Fully addressed	
10	**Is the method of fitting described and suitable?**	Is the method of fitting/calibrating the model clearly described? Is the method of model fitting/calibration suitable?	0 Not done, unsuitable method or poor/no description 1 Incomplete description or method not optimal 2 Complete description and suitable methods	Fitting/ validation: max 4 points
11	**Has the model been validated?**	Has an assessment of validity of the results been made by comparing across one or more different model structures, or against a validation data set?	0 Not considered 1 States criteria for validation	

			2 Validation undertaken	
12	**Have the results been clearly and completely presented, with a range of uncertainty?**	Have the outcome values and their uncertainty ranges for each intervention/scenario been reported? Do the results match the objectives? Are sensitivity analyses clearly reported?	0 Not reported, very unclear or not suited to research question 1 Stated, but ranges or planned sensitivity analyses missing and/or not directly aligned with research question 2 Values and ranges and planned sensitivity analyses reported and aligned with research question.	Results: max 4 points
13	**Are the results appropriately interpreted and discussed in context?**	Does the discussion reflect a fair and balanced interpretation of the results? Are the results of the study discussed in context and is generalisability considered? Are possible biases and limitations discussed?	0 No/poor discussion 1 Some discussion but key points, limitations or context missed 2 Full discussion of key points in context, generalisability considered, limitations discussed	
14	**Are the funding source and conflicts of interest reported?**	Is the funding and the role of the funder clearly stated? Is there a conflict of interest statement?	0 No statement of funding or conflicts 1 Funding or conflicts reported 2 Funding and conflict statement	Conflicts: Max 2 points

Overall Scoring: Max 28 points	
Very high	>22
High	19-22
Medium	14-18
Low	<14

Table A4: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	-
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	12
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	12/13/Table A1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	12/13, Box A1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Supp. M.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. M. Tab A2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12/13, Supp M Box A1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12/13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supp M Table A3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12/13

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, Supp M Fig A1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12/13; Supp M Table A2; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supp M Table A5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18/19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18/19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18/19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

** Protocol as per Harris et al (1) – Supplementary Appendix C, found at: https://dx.doi.org/10.1080%2F21645515.2016.1205769

Table A5: Results of Quality Appraisal

Author	Year	Aims & Objectives	Setting and Populations	Intervention / Comparators	Outcome measures	Model Structure and Time Horizon	Modelling Methods	Parameters, ranges, and data sources	Assumptions explicit and justified	Quality of data and uncertainty and/or sensitivity analyses	Method of fitting	Model validation	Presentation of results and uncertainty	Interpretation and discussion of results	Funding source and conflicts of interest	Final Score (/28)	Rating
Shrestha et al (4)	2016	Yes (2)	Yes (2)	Yes (2)	No (0)	Partial (1)	Yes (2)	Yes (2)	Partial (1)	Yes (2)	Yes (2)	No (0)	Yes (2)	Yes (2)	Yes (2)	23	Very high
Liu et al (5)	2017	Partial (1)	Partial (1)	No (0)	No (0)	Yes (2)	Partial (1)	Yes (2)	No (0)	Partial (1)	Partial (1)	No (0)	Partial (1)	No (0)	Partial (1)	11	Low
Shrestha et al (3)	2017	Yes (2)	Yes (2)	Partial (1)	Partial (1)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	No (0)	Yes (2)	Yes (2)	Yes (2)	24	Very high
Fu et al (6)	2018	Yes (2)	Partial (1)	Partial (1)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Partial (1)	Yes (2)	Yes (2)	No (0)	Yes (2)	Yes (2)	Yes (2)	23	Very high
Renardy and Kirschner (8)	2019	Partial (1)	Partial (1)	Partial (1)	No (0)	Yes (2)	Yes (2)	Yes (2)	Partial (1)	Yes (2)	Yes (2)	No (0)	Yes (2)	No (0)	Partial (1)	17	Medium
Harris et al (7)	2019	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	No (0)	Yes (2)	Yes (2)	Yes (2)	26	Very high
Awad et al (2)	2020	Yes (2)	Yes (2)	Partial (1)	Partial (1)	Yes (2)	Partial (1)	Yes (2)	Partial (1)	Yes (2)	Partial (1)	Partial (1)	Yes (2)	Yes (2)	Yes (2)	22	High
Harris et al (10)	2020	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	No (0)	Yes (2)	Yes (2)	Yes (2)	26	Very high
Median Score		2	2	2	1	2	2	2	1	2	2	0	2	2	2	23	Very high

Box A1: Inclusion and Exclusion Criteria for Literature Search

Inclusion

- Mathematical model
- Systematic review of models of novel/future/hypothetical TB vaccine, or commentary adding to the analyses/interpretation of models reported elsewhere
- Intervention is novel/future/hypothetical vaccine against tuberculosis or of an unspecified novel TB intervention with characteristics in-line with a vaccine
- Reported outcomes are of the epidemiological impact of vaccine(s) (e.g. incidence, prevalence, mortality, number needed to vaccinate, cost effectiveness)

Exclusion

- Within-host/immunological vaccine impact models
- Review of commentary not adding to existing body of knowledge
- TB epidemiological models not reporting impact of vaccine
- TB epidemiological models reporting only interventions other than vaccines
- Model only reporting on impact of BCG with single known/fixed efficacy
- Disease or infection caused by Mycobacterium bovis or other non-Mycobacterium tuberculosis strain

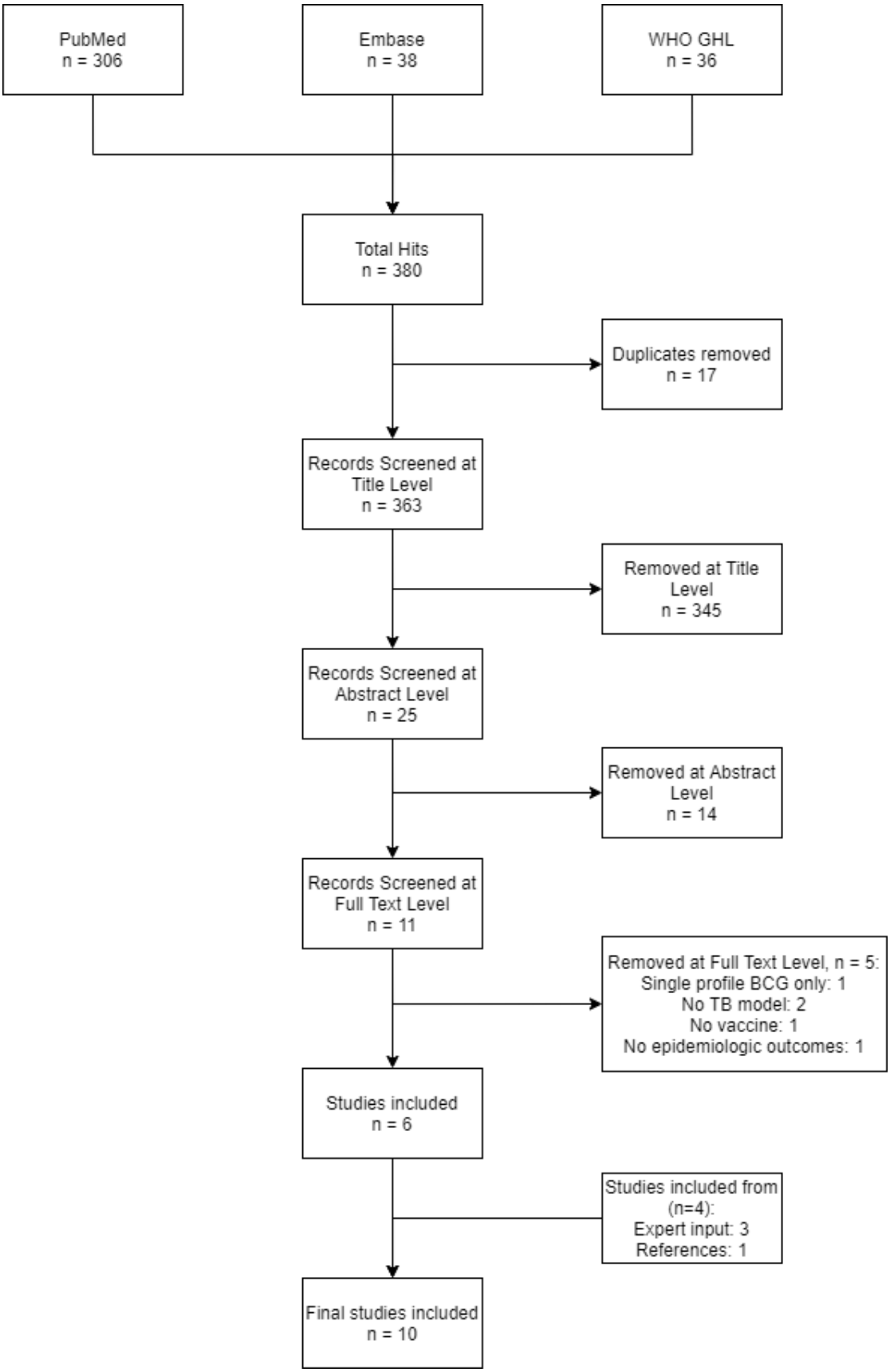

Figure A1. A flowchart of the literature screening for the updated search

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A.2 Research Paper 2: CHEERS Checklist

Consolidated Health Economic Evaluation Standards checklist for cost-effectiveness analysis included in Research Paper 2.

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	