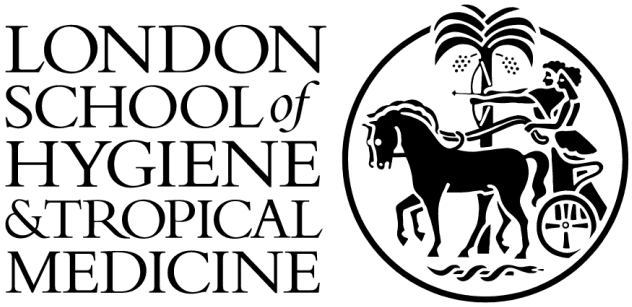

Mathematical modelling of the impact of adolescent/adult tuberculosis vaccines to inform global, national, and subnational policy and delivery

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy

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DECLARATION OF OWN WORK

I, Rebecca Anne Clark, confirm that the work presented in this thesis is my own. Where information has been derived from other sources or others have contributed to the work, I confirm that this has been indicated in the thesis.

Rebecca Anne Clark

1 December 2023

ABSTRACT

Background Tuberculosis is a leading cause of death worldwide from a single infectious agent, with an estimated 10.6 million new cases and 1.6 million deaths in 2021. The global burden of tuberculosis is highest in low- and middle-income countries (LMICs), and the largest burden of disease by country is found in India, accounting for around 30% of cases and deaths in 2021.

New tuberculosis vaccines could play a key role in reducing the global burden of tuberculosis. As of 2023, there were sixteen candidates in clinical trials, and the vaccine candidate M72/AS01$_E$ and BCG-revaccination are of particular interest, as they have recently completed Phase IIb trials with positive results. There is optimism that a new vaccine or a recommendation for policy change for an existing vaccine could come within the next decade.

It is important for decision makers to have information about the potential health and economic impacts of tuberculosis vaccines to support development and planning for vaccine introduction. However, decision makers will require different information to make informed decisions depending on their role. Global decision makers need to know the potential value of introducing tuberculosis vaccines to encourage continued development of candidates, whereas decision makers for national and subnational governments need information on country-level implementation of vaccines, such as M72/AS01$_E$ and BCG-revaccination, and the impact of any regional specific differences.

The overall aim of this thesis is to use mathematical modelling to generate appropriate evidence to provide decision makers globally, and at various levels of government in India, with estimates of health and economic impact to support tuberculosis vaccine development, policy, and introduction.

Methods I developed a new tuberculosis model to incorporate recent advances in the knowledge of tuberculosis natural history, including subclinical disease and self-clearance. To support decision makers globally and encourage investment in vaccine candidates, I independently calibrated the model to 105 LMICs representing 93% of the global tuberculosis burden. I estimated

the potential health impacts of vaccines meeting the WHO Preferred Product Characteristics for New Tuberculosis Vaccines by WHO region, World Bank income group, and WHO burden group.

To support country-specific decisions regarding vaccine delivery of M72/AS01$_E$ and BCG-revaccination in India overall, I developed a sophisticated country-level model to simulate tuberculosis vaccine introduction in India. The country-level model incorporated differences in public and private sector treatment, and calibration targets over time to constrain long-term dynamics. I simulated M72/AS01$_E$ and BCG-revaccination scenarios exploring uncertainty in product characteristics and delivery. I estimated reductions in tuberculosis cases and deaths by each scenario, as well as costs and cost-effectiveness from the health system and societal perspectives.

Finally, to assess potential differences between delivery strategies for M72/AS01$_E$ and BCG-revaccination within India, I developed subnational models for Delhi and Gujarat—two regions within India estimated to have the highest and lowest adult prevalence of tuberculosis disease respectively, incorporating regional specific differences in demography, infection prevalence, and treatment. I simulated M72/AS01$_E$ and BCG-revaccination scenarios to quantify and compare the predicted health and economic impacts.

Results Results from the multi-country modelling suggest that introducing new tuberculosis vaccines aligned with the WHO Preferred Product Characteristics could have a substantial impact in LMICs. Rapid introduction of an adolescent/adult vaccine could prevent up to 76.0 million cases and 8.5 million deaths before 2050. A booster infant vaccine could prevent up to 18.0 million cases and 2.6 million deaths before 2050.

Evaluating the delivery of specific vaccine candidates through country-level modelling in India, M72/AS01$_E$ vaccines could avert up to 19.3 million cases and 3.1 million deaths, and BCG-revaccination could avert up to 15.2 million cases and 2.6 million deaths by 2050. Nearly all vaccine scenarios were cost-effective at the most conservative country-level threshold compared to no new vaccine introduction, and the average annual cost of M72/AS01$_E$ vaccination was around four times greater than that of BCG-revaccination.

When comparing delivery strategies for specific vaccine candidates using the subnational models within India, M72/AS01$_E$ vaccines could avert up to 1.0 million cases in Delhi and 575 thousand cases in Gujarat, and BCG-revaccination could avert up to 626 thousand cases in Delhi and 222 thousand cases in Gujarat. Both subnational models predicted a larger impact of M72/AS01$_E$ vaccines than the impact of BCG-revaccination. The relative impact of BCG-revaccination for scenarios delivering the vaccine to older ages or all adults was higher in Gujarat compared to Delhi.

Conclusions New tuberculosis vaccines are likely to have a substantial health and economic impact globally and in India. The considerable reduction in cases and deaths estimated from multi-country modelling of tuberculosis vaccines in 105 LMICs supports the case for sustained investment in tuberculosis vaccine candidates throughout the pipeline to ensure success. While uncertainty in the actual vaccine characteristics exists, the modelling suggests that including a vaccination campaign, as well as rapidly introducing and scaling-up a new vaccine is crucial to obtain rapid impact by 2050.

Country-level modelling in India and subnational modelling in Delhi and Gujarat of M72/AS01$_E$ and BCG-revaccination were estimated to be impactful and cost-effective. Knowledge of the population demographics and age-specific prevalence of infection will be important for decision makers in India to consider when considering delivery strategies for vaccines which are not effective for all infection statuses.

Overall, these results suggest tuberculosis vaccines could be impactful and effective no matter the geographic scale of analysis, but at the national and subnational level, vaccine delivery strategies need to take into account regional variation in epidemiology and health care access to allow for the greatest possible impact. The evidence generated in this thesis has and can support global decision makers with vaccine investment decisions, and the Indian government with decisions regarding policy and vaccine delivery.

ACKNOWLEDGEMENTS

I could not have accomplished anything in the last four years without the support and guidance of my amazing supervisors, Professor Richard White, Dr Rebecca Harris, and Dr Chathika Weerasuriya. Richard, thank you for sharing your immense knowledge and passion for tuberculosis vaccine modelling with me, and for giving me every opportunity to succeed. Rebecca, thank you for your continued advice, encouragement, and invaluable guidance throughout, no matter how far you were. Chathika, you have been the most supportive "*friend/supervisor*" throughout my PhD, and I am sure you knew you had your work cut out for you with the events of the first Union trip to Hyderabad. Thank you for your academic and life guidance, which I hope you will continue to provide for years to come.

Thank you to LSHTM for accepting me into the programme, and to the TB Modelling Group for providing a supportive environment to share findings, discuss tuberculosis modelling, and socialise. Thank you to Dr Roel Bakker at KNCV for his help and excellent coding. Thank you to Allison Portnoy and Nick Menzies at Harvard for working with us and being very patient while I attempted to grasp health economics!

A huge thank you to the Bill and Melinda Gates Foundation for supporting my PhD, and in particular Ann Ginsberg and Geoff Garnett. Thank you to Nebiat Gebreselassie and Matteo Zignol for support and funding through the WHO Full Value of Vaccines Project. Thank you to the Canadian Centennial Scholarship Fund for supporting me with The Victor Dahdaleh Scholarship and numerous opportunities to stay connected with Canadians in the UK. To our colleagues in India—Dr Kiran Rade, Dr Sanjay Mattoo, and Dr Dheeraj Tumu—thank you for your collaboration and insight.

I want to acknowledge and extend my gratitude to everyone worldwide who participated in new tuberculosis vaccine trials. It is only through your participation that we are closer than ever to introducing a new tuberculosis vaccine, and your selflessness to trial a candidate will help to eventually prevent millions of deaths.

To my friends across the world, thank you for always being there for me, and not letting me slip into the depths of PhD and pandemic despair.

Thank you to Gordon and Marie for taking me in during the pandemic without hesitation and becoming my home away from home. I am so lucky to have such an amazing UK family.

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Thank you to my family, particularly those who are no longer with us, who I know have been by my side throughout this process, encouraging me and cheering me on. I am sorry you were not able to read the final thesis (as I am sure you may have been some of the only people to do so!).

And finally, a huge thank you to my parents, my brother Chris, and, of course, Sadie the dog, for never letting me forget that I could do this. I love you all very much.

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LIST OF ABBREVIATIONS

ABC	Approximate Bayesian computation
ACF	Active case finding
AFR	WHO African Region
AI	Any-infection
AMR	WHO Region of the Americas
AMR	Antimicrobial resistance
ART	Antiretroviral therapy
BCG	Bacillus Calmette–Guérin
CI	Current-infection
COVID-19	Coronavirus Disease 2019
DALY	Disability-adjusted life year
DM	Diabetes Mellitus
DR-TB	Drug-resistant tuberculosis
EMR	WHO Eastern Mediterranean Region
EUR	WHO European Region
GDP	Gross domestic product
HHC	Household contacts
HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon-gamma release assay
IRR	Incidence rate reduction
LIC	Low-income countries
LMIC	Lower-middle income countries
LMIC	Low- and middle-income countries
LTBI	Latent tuberculosis infection
MCMC	Markov chain Monte Carlo

MDR-TB	Multidrug-resistant tuberculosis
MRR	Mortality rate reduction
Mtb	Mycobacterium tuberculosis
NCI	No-current-infection
NFHS-5	2019–2021 National Family Health Survey
NTP	National Tuberculosis Programme
NTEP	National Tuberculosis Elimination Programme
PLHIV	People living with HIV
POI	Prevention of infection
POID	Prevention of infection and disease
POD	Prevention of disease
PPC	Preferred product characteristics
PPI	Pre- and post-infection
PPD	Purified protein derivative
PRI	Pre-infection
PSI	Post-infection
QFT	QuantiFERON-TB Gold
RNTCP	Revised National Tuberculosis Control Programme
RR	Relative risk
RR-TB	Rifampicin-resistant tuberculosis
SDG	Sustainable Development Goals
SEAR	WHO South-East Asian Region
TB	Tuberculosis
TPT	Tuberculosis preventive therapy
TST	Tuberculin skin tests
UMIC	Upper-middle income countries
UN	United Nations

UNHLM	United Nations High Level Meeting
USD	United States dollars
WHO	World Health Organization
WPR	WHO Western Pacific Region

CHAPTER 1 Introduction

1.1 Background

Tuberculosis causes significant morbidity and mortality worldwide. In 2021, an estimated 10.6 million people developed tuberculosis disease, and despite the availability of treatment, over 1.6 million people died, with the majority of deaths occurring in low- and middle-income countries (LMICs).[1] Global and country-specific elimination goals had been established, but progress was slow and has been negatively impacted by the COVID-19 pandemic, with delays in treatment seeking, reductions in case notifications, and an increase in the number of deaths from tuberculosis per year for the first time since 2005.[1]

Tuberculosis is caused by *Mycobacterium tuberculosis* (*Mtb*).[2] Historically, infection with *Mtb* was dichotomised into latent infection, where individuals are asymptomatic and unable to transmit, and clinical tuberculosis disease, with symptoms such as prolonged cough, weight loss, and night sweats, and the ability to transmit *Mtb* to others.[2] More recently, it has been recognised that infection with *Mtb* exists across a spectrum from uninfected to severe clinical tuberculosis.[3] Intermediate minimal and subclinical disease states may exist between latency and clinical tuberculosis, with regression and progression between states possible, and self-clearance may occur, where no viable *Mtb* is present to progress to tuberculosis disease without reinfection, suggesting that infection is not lifelong.[3–5]

India has the largest absolute number of tuberculosis cases per year of any country, accounting for around 30% of the global number of cases in 2021.[1] The burden of tuberculosis varies widely nationwide, with the disease prevalence in high burden areas such as Delhi almost six times as large as the disease prevalence in low burden areas such as Gujarat and Kerala.[6] The Government of India has ambitious plans to eliminate tuberculosis by 2025—five years before the United Nations Sustainable Development Goal of elimination.[7]

There is currently only one licensed tuberculosis vaccine recommended by WHO; the Bacillus Calmette–Guérin (BCG) vaccine, which has been available for over 100 years, and is now primarily administered in high burden settings to prevent severe childhood tuberculosis. However,

BCG has varying efficacy to prevent tuberculosis disease in adolescents and adults, the population with the highest burden. New tuberculosis vaccines that are effective at preventing disease in adolescents and adults are likely to be key to help reach elimination goals, and within the past decade, there have been promising developments. In 2015, the WHO established the Preferred Product Characteristics (PPCs) for New Tuberculosis Vaccines which described minimum preferred characteristics for a novel infant vaccine to be used independently or as a booster for neonatal BCG, and a vaccine to be used to prevent tuberculosis disease in adolescents and adults.[8]

As of July 2023, there were sixteen tuberculosis vaccine candidates in clinical trials.[9] In particular, results from a Phase IIb trial of the vaccine candidate M72/AS01$_E$ were published in 2018, and reported an efficacy of 49.7% (2.1–74.2) to prevent tuberculosis disease in adults with current *Mtb* infection.[10] Additionally, BCG-revaccination of adolescents was assessed as a third parallel arm during a trial for another vaccine candidate, and demonstrated an efficacy of 45.4% (6.4–68.1) to prevent sustained tuberculosis infection in uninfected adolescents.[11] There is hope that a new tuberculosis vaccine will be available within the next decade.

1.2 Rationale for the present study

With vaccine candidates approaching licensure, decision makers will need information about the potential population-level impact of introducing new tuberculosis vaccines to reduce delays in access and introduction. Different information will be needed by decision makers depending on their level (globally, nationally, or subnationally) and what types of decisions they will have to make.

Different evidence is also needed for candidates in different stages of the vaccine pipeline. For candidates early in the vaccine pipeline, evidence and information is needed to inform decisions around investment in trials. For candidates approaching licensure, evidence and information is needed to support planning for licensure, policy recommendations and introduction to shorten the time between trial completion and vaccine delivery in the country.

Within the past decade, mathematical models have been used to investigate the potential impact of new tuberculosis vaccines.[12,13] While there have been new discoveries in tuberculosis natural history which could influence vaccine protection assumptions,[3–5] these findings have yet to be incorporated in models evaluating vaccine impact. No modelling studies have investigated realistic vaccine delivery scenarios, the possible impact of vaccines with characteristics aligned with the WHO PPCs, or compared the impact of delivering M72/AS01$_E$ and BCG-revaccination.[12,13] The burden of tuberculosis varies widely across India, but no studies have compared the possible impact of novel tuberculosis vaccines between regions.[12,13]

1.3 Thesis aims

The overall aim of the thesis is to use mathematical modelling to generate appropriate evidence to provide decision makers globally, and at various levels of government in India, with estimates of health and economic impact to support tuberculosis vaccine policy and introduction.

The thesis has three specific aims:

Aim 1: Estimate the health impact of introducing new tuberculosis vaccines in LMICs under alternative delivery strategies to support investment in vaccine manufacturing and development,

Aim 2: Estimate the health and economic impact of introducing M72/AS01$_E$ vaccines and BCG-revaccination in India to provide evidence for country-level decision makers,

Aim 3: Estimate the health and economic impact of introducing M72/AS01$_E$ vaccines and BCG-revaccination in Delhi and Gujarat to compare the effect of different population-level characteristics on vaccine impact to provide evidence for subnational decision makers.

1.4 Thesis objectives

To address **Aims 1–3**,

Objective 1: Develop

a. a new tuberculosis model structure which incorporates key aspects of tuberculosis natural history and
b. a new vaccine model structure which allows for protection from multiple vaccines with varying product characteristics and is able to represent sophisticated and realistic vaccine delivery strategies.

To address **Aim 1**,

Objective 2: Using the tuberculosis model structure developed in Objective 1a:

a. Independently calibrate the model to historical tuberculosis epidemiology in LMICs
b. Simulate the introduction of vaccines with characteristics aligned with the WHO Preferred Product Characteristics for New Tuberculosis Vaccines under varying delivery strategies, and
c. Calculate and compare the health impact (cumulative cases, treatments and deaths averted) between vaccine delivery scenarios by WHO region, World Bank Income Group, and WHO burden level.

To address **Aim 2**,

Objective 3: Extend the multi-country tuberculosis model from Objective 1a to develop a sophisticated and detailed country-level model for India, incorporating differences in public and private sector treatment outcomes

a. Calibrate the country-specific model for India to multiple calibration targets over time to constrain long-term dynamics
b. Simulate the introduction of M72/AS01$_E$ vaccines and BCG-revaccination under varying delivery strategies, and
c. Estimate the health and economic impacts of each vaccine scenario.

To address **Aim 3**,

Objective 4: Further extend the country-level India tuberculosis model to develop subnational models for Delhi and Gujarat

a. Calibrate to region-specific estimates of tuberculosis prevalence and case-notifications
b. Simulate the introduction of M72/AS01$_E$ vaccines and BCG-revaccination under varying delivery strategies, and
c. Estimate and compare the health and economic impacts of vaccine scenarios from each region

1.5 Thesis structure

The six chapters of this thesis are structured as follows.

Chapter 1 introduces the reader to the thesis. I provide a brief summary of the topic and rationale for undertaking this study. I describe the three thesis Aims and the four thesis Objectives which I will address, and outline the structure and content of the six thesis chapters.

In **Chapter 2** I provide a comprehensive review of the tuberculosis literature, focussing on tuberculosis natural history, global and regional burdens of disease, tuberculosis vaccines, and mathematical modelling of tuberculosis vaccines to set the scene for the remainder of the thesis. I systematically review the mathematical modelling literature of tuberculosis vaccine impact to investigate gaps in knowledge which will be addressed in Chapters 3–5.

Chapter 3 is centred around the first research paper of the thesis, published in the *Lancet Global Health*, addressing thesis **Aim 1** and thesis **Objective 2**.[14] I calibrated an updated tuberculosis natural history structure to epidemiological data for each of 105 low- and middle-income countries, before introducing novel tuberculosis vaccines based on the WHO Preferred Product Characteristics for New Tuberculosis Vaccines. I estimated the cumulative number of cases, treatments, and deaths that could be averted with novel vaccines compared to no-new-vaccine introduction. The supplementary material of the multi-country modelling research paper is

included in section 3.3, and addresses thesis **Objective 1**, where I detail the methods used to update the tuberculosis natural history structure based on recent advances described in Chapter 2 and develop a new sophisticated vaccine structure.

Research paper 1 citation:
Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study. *Lancet Glob Health.* 2023; 11(4): E546-E555 https://doi.org/10.1016/S2214-109X(23)00045-1

Building off of the results from Chapter 3, **Chapter 4** extends the modelling to focus on India. In the second research paper, published in *BMC Medicine*, I investigated the health and economic impact of introducing two potential vaccines, M72/AS01$_E$ and BCG-revaccination, in India to address thesis **Aim 2** and thesis **Objective 3**.[15] I extended the developed model from Chapter 3 to create a detailed model structure for India and calibrated to nineteen India specific calibration targets. I compared the cumulative cases, deaths, and disability-adjusted life years averted, cost-effectiveness, and budget impact for thirteen M72/AS01$_E$ scenarios and twelve BCG-revaccination scenarios compared to no-new-vaccine introduction to generate information useful for country-level decision makers in India.

Research paper 2 citation:
Clark RA, Weerasuriya CK, Portnoy A, et al. New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination. *BMC Medicine;* 2023: 21(288). https://doi.org/10.1186/s12916-023-02992-7

Following from Chapter 4, **Chapter 5** extends the model further to investigate and compare the impact of M72/AS01$_E$ and BCG-revaccination within two specific regions in India. Delhi and Gujarat were estimated to have the highest and lowest all-age tuberculosis prevalence, respectively, in India from the National Tuberculosis Prevalence survey. Combined with differences in demography, differences in tuberculosis epidemiology between regions may

influence the estimated impact of vaccines. To address thesis **Aim 3** and thesis **Objective 4**, I calibrated the extended tuberculosis model to region specific disease prevalence and case notifications in Delhi and Gujarat, and simulated vaccine scenarios for M72/AS01$_E$ and BCG-revaccination similar to the scenarios modelled in Chapter 4. I compared the health and economic impact of scenarios between Delhi and Gujarat in Research Paper 3 to investigate the differences in impact by region and generate information useful for government decision makers.

Research paper 3 citation:

Clark RA, Portnoy A, Weerasuriya CK, et al. The potential health and economic impacts of new tuberculosis vaccines under varying delivery strategies in Delhi and Gujarat, India: a modelling study. *(In preparation for submission)*

Finally, in **Chapter 6**, I discuss the key results of each of the chapters, their associated limitations, and the potential impact of these findings for policy makers globally, at the national level in India, and for subnational vaccine introduction in India.

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CHAPTER 2 Background

2.1 Tuberculosis

Tuberculosis was one of the leading killers globally from a single infectious agent, second only to COVID-19 in 2021.[1] Despite the existence of treatment, over 1.6 million people died from tuberculosis, with the majority of deaths occurring in low- and middle-income countries (LMICs).[1] Due to impacts from the COVID-19 pandemic, previous slowly declining trends in tuberculosis incidence and mortality have reversed, and the World Health Organization (WHO) reported an increase in the number of deaths per year from tuberculosis between 2019 and 2021 for the first time since 2005.[1]

Tuberculosis occurs worldwide, but the health burden is concentrated in LMICs, accounting for 99% of the total cases in 2021. Adults represented 89% of the total incident cases in 2021 and made the greatest contribution to continued transmission.[1] Men have a significantly higher prevalence of tuberculosis compared to women.[1,2] It is estimated that a quarter of the world's population has been infected with the tuberculosis disease causing bacteria (*Mycobacterium tuberculosis [Mtb]*) and while infected has the potential to progress to active tuberculosis.[3]

Mortality remains increased, and quality of life decreased, despite successful treatment of tuberculosis,[4] demonstrating the importance of prevention in addressing the epidemic. Individuals who were successfully treated for active tuberculosis are also at an increased risk of subsequent disease episodes.[5,6]

The burden of tuberculosis disproportionately impacts the most disadvantaged populations, who are additionally more likely to be exposed to key risk factors. Evidence has shown that social determinants and environmental risk factors, including crowded, densely populated areas with poor ventilation, poverty and lower socioeconomic status, and exposure to indoor air pollution, can impact immune function and increase the likelihood of infection and progression to disease.[7–9]

A leading risk factor for developing tuberculosis is infection with human immunodeficiency virus (HIV). Depending on the country-specific prevalence of HIV, the risk of tuberculosis in people

living with HIV (PLHIV) ranges from 20–37 times that of those without.[10,11] PLHIV have an increased risk of progression to tuberculosis disease once infected with *Mtb* and increased mortality from tuberculosis disease compared to those without HIV.[9,10,12] Antiretroviral therapy (ART) can decrease the risk of progression to disease and tuberculosis mortality, but tuberculosis incidence in PLHIV on ART is still increased compared to people without HIV.[10] Over 710 thousand (6.7%) incident cases of tuberculosis and 187 thousand deaths (11.7%) in 2021 were in PLHIV.[1] For a number of countries in southern Africa with a high prevalence of HIV, over 50% of their reported tuberculosis cases were in people living with HIV.[1] In LMICs, tuberculosis is also the leading cause of death for PLHIV.[10]

Undernutrition, commonly defined as a body-mass index (BMI) less than 18.5 kg/m^2, is also a leading risk factor for tuberculosis, with over 2.0 million cases of tuberculosis attributed to undernutrition in 2021.[1,13] Studies have demonstrated an inverse relationship between BMI and tuberculosis incidence,[14] and there is substantial geographic overlap between countries with high tuberculosis incidence and high prevalence of undernutrition.[13] Undernutrition is thought to increase the risk of progression and reactivation to tuberculosis disease,[14] and severe undernutrition (individuals with a BMI less than 16 kg/m^2) was associated with a four times higher risk of death during tuberculosis treatment.[15] There is potential for the impact of undernutrition on the tuberculosis burden to increase in the coming decades, due to economic impacts of the COVID-19 pandemic,[16] higher energy and food prices caused by the war in Ukraine,[17] as well as climate change reducing the availability of food.[18]

Additional risk factors for tuberculosis include alcohol use disorders,[19,20] tobacco smoking,[21] and diabetes mellitus,[22] which can impair the immune system, leading to increases in susceptibility to tuberculosis infection and progression to disease, and worsen treatment outcomes. In 2021, approximately 740 thousand incident cases of tuberculosis were attributable to alcohol use disorders, 690 thousand cases due to tobacco smoking, and 370 thousand cases due to diabetes mellitus.[1]

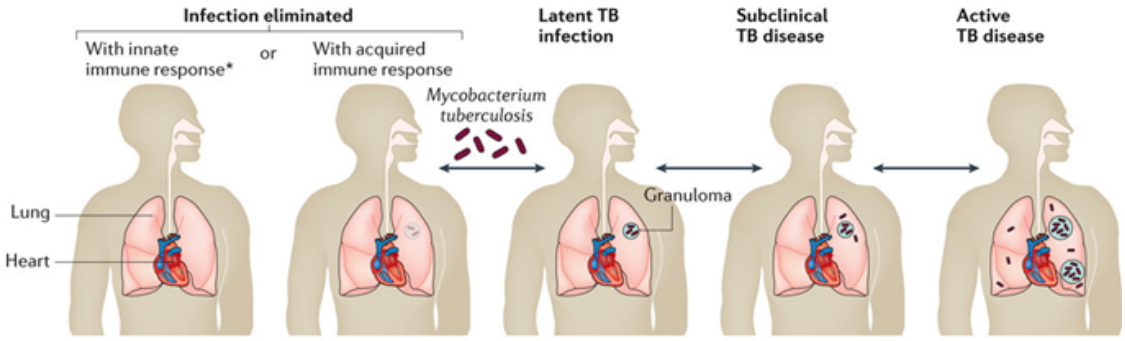
2.2 Tuberculosis natural history

Tuberculosis has a complex natural history which has still yet to be understood in full. An individual can become infected with *Mtb* by inhaling particles containing *Mtb* expelled by an infectious individual, but exposure to *Mtb* does not always result in tuberculosis infection or disease.[11] An individual with infectious tuberculosis may only infect 3–10 additional individuals per year, of whom only a small proportion will progress to tuberculosis disease themselves, with the risk of progressing increased due to the risk factors described above.[23] Clinically, tuberculosis disease can present as pulmonary tuberculosis which impacts the lungs, and extrapulmonary tuberculosis which occurs in sites other than the lungs.[11,24] Approximately 16.5% of incident tuberculosis cases reported to WHO in 2021 were extrapulmonary.[1]

Tuberculosis pathogenesis is complex, and our understanding of the underlying mechanisms and disease states is constantly evolving.[25] The ninth report by the WHO Expert Committee on tuberculosis from 1974 recommended that tuberculosis case finding strategies focus on individuals who displayed symptoms.[26] Individuals with no clinical symptoms but who had an immune response to tuberculin tests were classified as having inactive or latent infection.[25,27] Those with inactive or latent infection were not infectious, although were assumed to be at a lifelong risk of progression to tuberculosis disease.[25,27] Individuals with clinical symptoms (such as a prolonged cough, weight loss, and night sweats), and positive diagnostic tests were classified as having tuberculosis disease and able to transmit *Mtb* to others.[25,27] Given the assumption that those without symptoms were unable to transmit *Mtb*, the primary focus was on detecting and treating those with clinical tuberculosis.[26] Therefore, the guidelines inadvertently suggested a dichotomy based on symptoms, which persisted and became the basis of many interventions and mathematical modelling structures.[25,27]

However, there have always been those who observed that infection with *Mtb* existed on a spectrum. Recently, it has begun to be recognised by more researchers in the field that individuals exposed to *Mtb* can fall along a continuum of infection and disease, with progression and regression possible between stages, and the importance of these intermediate stages in global eradication efforts.[23,25,27]

An overview of the key stages is presented in Figure 1 below from Pai et al., 2016.[23]



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

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Figure 1 Stages of tuberculosis infection and disease from Pai et al., 2016.[23]

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Following exposure to *Mtb*, an individual's immune system can either promptly clear the bacteria or it can become an established infection.[23] Individuals with current tuberculosis infection, referred to by other terms such as *Mtb* infection or those with latent tuberculosis infection (LTBI), harbour viable bacteria which has the potential to reactivate and progress to tuberculosis disease, but they are not infectious, meaning they are unable to transmit the bacteria to others, and do not display any symptoms.[27,28] An individual is usually defined as a fast-progressor if they progress to active disease within two years of infection with *Mtb*.[29] Slow-progressors are those who do not progress to active disease within two years, but were assumed to remain at risk for reinfection and progression while they are in the tuberculosis infection state,[29] with the lifetime risk of reactivation between 5-10%.

There is evidence that current tuberculosis infection can provide protection against reinfection, with studies estimating a 15–40% reduction in risk of progression to disease following reinfection

for infected adolescents and adults.[30] That, combined with the long latency period of infection, can mean that individuals are infected for decades before potentially activating and progressing to active disease.[31] Screening for tuberculosis infection can help identify individuals who would benefit from preventative treatment, but the availability of reliable tools to accurately detect viable *Mtb* is limited, as will be discussed in Section 2.4.[32]

Historically, tuberculosis infection was thought to be lifelong. It was estimated that 25–30% of the population globally had latent infection and were at risk of progressing to disease at some point during their lives.[25] More recently it has been proposed that this may not be the case.[33,34] As Behr et al., 2019 discussed, the proportion of latent infection is inferred from immunoreactivity tests, which do not necessarily imply current viable infection—just having previously been infected.[33] By analysing the proportion of people from historical studies who were immunoreactive that progressed to disease when immunosuppressed (through either a solid organ transplant, stem cell transplant, or developing HIV), they observed a lower proportion of those who progressed to disease than expected if all had viable infection.[33] The results from Behr et al., 2019 suggested that between 1–11% of people who are immunoreactive have viable bacteria, and therefore the proportion of the population who are at risk of progressing to disease may be much lower than the 25% previously estimated.[33]

Emery et al., 2021 sought to provide a conservative lower estimate on the likelihood of clearing *Mtb* after infection by using mathematical modelling. Using a cohort model parameterised with data from immunoreactive test reversion studies and autopsy studies, they estimated that 24.4% (95% uncertainty interval = 17.8–32.6) of individuals who were infected would self-clear within 10 years of initial infection, and 73.1% (64.6–81.7) would self-clear over a lifetime.[34] A direct impact of this finding is a significant reduction in the size of the population believed to be at risk of progression to disease, thereby increasing the estimate of the lifetime risk of tuberculosis disease for those who maintained viable infection.[34]

We define individuals who have eliminated their *Mtb* infection, or are "self-cleared", as those were previously infected with *Mtb*, but were able to clear their infection naturally without treatment.[27,34] Self-clearance implies that there are no longer any viable bacteria remaining to reactivate naturally,

in contrast to those classified with tuberculosis infection, and individuals must be reinfected in order to progress to infection or active disease states.[27,34,35] Research on self-clearance is in its infancy, and it is unknown how self-clearance and protection from reinfection are related (would those individuals who self-cleared lose all protection from reinfection that they had when they were infected, and therefore increase the proportion of the population that is susceptible?), or how interventions such as vaccines, which may only be effective with either current viable infection or no infection at vaccination, will be impacted.

Subclinical tuberculosis has recently been recognised as an important "intermediate" stage between infection and clinical disease.[27,36,37] Subclinical tuberculosis can cause physiological changes, such as abnormal lung lesions, which may be detectable using a chest radiography and other imaging techniques, and would appear bacteriologically-positive when tested, but individuals do not report any symptoms which would be expected from someone with clinical tuberculosis.[27]

An important question arising from the recognition of subclinical tuberculosis is determining how much of the prevalent tuberculosis disease is subclinical. In a recent review of available prevalence surveys, Frascella et al. estimated that approximately 50.4% (36.1–79.7) of prevalent bacteriologically confirmed tuberculosis was subclinical.[37] Following the Frascella paper, the South Africa prevalence survey from 2017–2019 estimated that 57.7% of those with bacteriologically confirmed tuberculosis reported no symptoms,[38] and 56.4% of those with active tuberculosis detected during the National TB Prevalence survey in India from 2019–2021 had no symptoms.[39] The general consensus now is that approximately half of the prevalent tuberculosis is subclinical, and therefore active case finding strategies which rely on detecting clinical symptoms that would not be present in those with subclinical tuberculosis would not be as effective.

An ongoing debate is whether individuals with subclinical tuberculosis are infectious and if they contribute to *Mtb* transmission. A data analysis study of patient level data reported in a preprint by Emery et al. estimated the per-unit-time infectiousness of subclinical tuberculosis of 1.93 (prediction interval: 0.62–6.18) compared to clinical tuberculosis.[36] It is likely to be biologically

implausible that individuals with subclinical tuberculosis are more infectious per unit time than those with clinical tuberculosis, and possible that assumptions made by the authors and how the estimates from the patient level data were incorporated into the calculation may have contributed to this high estimate and upper bound.[36] The authors highlight that the main conclusion to be drawn from the study is that the lower bound of the range of infectiousness per unit time is greater than zero, implying that individuals with subclinical disease are infectious and important to consider during strategies to reduce *Mtb* transmission.

The most advanced stage of infection with *Mtb* is clinical tuberculosis (also known as active tuberculosis, however both clinical and subclinical tuberculosis can be considered active tuberculosis states as they are able to transmit *Mtb*). Individuals with clinical tuberculosis most commonly present with bloody sputum and cough, fever, night sweats, weight loss, and swollen lymph nodes.[23] Lung lesions including cavitation and obstruction may be detectable through chest radiography.[23]

Tuberculosis is not a highly infectious disease, but is associated with an long duration of infectiousness, which in some cases can last longer than a year.[23] Mortality from untreated clinical tuberculosis is high at approximately 60% in HIV negative individuals,[40] and tuberculosis is the leading cause of death for people living with HIV.[23] The presentation of clinical tuberculosis is also different in PLHIV that is not managed with ART, who have a higher risk of developing extrapulmonary and disseminated tuberculosis.[23]

Improving our understanding of the underlying natural history of tuberculosis is important, particularly as we aim for elimination, when thinking about the impact of the interaction between preventive measures, such as tuberculosis vaccines, with some of the novelties in natural history.

2.3 Geographical burden of tuberculosis

2.3.1 Burden of tuberculosis globally

Tuberculosis is a global disease, but the highest burden is concentrated in LMICs. Only 1% of the reported cases in 2021 occurred in high-income countries. The total number of cases in 2021 from the following nine LMICs combine to equal more than two thirds of the incidence globally: India (28.0%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%), and the Democratic Republic of the Congo (2.9%).[1]

While the current burden is highest in LMICs, tuberculosis was historically a leading cause of death in high-income countries such as the United Kingdom, Canada, and the United States of America. Improvements in socioeconomic status, living conditions, and the availability of anti-tuberculosis drug therapy are associated with the decrease in tuberculosis burden in high-income countries throughout the 20th century, and it is estimated that a majority of new tuberculosis cases in high-income countries are estimated to arise from reactivation in foreign-born individuals from high tuberculosis burden countries.

Having a low overall burden does not imply that tuberculosis is not an important consideration for high-income countries. An estimate of the combined burden can be misleading, particularly as tuberculosis is a disease associated with poverty and disproportionately impacts those who are most disadvantaged. Canada is an example of a country with a low overall burden of tuberculosis, with incidence and mortality rates in 2021 of 5.3 and 0.24 per 100,000 population respectively.[1] However, First Nations and Inuit communities have a disproportionately higher burden, with incidence rates greater than 41 and 296 times that of the Canadian-born non-Indigenous population respectively. Factors increasing the burden of tuberculosis in Indigenous communities include those associated with tuberculosis in LMICs such as reduced access to quality healthcare, food insecurity, and poor living conditions.

2.3.2 Burden of tuberculosis in India

Eliminating the burden of disease in India is crucial for global elimination. India was the country with the highest burden of tuberculosis in 2021, accounting for 28% of the global incident cases

and 36% of the global non-HIV tuberculosis deaths.[1] India is classified as one of the WHO top 30 high tuberculosis burden countries for 2021–2025, in addition to appearing on the high tuberculosis/HIV and drug-resistant tuberculosis lists.[41] The incidence rate of new tuberculosis cases in India in 2021 was estimated at 210 (178–244) cases per 100 000 population per year, with 24% of reported cases being extrapulmonary tuberculosis.[1]

After making large progress in decreasing tuberculosis incidence, mortality, and increasing the number of reported tuberculosis cases since 2000 (Figure 2), negative impacts from the COVID-19 pandemic have resulted in the reversal of positive trends. The estimated incidence increased in 2021, and estimated mortality increased in both 2020 and 2021. The largest estimate of unreported and undiagnosed tuberculosis cases in 2020 and 2021 were in India, accounting for over 40% in 2020 and almost 30% in 2021 of the total unreported and undiagnosed tuberculosis cases globally. 25% fewer cases were reported in India by the end of 2020 compared to 2019, and although some recovery was seen in the following year (over 330 thousand more cases reported in 2021 than in 2020), this was still 9.1% lower than the reported numbers from 2019.[1]

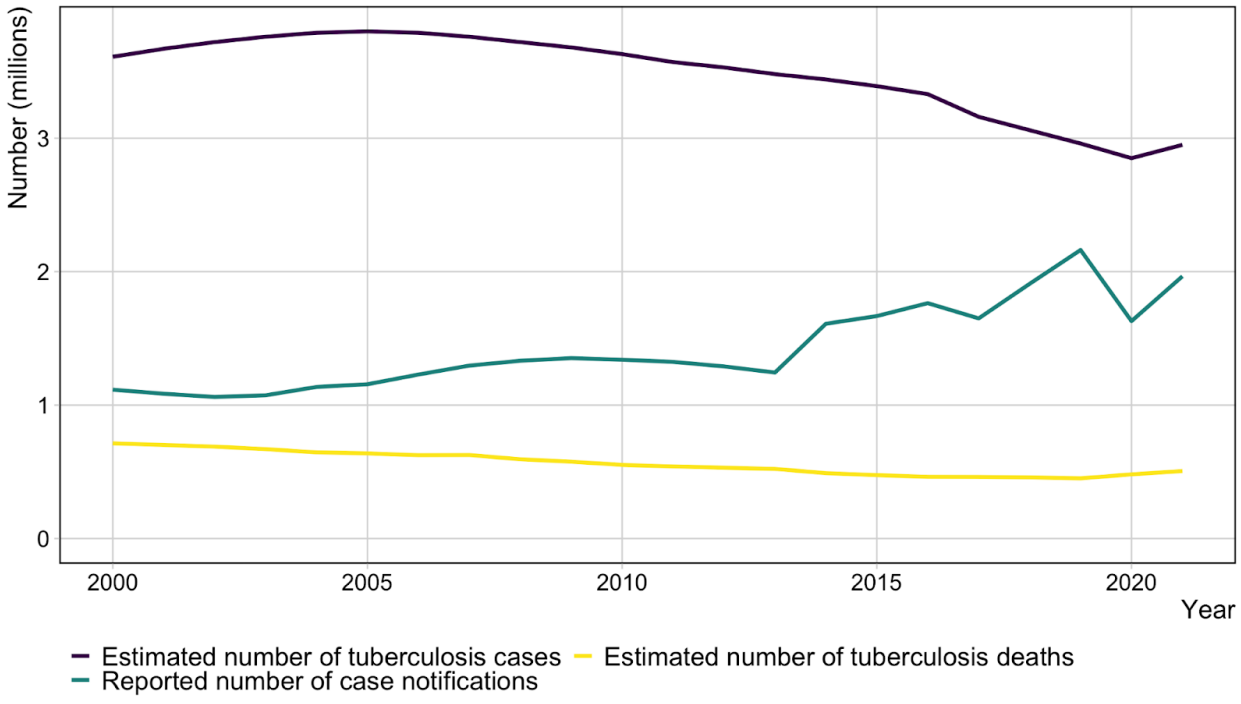

Figure 2 WHO trends in tuberculosis cases, reported cases, and mortality in India

The first national tuberculosis prevalence survey was conducted in India between 2019 and 2021 organised by the *Central TB Division* of the Government of India. Over 350 thousand individuals aged ≥15 were eligible to participate in the survey from clusters across the country, with States and Union Territories divided into 20 state groups.[39] 91% of the eligible study population underwent symptom screening and/or chest X-ray screening, with almost 42 thousand subsequently undergoing sputum screening. [39] A total of 981 individuals were found to have microbiologically confirmed pulmonary tuberculosis, leading to an estimated pulmonary tuberculosis prevalence for adults aged ≥15 of 316 (290–342) per 100,000 population.[39] After adjusting for children and extrapulmonary tuberculosis, the estimated prevalence for all ages and types of tuberculosis was 312 (286–337) per 100,000 population.[39] The India National Tuberculosis Elimination Programme is working with WHO to finalise and formally publish these analyses.

To estimate the national prevalence of tuberculosis infection in India, at least one cluster from each of the state groups was selected to undergo IGRA testing. The state of Gujarat was already planning widespread IGRA testing, and therefore all 31 clusters in Gujarat were IGRA tested.[39] After testing a total of 55 clusters, the estimated tuberculosis infection prevalence for adults aged ≥15 years was 31.4% (27.2–35.3).[39]

In India, financial and policy responsibility for the healthcare system falls to the federal government, including the tuberculosis programme, while the government of each state is responsible for healthcare delivery.[42] For healthcare services specific to tuberculosis, a systematic review from 2015 investigated the quality of tuberculosis care provided in India, and found that they were often lacking in major areas, including baseline knowledge of tuberculosis symptoms and standard treatment protocol.[43]

Although tuberculosis treatment is freely available from the public sector, evidence has shown a large proportion of patients are choosing to access care from the private sector.[44–47] A 2019 study from Arinaminpathy et al. estimated that the overall percent of treatment months completed in the public sector was 36% (33–39), ranging from 22% (17–25) in Bihar to 73% (63–79) in Himachal Pradesh.[44] Cases of tuberculosis treated in the private sector are less likely to be reported to the

national services, contributing to the gap between reported and actual cases of tuberculosis. While individuals may believe that care is superior in the private sector, studies have indicated that the quality of care provided by both public and private sectors have room for improvement.[48]

Access to high quality healthcare is variable between and within states, depending on the state level expenditure on health and the relative proportions of urban and rural communities.[47] States with an increased level of urbanisation have access to options in both the public and private sectors, with evidence showing that more resources are available in urban areas, including more available treatment facilities and healthcare professionals.[47] When the rurality is increased, states are restricted by the limited availability of local healthcare options, in addition to increased physical distance from facilities.[47]

India is a large country divided into twenty-eight states and eight union territories. The national prevalence survey demonstrated wide variation in the tuberculosis disease burden across the country and revealed that Delhi and Gujarat have the highest and lowest tuberculosis prevalence estimates per 100,000 population in 2021 for all ages respectively.[39]

The National Capital Territory of Delhi ("Delhi") is a geographically small and dense city and union territory, containing New Delhi, the capital city of India. According to the 2011 census, Delhi had a population of almost 17 million—the 19th largest of any state or union territory in the country—and by 2020, the estimated population had increased by 12% to almost 19 million.[49,50] Delhi is almost entirely urban with 97.5% of the population living in an urban setting. In the recent national prevalence survey, Delhi was estimated to have the highest pulmonary tuberculosis prevalence for adults at 534 (365–704) per 100,000 and the highest tuberculosis prevalence for all ages at 747 (510–984) per 100,000.[39] In the 2019–2021 National Family Health Survey (NFHS-5), 36.1% of participants in Delhi indicated they would not access care in a government health facility, with almost 70% of those choosing the private sector due to long wait times in public facilities and 40% indicating a perceived poor quality of care.[51] In 2022, Delhi reported over 100,000 tuberculosis cases, with 27% of reported notifications seeking care in the private sector.[52,53] 44% of new cases reported in 2021 were extrapulmonary tuberculosis—20 percentage points higher than the proportion of extrapulmonary tuberculosis cases in India overall.[53]

The state of Gujarat is the fifth largest state by area and located on the west coast of India. With an estimated 64 million people living in Gujarat in 2020, it is the ninth largest state by population.[49] Census data has indicated that Gujarat is increasingly becoming more urban, with around 50% of the population living in urban settings. In contrast to Delhi, Gujarat has one of the lowest estimated pulmonary tuberculosis prevalence for adults of 141 (78–203) per 100,000, the lowest estimated tuberculosis prevalence among all ages of 137 (76–198) per 100,000, as well as the lowest estimate of the prevalence to notification ratio (0.91).[39] 45.9% of participants in NFHS-5 from Gujarat indicated they would not access care in a government health facility, with the primary reasons being long wait times and no nearby facility.[51] In 2022, Gujarat reported over 150,000 tuberculosis cases, with 33% of reported notifications seeking care in the private sector.[52] A slightly lower proportion of cases reported in 2021 were extrapulmonary in Gujarat (18%) compared to India overall (24%).[53]

A subset of self-reported characteristics of participants in the NFHS-5 survey from Delhi and Gujarat are compared in Table 1 below:

Table 1 Characteristics of Delhi and Gujarat from NFHS-5[51]

Characteristic	Delhi	Gujarat
% rural	2%	57%
Households with basic drinking water	98%	95%
% age 6–17 attending school	91%	82%
Median age at first marriage	20.5	19.8
Total fertility rate	1.6 (urban), 2.5 (rural)	1.6 (urban), 2.0 (rural)
Infant mortality rate	25 / 1000	31 / 1000
BCG vaccination coverage	97%	95%
All basic vaccinations coverage	76%	76%
Children: Stunted (low height for age)	31%	39%
Children: Wasted (low weight for height)	11%	25%
Children: Severely wasted	5%	11%
Children: Underweight	22%	40%
Self-reported diabetes (per 100,000)	2,293 (women), 4,159 (men)	1,337 (women), 1,354 (men)
Too thin	10% (women), 9% (men)	25% (women), 20% (men)
Overweight / obese	41% (women), 38% (men)	23% (women), 20% (men)
Anaemia	69% (children), 50% (women), 13% (men)	80% (children), 65% (women), 27% (men)
Tobacco use	2% (women), 33% (men)	6% (women), 46% (men)
Alcohol use	1% (women), 28% (men)	0.1% (women), 6% (men)
Health insurance	25% of households	39% of households
Employment	25% (women), 79% (men)	39% (women), 85% (men)

2.4 Commitment and strategies to eliminate tuberculosis

2.4.1 Global strategies and progress

WHO declared tuberculosis a global emergency in April 1993–over 30 years ago.[54] This declaration aimed to bring tuberculosis to the forefront, but the issues described in the summer 1993 edition of *World Health: The Magazine of the World Health Organization* remain similar to those we face today: tuberculosis is the leading cause of death from a single infectious agent with a safe and effective treatment, but is neglected and a low priority on the global agenda.

WHO has been involved in numerous strategies to increase attention for tuberculosis. They support and recognise World TB Day every year on the 24th of March and have published an annual Global Tuberculosis Report since 1977. Among many other activities, they helped organise and deliver BCG vaccination throughout the twentieth century,[55] and promoted DOTS (directly-observed therapy, short-course) in the 1990s, a strategy composed of government commitment, microbiological testing of symptomatic individuals, and providing a short-course of anti-tuberculosis treatment to those who tested positive with treatment being directly observed.[56]

In 2014, WHO introduced the *End TB Strategy,* with the goal of reducing cases, deaths, and costs worldwide from tuberculosis, and ultimately bringing the global tuberculosis epidemic to an end.[11,57] The *End TB Strategy* outlined quantitative targets for global reductions in cases, deaths, and catastrophic costs, with intermediate milestones in 2020 and 2025, and an ambition to "End TB" by 2035, defined as a 90% reduction in cases and 95% reduction in mortality compared to levels in 2015.[57] The *End TB Strategy* also explicitly highlights the need for better diagnostics and treatments for both infection and disease, and new effective vaccines.[57]

In 2015, the General Assembly of the United Nations established 17 Sustainable Development Goals (SDGs) and 169 targets for the world to work toward by 2030.[58] Among others, the SDGs included declarations to end poverty, eradicate disease, reduce inequalities and inequities, take action on climate change, and promote peace. Specifically, tuberculosis is mentioned under Goal 3:[58]

Goal 3 Ensure healthy lives and promote well-being for all at all ages

*3.3 By 2030, end the epidemics of AIDS, **tuberculosis**, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases*

Table 2 describes the global targets including the *End TB Strategy* milestones in 2020 and 2025, the SDG target for ending the epidemic of tuberculosis by 2030, and the *End TB Strategy* target in 2035 to End TB.

Table 2 The End TB Strategy milestones and targets, reproduced from the WHO Global Tuberculosis Report, 2022[1]

Indicators	Milestones		Targets	
	2020	2025	2030	2035
Percentage reduction in the absolute number of tuberculosis deaths (compared with 2015 baseline)	35%	75%	90%	95%
Percentage reduction in the tuberculosis incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of tuberculosis-affected households experiencing catastrophic costs due to tuberculosis (level in 2015 unknown)	0%	0%	0%	0%

Progress toward the WHO *End TB Strategy* milestones and targets and the SDGs has been hindered by the COVID-19 pandemic, and unless urgent measures are taken, it is unlikely that the epidemic of tuberculosis will be 'ended' by the 2030 deadline. The 2020 milestones for reducing incidence and mortality were not met at the global level, with estimated global reductions in tuberculosis cases and deaths between 2015 and 2021 of only 10% and 5.9% respectively.[1] There were more deaths in the WHO South-East Asian Region and Western Pacific Region in 2021 than in 2015, and both cases and deaths were increased in the WHO Region of the Americas in 2021 compared to 2015.[1] Progress at this rate indicates that the world is not currently on track to meet the remaining milestones and goals.

However, the COVID-19 pandemic cannot take all the responsibility for a lack of progress toward tuberculosis elimination goals. The global trend of decline in incidence was 1.6% per year between 2000 and 2018, reaching a peak of 2.3% between 2018–2019.[59] Although the incidence decline varied geographically, with some regions and countries on track to achieve the 2020 targets, a global decline at that rate would not have been sufficient to reach WHO goals globally, even without the disruptions from the pandemic.[11,60]

Despite the setbacks, there have been some country and regional successes. Twenty-five countries reached the 2020 milestone for reducing tuberculosis deaths by 35%, including six high tuberculosis burden countries and one global tuberculosis watchlist country, and 77 countries reached the 2020 milestone for reducing tuberculosis incidence by 20%, including seven high tuberculosis burden countries and three global tuberculosis watchlist countries.[1] The WHO African region is close to achieving the 2020 milestone for reducing tuberculosis deaths (currently a 26% reduction compared to 2015), and achieved the milestone for reducing tuberculosis incidence along with the WHO European region.[1]

The first United Nations High Level Meeting (UNHLM) on Tuberculosis took place in New York on 26th September 2018, and was attended by over 1,000 representatives from across the world. The meeting resulted in ten key targets for 2022, which specifically included commitments to provide preventive treatment to 30 million people by 2022 (6 million to PLHIV, 4 million to household contacts <5 years of age, and 20 million to household contacts ≥ 5 years of age), and treat 40 million people with anti-tuberculosis drugs by 2022 (3.5 million children, 1.5 million people with drug-resistant tuberculosis including 115 thousand children).[61]

Progress toward the targets outlined at the UNHLM has been mixed. Between 2018 and 2021, 26.3 million people have been successfully treated (66% of the target of 40 million) and 12.5 million people have been provided with tuberculosis preventive treatment (42% of the 30 million target).[1] 10.3 million of the preventive treatments were delivered to PLHIV, surpassing the 6 million goal by over 70%.[1] However, 17,700 children with drug-resistant tuberculosis received treatment between 2018 and 2021—only 15% of the target.[1] The next UNHLM on Tuberculosis is scheduled

for September 2023, which will bring representatives from countries together again to recommit to working toward meeting the targets to address the tuberculosis burden.

2.4.2 Strategies and progress in India

Elimination of tuberculosis has been a key focus for the Indian government for over 60 years. The *National Tuberculosis Programme* (NTP) was established in 1962 and focused on the national implementation of BCG vaccination, as well as diagnosing and treating cases across the country. The NTP promoted treatment integrated within the existing health system, as opposed to in separate tuberculosis hospitals or sanatoria. In 1997, the *Revised National Tuberculosis Control Programme* (RNTCP) was launched, replacing the previous NTP.[62] The initial focus of the RNTCP was the national implementation of DOTS following WHO recommendations, and managed to cover the entire country by 2006.[62] In 2002, *Ni-kshay*, an electronic reporting system to monitor patient notifications and progress, was launched.

In 2017, the Prime Minister announced that India would work toward meeting the 2030 SDG of eliminating tuberculosis by 2025—five years early.[63] This announcement aligned with the release of the National Strategic Plan for Tuberculosis Elimination for 2017–2025, which outlined goals to further accelerate the decline in incidence and mortality, and the name of the RNTCP was changed to the *National Tuberculosis Elimination Programme* (NTEP) to reflect the desire to meet the elimination goals. In 2020, the National Strategic Plan was subsequently revised to the National Strategic Plan for Tuberculosis Elimination for 2020–2025, with a re-emphasised focus of *Prevent–Detect–Treat*, including goals to increase access to preventive treatment for tuberculosis infection and treatment for tuberculosis disease, amplify case detection, and scale-up private sector engagement.[64]

Despite the COVID-19 pandemic, progress toward elimination of tuberculosis in India has been made. The country introduced "bi-directional screening" for COVID-19 and tuberculosis, where all confirmed and suspected COVID-19 patients were tested for tuberculosis and vice versa.[53] Tuberculosis treatment was brought into the community, through integration with Ayushman Bharat Health and Wellness Centres, and more diagnostic laboratories became available at the subdistrict level.[53] Patients were provided with more treatment doses and "door-step delivery" to

reduce the likelihood of missing treatment due to the inability to attend clinics during lockdown periods.[53]

To encourage states and districts to meet the 2025 goal, the NTEP established the subnational certification of disease free status, which consists of monetary awards and non-monetary recognition for meeting levels of decline in tuberculosis incidence (Table 3). According to the India TB Report 2023, nine unique states and union territories were awarded at some level by 2021 (Table 3), with many more subnational districts receiving recognition. Of note, in 2020, the Union Territory of Lakshadweep was the first State or Union Territory to be declared *TB Free*, and Kerala and Puducherry received Bronze in 2020 and progressed to Silver in 2021.[53,65] Separately, in a statement given on World Tuberculosis Day 2023, the Prime Minister indicated that Karnataka was awarded Silver, and Jammu and Kashmir was awarded Bronze.[66,67]

Table 3 Progress towards TB Free Certification [53,65,67]

Award	Percent decline in incidence compared to 2015	States and Union Territories		
		Awarded in 2020	Awarded in 2021	Awarded in 2022
Bronze	≥20%	Kerala, Puducherry	Gujarat, Himachal Pradesh, Sikkim, Tripura, Ladakh	Jammu and Kashmir
Silver	≥40%	–	Kerala, Dadra & Nagar Haveli and Daman & Diu, Puducherry	Karnataka
Gold	≥60%	–	–	–
Tuberculosis Free District or State	≥80%	Lakshadweep	–	–

2.4.3 Drugs and diagnostics

Developing new treatments, repurposing existing treatments, detecting and treating more cases, and introducing novel vaccines (examined in detail in Section 2.5) are all potential methods to accelerate the decline in tuberculosis incidence and reduce the burden.

The primary tests recommended to infer tuberculosis infection are the tuberculin skin test (TST) and interferon-gamma release assays (IGRA).[23,32,68] TST and IGRA are unable to confirm viable *Mtb* infection, but instead indicate whether an immune response indicating prior exposure to *Mtb* is present. TST is beneficial as it can be used at the point-of-care, and involves injecting individuals with tuberculin purified protein derivative (PPD).[23,32] Depending on the level of skin reaction to PPD while considering additional risk factors, an individual is said to be positive for tuberculosis infection.[23,32] TST has a low probability of identifying tuberculosis infection in immunosuppressed individuals, such as PLHIV, and has a high probability of falsely indicating tuberculosis infection in people who have recently been vaccinated with BCG, as it is unable to accurately distinguish between current infection and previous vaccination.[23] In contrast, IGRA, a blood test which works by quantifying the amount of interferon gamma that is released by T-cells when exposed to *Mtb* antigens, is able to distinguish between current infection and previous BCG vaccination (a limitation of TST).[23,32,68] However, neither test is able to differentiate infection from active disease.[23,32,68]

WHO recommends that people at the highest risk of progressing to tuberculosis disease following infection should receive tuberculosis preventive therapy (TPT), which generally involves daily or weekly regimens of treatment containing isoniazid and/or rifampicin.[28] Groups eligible to receive TPT include PLHIV as well as household contacts of people with active tuberculosis once active disease is ruled out, and in some cases even if tuberculosis infection testing is not available.[28]

A combination of tests can be used to diagnose clinical disease. Screening for commonly associated symptoms, such as persistent cough lasting for more than three weeks, weight loss, and night sweats, in addition to observing changes, lesions, or cavities on a chest X-ray can indicate that an individual should be referred for further bacteriological diagnostics, such as sputum smear microscopy, culture-based methods, and molecular tests such as GeneXpert, the latter two of which

are also able to test for drug-resistance. Treatment for drug-sensitive tuberculosis is generally six months and has a high success rate when completed.[69] The first two months generally involve daily or almost daily treatment with the first-line drugs to treat tuberculosis: rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by four months of rifampicin and isoniazid only.[69] Treatment for drug-resistant tuberculosis is more difficult, and a longer treatment course is recommended (either 9–12 or 18–24 months) often including second-line drugs.[70]

Active case finding (ACF) strategies, which can involve activities such as mass population, door-to-door, or targeted screening to detect and treat more cases have been implemented by many countries to reduce time between disease and accessing treatment.[71–73] Targeted ACF is a key component of the India National Strategic Plan for Tuberculosis Elimination for 2020–2025.[64,74] With sufficient coverage and intensity, ACF strategies have been found to have a positive impact on the tuberculosis epidemic, but while this strategy may have a short term benefit, it must be maintained over a long time period.[71–73] As drug and diagnostic interventions alone have not been enough to eliminate tuberculosis, strategies that have a longer term effect, such as new tuberculosis vaccines with a long duration of protection as discussed in Section 2.5, are likely to be needed to supplement ongoing ACF efforts to reach elimination.

2.5 Tuberculosis vaccines

There is only one tuberculosis vaccine currently recommended by WHO to prevent tuberculosis: the Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated vaccine first administered to humans in 1921.[75] Neonatal BCG vaccination is recommended for all countries with a high-incidence of tuberculosis, and for populations within low-incidence countries that have a disproportionately high incidence. Global coverage of neonatal BCG vaccination in 2019 was 88%, however disruptions to routine services during the COVID-19 pandemic have resulted in the coverage falling to 84%.[1]

BCG is effective at preventing serious childhood miliary and meningeal tuberculosis which are associated with high mortality rates,[76,77] but has shown variable protection for adolescents and adults against any form of tuberculosis.[78] As a live vaccine, BCG is contraindicated in high-risk populations, such as people living with HIV. A recent meta-analysis investigated the lifetime

impact of neonatal BCG for the prevention of tuberculosis. Overall, the effectiveness of BCG for preventing all forms of tuberculosis was 18%.[78] However, when stratified by age, the study only identified significant protection from BCG for participants under five years of age, with an adjusted odds ratio for those who received neonatal BCG vaccination compared to those who did not of 0.63 (95% confidence interval = 0.49–0.81).[78] Duration of protection from BCG is likely to wane over time, with studies showing that protection could last for up to 10–20 years, and BCG efficacy has been observed to vary by geography and baseline exposure to mycobacteria.[75,79]

2.5.1 Classifying tuberculosis vaccines

Tuberculosis vaccines are characterised on four key characteristics: the vaccine efficacy, the host infection status required for the vaccine to be efficacious, the mechanism of effect, and the duration of protection. Vaccine efficacy defines the magnitude of protection induced by the vaccine. Vaccine efficacy typically is assumed to be either "take", where the vaccine offers full protection to a subset of individuals (equal to the vaccine efficacy) who were vaccinated, or "degree", where the vaccine offers partial protection to all individuals who received the vaccine.

The host infection status required for the vaccine to be efficacious defines the *Mtb* infection status required of the recipient for the vaccine to work (i.e., to execute its mechanism of effect). Host infection status has historically been divided into pre-infection (PRI), where the vaccine is efficacious in uninfected populations only, post-infection (PSI), meaning the vaccine is efficacious in populations with current or previous infection with *Mtb* (latent or recovered populations) only, or both pre- and post-infection (PPI) populations.

The vaccine mechanism of effect type determines how the vaccine will offer protection. A prevention of infection (POI) vaccine protects individuals from infection or reinfection with *Mtb*, whereas a prevention of disease (POD) vaccine functions by preventing individuals who may be uninfected or infected with *Mtb* from progressing to active disease. A prevention of infection and disease vaccine (POI&D) prevents both infection and disease. Finally, the duration of protection represents the length of time following vaccination that individuals are protected.

2.5.2 Vaccine pipeline

A new vaccine effective at preventing tuberculosis disease in adolescents and adults is likely to be useful.[80] WHO established Preferred Product Characteristics (PPCs) for New Tuberculosis Vaccines in 2018, which outlined desirable characteristics for a new adolescent/adult and, separately, a new infant vaccine or booster for BCG.[81] In order to meet the 2035 End TB goal of a 90% reduction in incidence compared to 2015, WHO suggests that the development of new tools for individuals with current tuberculosis infection, such as a new tuberculosis vaccine, are required.[82]

Vaccine researchers globally have been working toward developing a new tuberculosis vaccine. As of May 2023, there were fifteen prophylactic tuberculosis vaccine candidates throughout the pipeline.* [83,84] The vaccine candidates vary biologically from viral-vectored to live-attenuated, with BNT164 vaccines using messenger RNA technology, and span a range of host infection statuses (PRI, PSI, PPI) and mechanisms of effect (POI, POD, POI&D).[83,84]

A summary of the key findings from current and previous trials of the seven vaccines that are currently in or planning Phase III trials is provided in Table 4. VPM1002, GamTBvac, MTBvac, and BCG-revaccination are currently undergoing Phase III trials with results expected within the next four years, and Phase III trials are being planned for ID93/GLA-SEl and M72/AS01$_E$. Table 5 summarises the completed and ongoing trials for vaccine candidates in Phase I or Phase III trials. As of May 2023, only three candidates (BNT164, H56:IC31, and AEC/BC02) had ongoing trials with results anticipated within the next two years. Additional Phase I trials are being planned for BNT164, TB/FLU-01L, and TB/FLU-05E, but more candidates in early clinical trial phases are needed to increase the likelihood of obtaining a successful vaccine candidate.

** To note, the vaccine candidate RUTI is also commonly included in versions of the tuberculosis vaccine pipeline. However, as the primary evaluation of RUTI is as a therapeutic and not a preventative vaccine, I have excluded it from the prophylactic tuberculosis vaccine summary table.*

Table 4 Tuberculosis vaccine candidates with planned or ongoing Phase III trials

Candidate	Phase I / Phase IIa	Phase IIb	Phase III
ID93/GLA-SEl (QTP101)	NCT03806686: *Completed April 2021* Phase IIa safety, immunogenicity, and efficacy study in 107 BCG- vaccinated, *Mtb*-uninfected healthcare workers aged 19–64 in South Korea demonstrated it was safe and immunogenic. NCT03806699: *Completed May 2021* Phase I safety/immunogenicity study in 36 BCG-vaccinated, *Mtb*-uninfected adolescents aged 14–18 in South Korea. NCT03722472: *Completed June 2020* Phase I safety/immunogenicity study in 48 *Mtb*-uninfected adult volunteers in the United States.	*Planning* Dose exploration, efficacy, safety and immunogenicity evaluation in 288 BCG-vaccinated and HIV-negative participants aged 14–55 from Indonesia, Philippines, South Korea, Thailand and Vietnam (both *Mtb*-infected and *Mtb*-uninfected) (Outcome: POD / PPI)	*Planning* A Phase III study will follow the planned Phase IIb study to evaluate POD efficacy in 8,778 participants from the same population who are *Mtb*-infected. (Outcome: POD / PSI)
Immuvac (MIP)	–	–	CTRI/2019/01/017026: *Primary completion 2022* Efficacy, safety, and immunogenicity trial of MIP and VPM1002 in 12,721 HIV-negative household contacts of people with tuberculosis in India to prevent disease (POI as secondary outcome). (Outcome: POD / PPI) *Although the primary completion of the trial was indicated as 2022, as of May 2023, no publicly available results are available.*

VPM1002	NCT05539989: *Planning* Phase I/II safety/immunogenicity study of BCG-revaccination or VPM1002 in 480 people living with and without HIV aged 8–14 years with and without *Mtb* infection in South Africa.[85,86] NCT02391415: *Completed November 2017* Safety and non-inferiority (vs. BCG) trial of 416 HIV-exposed and -unexposed infants in South Africa.	–	NCT04351685: *Ongoing, results expected 2024* Efficacy/safety trial (vs. BCG) in 6,940 HIV-exposed and HIV-unexposed infants in Gabon, Kenya, South Africa, Tanzania, and Uganda (Outcome: POI / PRI) NCT03152903: *Ongoing, results expected 2024* Efficacy/safety trial in 2,000 adults aged 18–55 with successfully treated pulmonary tuberculosis to investigate prevention of recurrence. (Outcome: POR / PSI) CTRI/2019/01/017026: *Primary completion 2022* Efficacy, safety, and immunogenicity trial of MIP and VPM1002 in 12,721 HIV-negative household contacts of people with tuberculosis in India to prevent disease (POI as secondary outcome). (Outcome: POD / PPI) *As of May 2023, no publicly available results are available.*
MTBVAC	*Planning, anticipated to start in 2023* Phase Ib safety/immunogenicity study in PLHIV NCT03536117: *Completed March 2022* Phase IIa dose-defining study in 99 infants from South Africa to inform dose selection for Phase III trial.	–	NCT04975178: *Ongoing, expected completion in 2027* Efficacy, safety, and immunogenicity study in 6,960 *Mtb*-uninfected infants who were both HIV-unexposed and HIV-exposed in South Africa, Senegal, and Madagascar. (Outcome: POI / PRI)

	NCT02933281: Completed September 2021 Phase Ib/IIa study in 144 BCG-vaccinated adults aged 18–50 with and without *Mtb*-infection in South Africa.		
GamTBvac	NCT03878004: *Completed May 2020* Phase II safety/immunogenicity study in 180 adults aged 18–49 who were BCG-vaccinated. NCT03255278: *Completed December 2017* Phase I safety study in 60 *Mtb*-uninfected adults aged 18–49 who were BCG-vaccinated.	–	NCT04975737: *Ongoing, expected completion November 2025* Efficacy, safety, and immunogenicity study in 7,180 *Mtb*-uninfected, HIV-negative, BCG-vaccinated adults aged 18–45 in Russia to prevent disease. (Outcome: POD / PRI)
BCG-revaccination	NCT05539989: *Planning* Phase I/II safety/immunogenicity study of BCG-revaccination or VPM1002 in 480 people living with and without HIV aged 8–14 years with and without *Mtb* infection in South Africa.[85,86]	NCT04152161: *Ongoing, primary completion expected April 2023, study completion in 2026* Efficacy, safety, and immunogenicity study in 1,820 adolescents aged 10–18 years in South Africa who were previously BCG-vaccinated and are *Mtb*-uninfected. Confirmatory trial of the result from NCT02075203. (Outcome: POI / PRI) NCT02075203: *Completed, October 2017* Demonstrated an efficacy of 45.4% (95% CI: 6.4–68.1) against sustained IGRA conversion (Outcome: POI / PRI)	NCT04453293: *Ongoing, expected completion in May 2024* Trial of pre-travel BCG-vaccination for 2,000 healthcare workers and travellers to high tuberculosis burden countries from the United States of America aged 18–65 who are *Mtb*-uninfected and were not BCG-vaccinated. (Outcome: POI / PRI) NCT05330884: *Ongoing, expected completion in June 2025* Phase III trial comparing BCG-revaccination and tuberculosis preventive treatment in 9,200 BCG-vaccinated HIV-negative participants aged 6–18 who are household contacts of people with tuberculosis in India. (Outcome: POD / PPI)

M72/AS01E (Previously known as GSK692342)	NCT04556981: *Ongoing, expected completion August 2022* Assess safety and immunogenicity in ~400 PLHIV aged 16–35 who are on ART and virally suppressed	NCT01755598: *Completed, November 2018* POD efficacy 49.7% (90% CI: 12.1–71.2) in HIV- IGRA+ adults (Outcome: POD / PSI)	*Planning, expected to start in 2023* Phase III trial in ~26,000 people (*Mtb*-infected and uninfected) aged 15–44 years. (Primary outcome: POD/PSI, secondary POI/PRI & POD/PSI for PLHIV)

Abbreviations: ART = antiretroviral therapy, BCG = bacillus Calmette–Guérin, CI = confidence interval, IGRA = interferon gamma release assay, Mtb = Mycobacterium tuberculosis, PLHIV = people living with HIV, POD = prevention of disease, POI = prevention of infection, POID = prevention of infection and disease, PPI = pre- and post-infection, PRI = pre-infection, PSI = post-infection

Table 5 Tuberculosis vaccine candidates with only recently completed or ongoing Phase I and Phase II trials

Candidate	Phase I	Phase IIa/IIb
AEC/BC02	NCT04239313: *Completed June 2022* Phase Ib safety and immunogenicity study in 30 *Mtb*-uninfected adults aged 18–45 in China	NCT05284812: *Ongoing, expected completion June 2024* Phase IIa safety and immunogenicity study in 200 adults (aged 18 or older) in China (20 *Mtb*- uninfected participants and 180 *Mtb*-infected participants)
AdHu5Ag85A (aerosol)	NCT02337270: *Completed September 2021* Safety/immunogenicity study in 36 BCG-vaccinated participants aged 18–55.	–
BNT164 vaccines (BNT164a1 and BNT164b1)	NCT05537038: *Ongoing, expected completion June 2025* Phase Ia safety and immune response study in 96 *Mtb*-uninfected participants aged 18–55 without prior BCG-vaccination in Germany. NCT05547464: *Planned to start July 2023, expected completion October 2024* Phase Ib safety, dose-finding and immunogenicity study in 144 BCG-vaccinated, HIV-uninfected, *Mtb*-infected and *Mtb*-uninfected participants aged 18–55 in South Africa as well as other countries in Africa (not currently specified).	–
ChAdOx1.85A + MVA85A	NCT04121494: *Completed August 2020* Safety, immunogenicity, and dose-escalation study in 39 adults aged 18–55 (both BCG-vaccinated and not BCG-vaccinated) in Switzerland	NCT03681860: *Completed May 2021* Phase I/IIa study comparing the dose escalation, age de-escalation, and immunogenicity of a ChAdOx1 85A prime vaccine followed by MVA85A boost vaccine (vs BCG) in 72 adolescents ≥12 years in Uganda
DAR-901	–	NCT02712424: *Completed February 2020* Phase IIb study, did not prevent primary or sustained IGRA conversion in 625 HIV-uninfected, *Mtb* uninfected participants aged 13–15 in Tanzania[87] (Outcome: POI / PRI)

H56:IC31	NCT02503839: *Completed March 2020* Phase I/II study assessing safety and tolerability in 39 participants with active drug-susceptible tuberculosis aged 18–70 demonstrated that it was safe and immunogenic.	NCT03512249: *Ongoing, expected completion 2023* Phase IIb Study estimating prevention of disease recurrence in ~900 HIV negative individuals ages 18–60 in South Africa and Tanzania with a confirmed diagnosis of drug-susceptible tuberculosis[88] (Outcome: POD / PSI)
TB/FLU-01L & TB/FLU-04L	*Planning* Phase I safety/immunogenicity study of TB/FLU-01L. NCT03017378: *Completed January 2017* Safety/immunogenicity study of TB/FLU-01L in 36 BCG-vaccinated participants ages 18–50 in Kazakhstan. NCT02501421: *Completed February 2015* Safety/immunogenicity study of TB/FLU-04L in 44 BCG-vaccinated participants aged 18–50.	*Started but not completed (recruitment challenges)* Phase IIa study of TB/FLU-04L in *Mtb*-infected adult men.
TB/FLU-05E (aerosol)	*Planning* Safety/immunogenicity study in BCG-vaccinated participants aged 18–50.	–

Abbreviations: BCG = bacillus Calmette–Guérin, Mtb = Mycobacterium tuberculosis, POD = prevention of disease, POI = prevention of infection, PRI = pre-infection, PSI = post-infection

Two recently completed phase IIb trials in particular have demonstrated encouraging efficacy results, and provided hope to the tuberculosis vaccine community that there may be a new vaccine candidate or policy recommendation within the next decade. A summary of M72/AS01$_E$ and BCG-revaccination of adolescents is provided below.

M72/AS01$_E$

The M72/AS01$_E$ candidate vaccine is a subunit vaccine for which results from a completed Phase IIb trial were published at the end of 2019.[89] After three years of follow-up, the efficacy of M72/AS01$_E$ at preventing disease in adults positive by IGRA from South Africa, Zambia, and Kenya was estimated at 49.7% (2.1–74.2).[89] A subsequent Phase II trial (NCT04556981) is underway in South Africa enrolling approximately 400 participants aged 16–35 living with HIV who are on ART and virally suppressed to assess safety and immunogenicity only.[90]

Preparations for a larger Phase III trial to confirm the findings from the Phase IIb trial have been underway since 2019. The trial is expected to begin in 2024, and the earliest results could be available by 2028.[86] Primarily, this trial will be to confirm the prevention of disease endpoint in participants aged 15–44 who are *Mtb*-infected, however a small proportion of the 26,000 participants are likely to be enrolled without *Mtb*-infection in order to test the secondary outcome of prevention of infection and safety.

However, many questions remain. Results from the M72/AS01$_E$ Phase IIb trial have been available for over four years, but the follow-up trial has still not yet started. Currently M72/AS01$_E$ has only been evaluated in participants with a positive IGRA test, and it is unknown if those who are *Mtb*-uninfected will have protection against infection or disease as well. People living with HIV are an important population to make sure a vaccine works in, but no results are available from the Phase II trial in PLHIV even though they were expected in 2022.

BCG-revaccination

BCG-revaccination, administering a second dose of BCG later in life to those who were vaccinated neonatally, was previously implemented in many countries, however it is no longer recommended by WHO after evidence did not support the effectiveness of this practice.[91] Interest in BCG-

revaccination has recently been renewed following results from a trial for the vaccine candidate, H4:IC31 (NCT02075203).[92] BCG-revaccination was assessed as a third parallel arm alongside H4:IC31 and a placebo in a Phase IIb trial of 990 *Mtb*- and HIV-uninfected adolescents aged 12–17 in South Africa.[92] Although neither vaccine appeared efficacious at preventing IGRA conversion (the primary outcome), BCG-revaccination appeared efficacious at preventing sustained IGRA conversion (defined as three consecutive positive tests after day 84) with an efficacy of 45.4% (6.4–68.1).[92]

In order to confirm this finding, an additional Phase IIb study (NCT04152161) of BCG-revaccination against placebo is being conducted in 1,820 *Mtb*- and HIV-uninfected adolescents in South Africa aged 10–18.[86,93] The confirmatory study will evaluate sustained IGRA conversion as the primary outcome, with a higher number of participants, slightly extended age group, and more trial sites across South Africa than in the original Phase IIb trial.[86,93] Initial results are anticipated later 2023. The Tuberculosis Research Centre in India is also planning a Phase III trial of BCG-revaccination compared to tuberculosis preventive treatment to prevent disease (NCT05330884).[94] The study will evaluate safety and immunogenicity in 9,200 HIV-uninfected participants aged 6–18 who were previously BCG-vaccinated and are household contacts of tuberculosis patients in India, with primary results expected in 2025.

The future of BCG-revaccination policy depends on the results from the trials, and there are a number of additional unknowns. If a positive result is found from the confirmatory trial, this could result in a policy change for recommending BCG-revaccination, particularly for countries such as South Africa where the trial is being conducted. However, it remains unknown if there is any prevention of disease effect from a vaccine that has been tested to prevent sustained IGRA conversion. It is possible for positive results from the POI trial to support a larger POD trial, however a POD trial would be more expensive and lengthier to conduct. Whether countries aside from India would want to wait for the completion of a Phase III trial before introducing BCG-revaccination considering how cheaply BCG is available is another consideration.

2.5.3 Review of the literature on mathematical modelling of tuberculosis vaccines

Evaluating infectious disease dynamics using mathematical models has many advantages. Mathematical models can quickly be developed to explore the implications of new interventions before the financial and resource costs of implementing large scale clinical trials and studies are expended. Models are also able to assess situations and interventions which may not be ethical to evaluate in reality, and provide a quick method for comparing multiple scenarios on one population to assist in decision making.

Mathematical modelling is particularly important for tuberculosis vaccines, as the long latency period of *Mtb* infection and the lack of a confirmed immune correlate for protection[95] makes vaccine trials lengthy and expensive. Two systematic reviews evaluating the mathematical modelling literature on the epidemiological impact and cost-effectiveness of tuberculosis vaccines have been conducted since 2016. The first review, Harris et al., 2016,[96] evaluated 23 papers and reported that efficacious tuberculosis vaccines would be beneficial and cost-effective, and that an adolescent or adult vaccine would have a faster and greater impact on reducing the tuberculosis epidemic compared to a neonatal vaccine. In terms of research gaps, Harris et al. identified the need for an improved evaluation of the setting-specific impact of different vaccines, age targeting of vaccines, more sophisticated HIV inclusion, and assessment of multidrug-resistance in future models.

The second review that I contributed substantially to, Weerasuriya, Clark, et al., 2020,[97] provided an update on this literature with modelling papers published between January 2016 and June 2020. We identified eight published studies that evaluated the epidemiological impact of vaccines, with seven studies evaluating the impact of introducing a novel vaccine, and one study assessing the impact of discontinuing BCG vaccination in a medium burden setting.[84]

Vaccine targeting was expanded in the updated review by Weerasuriya, Clark, et al., 2020 to include some specific age and risk groups. Harris et al., 2019 evaluated targeting POD vaccines to older adults versus adolescents in China.[19] In the ageing population and reactivation driven epidemic in China, it was concluded that vaccinating older adults with a vaccine effective in those who were already infected would have the greatest epidemiological impact.[98] Awad et al., 2020

evaluated the impact on the tuberculosis epidemic of targeting a vaccine to individuals in India with diabetes, and found that this would be an effective method for decreasing the incidence of tuberculosis in India overall.[99]

In 2016, Shrestha et al. published a study evaluating targeting spatial hotspots of tuberculosis incidence and *Mtb* transmission for vaccination, and found that the epidemiological impact of vaccinating hotspots would be increased with increasing mixing between the hotspots and the community, and a larger tuberculosis incidence in the hotspot compared to the community.[100] Miners were targeted for vaccination in a 2017 paper from Shrestha et al., which compared targeting vaccines to the labour sending community or the miners themselves (all adult males).[101] Vaccinating miners averted 1.46 times more tuberculosis cases, likely due to the associated higher burden of tuberculosis in that demographic group.[101] While HIV is an established risk factor for tuberculosis, and tuberculosis is the leading cause of death for PLHIV, most studies excluded PLHIV from receiving the vaccine, or assumed that the vaccine would have the same efficacy in PLHIV as those without, even though infection with HIV can result in lower immunogenicity of a vaccine.

Below I describe my rerunning of the search using the same search terms as Harris et al., 2016. I identified seven new papers published between June 2020 and May 2023 (excluding papers published related to this thesis, which will be described in detail in the subsequent chapters).[102–108] Overall, depending on the assumed characteristics, vaccines were found to be impactful and cost-effective in the countries evaluated.

Five studies evaluated the introduction of a hypothetical vaccine,[102–104,106,108] and two papers evaluated an M72/AS01$_E$-like vaccine.[105,107] Three studies only investigated the health impact of introducing vaccines,[102,106,108] while four studies presented both health and economic impacts.[103–105,107] As with previous reviews, the new papers primarily modelled vaccine introduction in China, India, and South Africa,[103–108] although Fu et al. investigated the impact of a vaccine in thirty high drug-resistant tuberculosis burden countries.[102]

The vaccine was delivered to adolescents and adults in all new studies. Fu et al., Weerasuriya et al. (*BMC Med*), and Jayawardana et al. modelled vaccine delivery with an annual routine component as well as mass vaccination campaigns.[102,103,107] Harris and Quaife delivered the vaccine routinely to those aged 10, 15, or 18,[105] Wen et al. evaluated routine delivery to those aged ≥15,[106] and Weerasuriya et al. (*Vaccines*) compared the impact of vaccine delivery through mass campaign delivery to all individuals aged ≥10 or to ten-year age groups.[104] In Arinaminpathy et al., the vaccine was delivered to 50% of the unvaccinated population aged 16+ each year.[108]

All studies modelled scenarios with vaccine efficacy of at least 50% based on the Phase IIb M72/AS01$_E$ efficacy result, and multiple studies performed sensitivity analyses with higher and lower efficacy values. Four studies investigated a post-exposure prevention of disease vaccine,[102,104,105,107] and three studies investigated a pre- and post-exposure prevention of disease vaccine.[103,105,108] The vaccine effect in Wen et al., 2022 involved moving vaccinated individuals from the susceptible to recovered categories (a pre-infection, prevention of infection and disease vaccine).[106]

Studies identified in the most recent literature search have begun to address the questions and gaps that Weerasuriya, Clark, et al. highlighted in 2020. There were three studies which dynamically modelled drug-resistant tuberculosis, of which two studies evaluated the impact of targeting individuals with drug-resistant tuberculosis on the overall epidemic.[102–104] Harris and Quaife explicitly investigated differential vaccine efficacy in PLHIV compared to HIV-negative populations.[105]

Table 6 Model and vaccine characteristics for the seven additional studies

Author and year	Modelling aim	Methods	Setting	Host infection status	Effect type	Efficacy	Coverage	Proportion immunised	Duration of protection	Age targeting	Infection status targeting	Schedule	Time horizon	Outcomes
Fu, 2021[102]	Impact of a post-exposure TB vaccine on rifampicin-resistant TB	DE	30 countries accounting for 90% of the global drug-resistant tuberculosis incidence in 2018	PSI	POD	50%	Peak Coverage = 72-75%	36–37.5%	10 years	Routine: 15 yo Catch-up campaigns: All adults > 15 yo	Latent	Routine 15yo 2025–2035 2-y catch-up campaigns every 5 yo for adults	16 years (between 2020 and 2035)	M72/AS01$_E$-like vaccines could avert 620,000 cases (516,000–867,000) of RR-TB and avert 10% (9.7–11.0) of RR-TB cases between 2020 and 2035. ~2,500 adolescents and adults with infection would need to be vaccinated to avert 1 RR-TB case. If vaccination was combined with new tools, impact would increase to 831,000 (643,000–1,170,000) cases averted during 2020–2035.
Weerasuriya, 2021(*BMC Med*)[103]	Impact and cost-effectiveness of new TB vaccines on the burden of MDR-TB	DE	China and India	PPI	POD	50%	Routine: 80% Mass: 70%	Routine: 40% Mass: 35%	10 years	Routine: 9 yo Mass: ≥10 yo	All infection statuses, but no active disease or on-treatment	Routine: Annual Mass: 10-yearly	24 years (between 2027 and 2050)	RR/MDR-TB impacts in / by 2050: CHN: IRR = 73% (66–76), MRR = 67% (59–72), Cases averted = 2.1 mil (1.1–2.7); IND: IRR = 72% (65–77), MRR = 69% (60–75), Cases averted = 2.0 (1.4–4.1) All TB impacts in / by 2050: CHN: IRR = 56% (53–59), MRR = 53% (48–58), Cases averted = 10.5 (8.9–12.0); IND: IRR = 67% (59–71), MRR = 66% (59–71), Cases averted = 57.1 (45.9–70.0) PPI vaccines priced at US$10 likely to be CE in IND and CHN at the 1xGDP and upper HCOC thresholds. In IND, P&PI vaccines also likely to be CE at the lower HCOC threshold.
Weerasuriya, 2021 (*Vaccines*) [104]	Affordability of adult TB vaccines	DE	China and India	PSI	POD	50%	70%	35%	10 years	All-ages: ≥10 yo	All infection statuses, but no active disease or on-treatment	Mass campaigns in 2027, 2037 and 2047	24 years (between 2027 and 2050)	Averted DALYs (total): IND = 52.67M (42.79–65.18); CHN = 3.79M (2.96–4.89) Averted DALYs (per vaccine):

														IND = 0.019 (0.015–0.023); CHN = 0.001 (0.001–0.002) Mass vaccination of all adults/ adolescents, deemed CE, will likely impose a substantial budgetary burden.
Harris and Quaife, 2022[105]	Cost-effectiveness of routine adolescent vaccination with an M72/AS01$_E$-like vaccine	DE	India and South Africa	PSI or PPI	POD	50%	80% for scenarios targeting age 10 or 15 50% for scenarios targeting age 18	40% for scenarios targeting age 10 or 15 25% for scenarios targeting age 18	5, 10, or 15 years	Separate scenarios targeting age 10, 15, or 18	All infection statuses, but no active disease or on-treatment	Routine vaccination with immediate scale-up in 2025	26 years (between 2025 and 2050)	For South Africa, all vaccines and scenarios were highly cost-effective compared to the country-specific cost-effectiveness threshold. In India, a vaccine which prevented disease irrespective of recipients' *Mtb* infection status was highly cost-effective, however a vaccine preventing disease only if a recipient was already infected was unlikely to be cost-effective.
Wen, 2022[106]	Effect of different interventions for latent TB infections in China, including vaccination	DE	China	PRI (vaccine effect for those in the susceptible category)	POID (the vaccine moves individuals from the susceptible to recovered boxes)	100% or lower (lowest efficacy of 50%)	Initial size of eligible pop aged 15+: 572m Number of annual doses: 7.2m, 9.6m, 12m, 14.4m Coverage of eligible pop in year one: 1.3%, 1.7%, 2.1%, 2.5%	Coverage of eligible pop in year one: 1.3%, 1.7%, 2.1%, 2.5%	Lifelong (unless they relapse from the recovered category)	Ages 15+	Uninfected (Vaccination applied to the susceptible compartment)	Introduced in 2021	15 years (between 2021 and 2035)	A new TB vaccine introduced in China to adults could help to reach the 2035 End TB goals if at least 10.5 million vaccines were delivered annually to each targeted age group.
Jayawardana, 2022[107]	Cost-effectiveness and budget impact analysis of novel adult TB vaccination	DE	South Africa	PSI	POD	50% Sensitivity analyses conducted for 30%, 70%, and varying efficacy for PLHIV	Age 18–50: 60% (mass) 40% (routine) PLHIV scenarios: 60% (mass), 70% (routine) Sensitivity analyses with 40% or 80% for mass	Age 18–50: 30% for mass campaigns, 20% for routine PLHIV scenarios: 30% (mass) 35% (routine)	5 years Sensitivity analyses conducted for 3 years, and 10 years.	Ages 18–50	All infection statuses, but no active disease or on-treatment	One mass campaign in 2025 for 18–50yo, then routine 18yo Mass campaigns in 2025 and 2035 for 18–50yo Scenarios with PLHIV	26 years (between 2025 and 2050)	An M72/AS01$_E$ vaccine delivered as two mass campaigns to 18–50 yo in South Africa would be the most CE strategy.

Arinamin-pathy, 2023[108]	The potential impact of vaccination on TB burden in India	DE	India	PPI	POD POI	50%	50% of unvaccinated per year	Year 1: 25%	10 years	All adults ages ≥16	All infection statuses, but no active disease or on-treatment	Mass campaign vaccinating 50% per year unvaccinated	8 years (between 2023 and 2030)	A POD vaccine would have a greater impact than a POI vaccine by 2030. A POD vaccine could avert 29% (24–34) of the cumulative tuberculosis incidence between 2023–2030, compared to 12% (4–28) from a POI vaccine. 40% of the burden averted could be averted by only targeting a vulnerable population (accounting for 16% of the population) at a high risk of progressing to tuberculosis.

Abbreviations: CE = Cost-effective, CHN = China, DALY = disability-adjusted life years, HCOC = healthcare opportunity cost, IND = India, n/s = not specified, PLHIV = People living with HIV, POD = prevention of disease, POI = prevention of infection, POID = prevention of infection and disease, pop = population, PPI = pre- and post-infection, PRI = pre-infection, PSI = post-infection, yo = year olds

Eight recommendations for areas that future tuberculosis vaccine models can evaluate that were outlined in and remain from the previous systematic reviews and the seven recent publications are listed below:

1. *Realistic vaccine delivery*

   For models to provide useful results for policy makers, realistic vaccine delivery strategies need to be evaluated, with evidence supporting how they would likely be implemented. "Immediate scale up and 100% coverage" of a vaccine is unrealistic, unattainable, and may overestimate the health and economic impact of a vaccine.

2. *Modelling the impact of specific vaccine candidates or preferred product characteristics*

   Two studies investigated M72/AS01$_E$-like vaccines, but no studies have looked at estimating the impact of other candidates in late-stage and Phase III trials such as BCG-revaccination, VPM1002, or MTBvac, or evaluated vaccine characteristics aligned specifically with the recommendations from WHO Preferred Product Characteristics for New Tuberculosis Vaccines.

3. *Incorporating new knowledge of tuberculosis natural history*

   Novel aspects of natural history, such as *Mtb* infection self-clearance and subclinical tuberculosis disease have not yet been incorporated in vaccine models, even though, as outlined in Section 2.2, these aspects could potentially have an important impact on vaccines depending on the host infection status required for the vaccine to be efficacious and whether vaccines are anticipated to work in people with subclinical disease. Similarly, the current classifications of host infection status at the time of vaccination required for the vaccine to be efficacious may not be inclusive to recognition of new aspects.

4. *Vaccine delivery settings*

   The geographic setting is an important factor to consider, as tuberculosis burden varies globally, as well as within countries. Predominantly, vaccine models have commonly been implemented in China, India, and South Africa; regions which will play a large role in tuberculosis elimination. However, modelling of vaccines is also needed in other countries

that will be crucial to end tuberculosis, such as those in sub-Saharan Africa, South-East Asia, and the Western Pacific. More subnational models within key countries such as India are also needed, as the strategies and vaccine impact may differ depending on how the burden of disease and epidemiology varies geographically.

5. *Non-random (heterogenous) mixing patterns between populations*

Individuals in a population do not mix randomly by socioeconomic status, by age or geographic location, and incorporating more realistic mixing patterns in addition to realistic delivery strategies can allow for improved estimation.

6. *Age-targeting of vaccines*

Depending on the underlying driver of the epidemic (recent transmission vs. reactivation) and the relationship with age of the population, the most effective age to target may differ, and therefore it is important to consider age targeting of vaccines, and the programmatic implications of vaccinating specific high risk, high burden age groups.

7. *Sophisticated HIV inclusion and targeting*

For countries where HIV-tuberculosis co-infection is a large driver of the tuberculosis epidemic, modelling a sophisticated representation of HIV can help to assess the varying potential benefits if a vaccine happens to be contraindicated or differentially effective in people living with HIV.

8. *Risk group targeting*

Awad et al. investigated the impact of targeting individuals with diabetes mellitus, and Arinaminpathy et al. incorporated a vulnerable population representing those with undernutrition who may be targeted for vaccination, but other risk groups such as those experiencing low-socioeconomic status, alcohol-use disorders, and tobacco smoking need to be investigated as potential targets for vaccine delivery.

2.6 Summary

In Chapter 2, I attempted to provide a succinct but complete overview of tuberculosis to support my thesis research. I highlighted recent advances in natural history, such as self-clearance and subclinical tuberculosis, that may have implications for vaccine modelling. The highest burden of tuberculosis globally is in LMICs, and specifically in India, where the national prevalence survey has indicated that the burden varies widely across the country. There are strong global and country-level commitments to work toward eliminating tuberculosis, but progress needs to be accelerated to meet the deadline. With numerous vaccine candidates currently in trials, I am hopeful that following positive results from current and upcoming Phase III trials, there will be a new tuberculosis vaccine available to introduce within the next decade.

Collating the information from Chapter 2 I identified the following gaps to address in the remainder of my thesis:

- There are newly recognised aspects of tuberculosis, such as self-clearance and subclinical tuberculosis, which have not yet been incorporated into vaccine modelling **(Chapters 3–5)**
- No tuberculosis vaccine models have evaluated realistic vaccine delivery, where vaccines are not assumed to be introduced and scaled-up instantly **(Chapters 3–5)**
- WHO established preferred product characteristics for new tuberculosis vaccines, but the health impact possible with vaccines aligned with the characteristics has not yet been evaluated in LMICs **(Chapter 3)**
- No subnational modelling in India has compared the health and economic impact of specific vaccine candidates in regions with differing population characteristics and burdens of disease **(Chapter 5)**

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CHAPTER 3 Multi-country modelling: The impact of novel tuberculosis vaccines in low- and middle-income countries

Chapter 3 contains Research Paper 1 in section 3.2 which addresses thesis **Aim 1** and thesis **Objective 2**. The supplementary material for Research Paper 1 is provided in section 3.3 and addresses thesis **Objective 1**.

3.1 Introduction

Previous studies have shown that tuberculosis vaccines are likely to have a positive health impact and will be key to reaching elimination goals. In 2018, WHO established Preferred Product Characteristics (PPCs) for New Tuberculosis Vaccines to provide preferred product specifications for vaccine manufacturers to aim for during vaccine development of a tuberculosis vaccine candidate.[1] The PPCs define an adolescent/adult vaccine which would work by preventing disease in all individuals, and separately, an infant vaccine to be used either independently or as a booster with neonatal BCG.[1]

There have been no studies which evaluated the potential impact of vaccines with characteristics based off of WHO PPCs in LMICs, used model structures which incorporated recent advances in the knowledge of tuberculosis natural history, or varied vaccine introduction characteristics by country. Having this information is important to provide evidence for global investors and to support vaccine manufacturing and development.

I address these questions with Research Paper 1 which was published in *The Lancet Global Health* in 2023 and is reproduced in section 3.2 with no modifications or adaptations from the published version.

3.2 Research paper 1 – The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1804462	**Title**	Ms
First Name(s)	Rebecca Anne		
Surname/Family Name	Clark		
Thesis Title	Mathematical modelling of the impact of adolescent/adult tuberculosis vaccines to inform global, national, and subnational policy and delivery		
Primary Supervisor	Richard 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?	The Lancet Global Health		
When was the work published?	14 March 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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 developed the updated natural history model structure to incorporate novel advances in natural history, and the updated vaccine structure to allow for realistic vaccination delivery. I set up the calibration and vaccine impact estimation procedure. I contributed to collecting relevant epidemiologic data from the literature and establishing the three alternative delivery strategies. I calibrated the LMICs and generated the impact data from the calibrated models. I prepared the results and wrote the first full draft of the paper. I revised the paper based on comments from co-authors. I submitted the manuscript for publication, wrote the response to reviewers, and incorporated editor revisions.

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study

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Summary

Background Tuberculosis is a leading infectious cause of death worldwide. Novel vaccines will be required to reach global targets and reverse setbacks resulting from the COVID-19 pandemic. We estimated the impact of novel tuberculosis vaccines in low-income and middle-income countries (LMICs) in several delivery scenarios.

Methods We calibrated a tuberculosis model to 105 LMICs (accounting for 93% of global incidence). Vaccine scenarios were implemented as the base-case (routine vaccination of those aged 9 years and one-off vaccination for those aged 10 years and older, with country-specific introduction between 2028 and 2047, and 5-year scale-up to target coverage); accelerated scale-up similar to the base-case, but with all countries introducing vaccines in 2025, with instant scale-up; and routine-only (similar to the base-case, but including routine vaccination only). Vaccines were assumed to protect against disease for 10 years, with 50% efficacy.

Findings The base-case scenario would prevent 44·0 million (95% uncertainty range 37·2–51·6) tuberculosis cases and 5·0 million (4·6–5·4) tuberculosis deaths before 2050, compared with equivalent estimates of cases and deaths that would be predicted to occur before 2050 with no new vaccine introduction (the baseline scenario). The accelerated scale-up scenario would prevent 65·5 million (55·6–76·0) cases and 7·9 million (7·3–8·5) deaths before 2050, relative to baseline. The routine-only scenario would prevent 8·8 million (95% uncertainty range 7·6–10·1) cases and 1·1 million (0·9–1·2) deaths before 2050, relative to baseline.

Interpretation Our results suggest novel tuberculosis vaccines could have substantial impact, which will vary depending on delivery strategy. Including a one-off vaccination campaign will be crucial for rapid impact. Accelerated introduction—at a pace similar to that seen for COVID-19 vaccines—would increase the number of lives saved before 2050 by around 60%. Investment is required to support vaccine development, manufacturing, prompt introduction, and scale-up.

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For the French translation of the abstract see **Online** for appendix 1

For the Spanish translation of the abstract see **Online** for appendix 2

For the Italian translation of the abstract see **Online** for appendix 3

For the Dutch translation of the abstract see **Online** for appendix 4

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Introduction

Tuberculosis is one of the leading causes of infectious disease death worldwide, second only to COVID-19.[1] The negative impact of COVID-19 on tuberculosis-related health services, such as delays in diagnosis, treatment, and neonatal vaccination has paused and reversed slowly declining trends in mortality.[1,2]

WHO established the End TB Strategy in 2015, with the goal of reducing disease incidence, deaths, and costs worldwide from tuberculosis.[3] Targets for 2025 include reductions in the absolute number of deaths from tuberculosis by 75% and in incidence by 50%, and targets for 2035 include reductions in the absolute number of deaths by 95% and in incidence by 90%, both compared with 2015 rates.[3] However, most countries are not on track to achieve these targets.[1,4]

The 2035 End TB targets explicitly assumed the introduction of new tools, including a novel tuberculosis vaccine, by 2025.[3] WHO has proposed preferred product characteristics for new tuberculosis vaccines,[5] which were developed through a highly consultative process, including regulators and policy makers from high-burden countries. Although progress has been made, the 2025 target for novel tuberculosis vaccine introduction is unlikely to be achieved.

A phase 2b trial of the M72/AS01$_E$ candidate vaccine showed an efficacy of 49·7% (95% CI 2·1–74·2) for preventing disease in adults positive by interferon-gamma

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Research in context

Evidence before this study

Two systematic reviews in the previous 7 years have highlighted the benefits that novel tuberculosis vaccines could have on reducing the tuberculosis burden globally, and that vaccines are likely to be crucial to achieve elimination. These studies indicate that the impact of novel tuberculosis vaccines will depend on the characteristics of the setting, the vaccine, and the delivery strategy. We searched PubMed on Nov 2, 2022, with no date or language restrictions, to find all studies modelling the impact of vaccines aligned with the WHO preferred product characteristics for new tuberculosis vaccines, using the search terms ((tuberculosis) OR (Mtb)) AND ((vaccine) OR (immunisation)) AND ((WHO) OR (World Health Organization)) AND (preferred product characteristics). We found no studies estimating the potential health impacts of introducing a vaccine with characteristics aligned with the WHO preferred product characteristics in low-income and middle-income countries, and existing literature remains limited in terms of how realistic the modelled vaccine introduction and scale-up scenarios were.

Added value of this study

We estimated the potential impact on tuberculosis cases and deaths of vaccines for infants and for adolescents and adults meeting WHO preferred product characteristics in 105 low-income and middle-income countries that accounted for 93% of the global tuberculosis incidence and mortality in 2019. We evaluated more complex and realistic base-case vaccine delivery scenarios than previously modelled by including country-specific introduction years between 2028 and 2047, and scaling up to target vaccine coverage across 5 years upon initial country introduction. The vaccine for infants was assumed to be delivered routinely to neonates, and the vaccine for adolescents and adults was assumed to be introduced routinely to those aged 9 years and as a one-off campaign for those aged 10 years and older. We compared the base-case scenarios to accelerated introduction and scale-up in all countries in 2025, at a speed similar to the pace of COVID-19 vaccine introduction, to estimate the implications of not meeting the End TB strategy target to develop and license a new tuberculosis vaccine by 2025, and scale up quickly. We also compared the base-case scenario for the adolescent and adult vaccine with a less ambitious routine-only introduction (no one-off vaccination for those aged 10 years and older). We grouped countries by WHO region, income group, and tuberculosis burden to identify where the largest impacts of a novel vaccine could be realised and identified the key implications of these findings.

We found novel tuberculosis vaccines meeting the WHO preferred product characteristics could have a substantial impact, which would vary depending on delivery and vaccine characteristics. Inclusion of a vaccination campaign would be crucial for rapid impact. Most lives could be saved by novel vaccine introduction in the WHO South-East Asian region and African region, and higher rate reductions could be seen in low-income countries. Failing to meet the End TB target to develop and license a vaccine for adolescents and adults by 2025, and to quickly scale up roll-out in all countries, could lead to around 3 million more deaths in low-income and middle-income countries, whereas introduction at a pace similar to that achieved with COVID-19 vaccines could increase the number of lives saved before 2050 by around 60%.

Implications of all the available evidence

Our new evidence supports investment decisions in vaccine development, manufacturing, and delivery. Millions of additional deaths could be averted with rapid development and licensing of novel tuberculosis vaccines, and preparations should be made for their prompt introduction, including in campaigns, ideally at the pace that COVID-19 vaccines have been introduced.

release assay after 3 years of follow-up,[6] and a trial of BCG-revaccination appeared efficacious at preventing sustained infection in a cohort of adolescents negative for interferon-gamma release assay, with an efficacy of 45·4% (6·4–68·1).[7] Unfortunately, the phase 3 trial of M72/AS01$_E$ has not started, and therefore the realistic licensure date, should a positive result be found, might not be for many years. Policy changes on BCG-revaccination in adolescents could happen sooner in settings such as South Africa, but BCG-revaccination has not been tested in individuals positive for tuberculosis infection—a population shown previously to be epidemiologically important for rapid population-level impact.[8]

This situation raises crucial questions for global and country decision makers, including the following: how many lives will be lost if we fail to roll out a novel tuberculosis vaccine by 2025? What is the potential impact if, instead, vaccines are introduced and rolled out following more traditional timelines? And how would these impacts vary by WHO region, income level, and tuberculosis burden?

We aimed to estimate the potential impact of vaccines meeting the WHO specifications[5] in low-income and middle-income countries (LMICs) across a range of introduction and scale-up scenarios.

Methods

Model development and calibration

To estimate the impact of novel tuberculosis vaccines, we developed a compartmental age-stratified dynamic *Mycobacterium tuberculosis* transmission model by adapting features of previous models.[8,9] We represented tuberculosis natural history with eight compartments, allowing for *M tuberculosis* infection along a spectrum from uninfected to active clinical disease.[10,11] A detailed description is provided in appendix 5 (pp 3–14).

See Online for appendix 5

We incorporated an access-to-care structure to represent systematic differences in tuberculosis burden, social protection, and health-care access by socioeconomic status.[12] The access-to-care structure contains a high-access-to-care category, representing the top three income quintiles (ie, 60% of the population per country), and a low-access-to-care category, representing the bottom two income quintiles (ie, 40% of the population per country). We assumed no transition between strata, and random mixing (appendix 5 pp 9, 10).

To account for the influences of HIV and antiretroviral therapy (ART) on the risk of infection and progression to disease,[13,14] we classified countries as having a higher tuberculosis burden due to HIV if more than 15% of tuberculosis cases were among people living with HIV and HIV prevalence was greater than 1% (appendix 5 pp 21, 22). We modelled an HIV structure including categories in which people were classified as HIV-uninfected, HIV-infected and not on ART, and HIV-infected and on ART. The tuberculosis mortality rate and progression risk were increased in both HIV-infected compartments, with greater increases in those not on ART.

For each country, we calibrated a model to epidemiological data using history matching with emulation through the hmer R package,[15] generating at least 1000 fitted parameter sets per country. Each country model was independently fitted to nine calibration targets in 2019: the country-specific tuberculosis incidence rate (for all ages, those aged 0–14 years, and those 15 years and older, separately), country-specific tuberculosis case notification rate (for all ages, those aged 0–14 years, and those 15 years and older, separately), country-specific tuberculosis mortality rate (for all ages), the global fraction of subclinical tuberculosis among active tuberculosis, and the global risk ratio of active tuberculosis for high-access-to-care relative to low-access-to-care. Models for countries classified as having a high tuberculosis burden due to HIV were fit to four additional country-specific all-age targets in 2019: HIV prevalence, ART coverage, tuberculosis incidence rate in people living with HIV, and tuberculosis mortality rate in people living with HIV. We used the distribution of results produced by these parameter sets to quantify estimation uncertainty.[16]

Policy scenarios

For each country, a primary baseline scenario with no novel vaccine introduction was simulated, assuming non-vaccine tuberculosis interventions continue at current trends (ie, the status quo, no-new-vaccine baseline scenario). Because reported country-level data include the high coverage of neonatal BCG vaccination and we anticipate no discontinuation across the model time horizon,[17] neonatal BCG vaccination was not explicitly modelled.

Aligning with the product characteristics described in the WHO preferred product characteristics, we evaluated a novel tuberculosis vaccine for adolescents and adults, and a novel vaccine for neonates and infants.[5] Vaccines were assumed to prevent disease by reducing progression to subclinical disease and confer a mean protection of 10 years. We assumed the vaccine for adolescents and adults would be efficacious in individuals in any tuberculosis infection state at the time of vaccination (ie, pre-infection and post-infection), with 50% vaccine efficacy. We assumed the vaccine for infants would be efficacious in individuals who were not infected with *M tuberculosis* at the time of vaccination (ie, pre-infection), with 80% efficacy (appendix 5 p 26).

Roll-out of the vaccine for infants was simulated in two scenarios, and, separately, roll-out of the vaccine for adolescents and adults was simulated in three scenarios, with assumptions confirmed through consultation with a range of global tuberculosis vaccine experts involved in research, government, academia, and policy making. The base-case and accelerated scale-up scenarios for the infant vaccine involved routine neonatal vaccination with 85% coverage. The base-case and accelerated scale-up scenarios for the adolescent and adult vaccine involved routine vaccination of those aged 9 years (80% coverage), with a one-time vaccination campaign for all individuals aged 10 years and older (70% coverage). The routine-only scenario (ie, the vaccine for adolescents and adults only) assumed routine vaccination of those aged 9 years (80% coverage). We assumed no differential vaccination by HIV infection or access-to-care status.

We evaluated vaccine delivery scenarios by varying the introduction year and scale-up trends between scenarios and countries (table 1; appendix 5 pp 26–30). In the base-case and routine-only scenarios, based on data from historical vaccine introduction, vaccines were assumed to be introduced in country-specific years and linearly scaled up to coverage targets across 5 years. To estimate introduction years, countries were divided into those that would be procuring with support from Gavi, the Vaccine Alliance and those that would be self-procuring. Factors influencing the timing of vaccine introduction were identified through expert consultation, and included disease burden, previous early adopter status, timelines for Gavi processes, capacity for immunisation, country-specific registration timelines, and commercial prioritisation. A scoring system was applied to each factor, and countries were assigned an aggregate score ranking their introduction position. The number of countries introducing the vaccine per year was informed by pneumococcal vaccine scale-up.[18] In the accelerated scale-up scenarios, to more resemble the pace of COVID-19 vaccine introduction, all countries introduced vaccines in 2025 with coverage targets reached instantly.

Health impact indicators

We calculated the cumulative number of tuberculosis cases, treatments, and deaths averted between vaccine

	Scenarios for the infant vaccine		Scenarios for the adolescent and adult vaccine		
	Base-case	Accelerated scale-up	Base-case	Accelerated scale-up	Routine-only
Ages targeted	Routine for infants	Routine for infants	Routine for those aged 9 years and a one-time vaccination campaign scaled up across 5 years for those aged 10 years or older	Routine for those aged 9 years and a one-time vaccination campaign in 2025 for those aged 10 years or older	Routine for those aged 9 years
Introduction year	Country-specific	2025	Country-specific	2025	Country-specific
Vaccine roll-out trend	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage
Coverage target (low, medium, and high)	75%, 85%, and 95%	75%, 85%, and 95%	70%, 80%, and 90% for those aged 9 years; 50%, 70%, and 90% for those aged 10 years and older	70%, 80%, and 90% for those aged 9 years; 50%, 70%, and 90% for those aged 10 years and older	70%, 80%, and 90% for those aged 9 years; 50%, 70%, and 90% for those aged 10 years and older

Table 1: **Characteristics of modelled vaccine delivery scenarios**

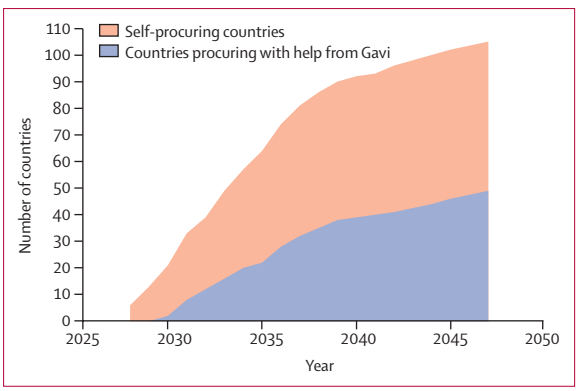

Figure 1: **Assumed cumulative number of countries introducing the novel vaccine by year for the base-case and routine-only scenarios**
Base-case assumes introduction of routine vaccination for those aged 9 years and one-off vaccination for those aged 10 years and older. Routine-only assumes introduction of routine vaccination among those aged 9 years only. The earliest vaccine introduction occurs in 2028 and the latest in 2047. See appendix 5 (pp 26–33) for full details.

introduction and 2050, compared with the number estimated by the baseline scenario between the corresponding years, and we calculated tuberculosis incidence and mortality rate reductions in 2050 for each vaccine scenario compared with the rates estimated by the baseline in 2050. Incidence rates in 2035 for each vaccine scenario were estimated to investigate the feasibility of meeting the 2035 End TB target. Results are presented as the median and 95% uncertainty range for all countries modelled, WHO region, World Bank income group,[19] and WHO tuberculosis burden level.[1]

Additional scenario analyses

We conducted scenario analyses to evaluate alternative assumptions regarding vaccine characteristics, delivery, and the baseline scenario. We simulated vaccine scenarios with lifelong protection for both vaccines, as well as scenarios with efficacy of the vaccine for adolescents and adults increased to 75%. For each scenario, low-coverage and high-coverage targets were compared with the medium-coverage targets used for the main analyses. We explored an alternative baseline: the 2025 End TB no-new-vaccine baseline, which assumed strengthening of non-vaccine tuberculosis interventions to meet the 2025 End TB incidence target,[3] providing an alternative estimate of impact assuming more effective deployment of existing measures (appendix 5 p 25).

Role of the funding source

The funder was involved in the development of the research question, study design, and provided comments on the manuscript draft, but had no role in the collection, analysis, and interpretation of the data, or writing of the report.

Results

Epidemiological and demographic data were available to model 115 of 135 LMICs. We successfully calibrated 105 of 115 countries, accounting for 93% of global tuberculosis cases and deaths in 2019. Calibrated model incidence and mortality rate trends for WHO regions, WHO tuberculosis burden levels, and World Bank income groups are given in appendix 5 (p 41). Country-specific vaccine introduction years (used in base-case and routine-only scenarios) ranged between 2028 and 2047 (appendix 5 pp 35–38). Figure 1 shows the cumulative number of countries introducing the vaccine per year, with 50% of countries introducing the vaccine by 2034.

Our findings suggest that a vaccine for adolescents and adults with 50% efficacy and 10-years of protection in the base-case scenario could avert approximately 44·0 million (95% uncertainty range 37·2–51·6) cases for all countries compared with the status quo no-new-vaccine baseline, including 1·4 million (1·2–1·6) cases of drug-resistant tuberculosis (table 2; appendix p 69). High numbers of cases overall could be averted in the WHO African region and South-East Asian region, which contribute the highest number to the global total, and 34·3 million (28·6–40·3) cases could be averted in lower-middle-income countries (table 2, figure 2). By 2050, 5·0 million (95% uncertainty range 4·6–5·4) deaths could be averted across all countries, including 2·2 million in the South-East Asian region, 2·1 million in the African region, and 4·1 million in lower-middle-income countries (table 2, figure 2). By

2050, 24·9 million (95% uncertainty range 21·9–27·3) treatments could be averted, with 11·7 million (10·1–13·4) averted treatments in the South-East Asian region alone. In the 27 countries categorised by WHO as having a high tuberculosis burden of the 105 countries modelled, 39·8 million (95% uncertainty range 33·7–46·7) cases, 22·6 million (19·9–24·8) treatments, and 4·5 million (4·2–4·9) deaths could be averted by 2050; around ten times higher than those averted in all other countries combined (table 2, figure 2).

Introducing the vaccine for adolescents and adults in the base-case scenario was predicted to reduce tuberculosis incidence by 25·4% (23·9–27·7) and deaths by 27·1% (25·6–30·1) in 2050, compared with the status quo no-new-vaccine baseline scenario (table 2). The incidence reduction ranged from 15·9% in the WHO region of the Americas to 27·0% in the African region (table 2, figure 2). Deaths from tuberculosis were estimated to reduce by 17·7% in the region of the Americas to 28·1% in the Eastern Mediterranean region by introducing the adolescent and adult vaccine in the base-case scenario. By income group, the relative impact of the adolescent and adult vaccine was higher in low-income and lower-middle-income countries than in upper-middle-income countries (table 2, figure 2).

In both the base-case and accelerated scale-up scenarios, a lower impact of the infant vaccine (compared with the vaccine for adolescents and adults) was estimated before 2050, including 0·4–0·6 times

	All modelled countries	WHO region						WHO tuberculosis burden level		World Bank income group		
		African region	Region of the Americas	Eastern Mediterranean region	European region	South-East Asian region	Western Pacific region	High-burden countries	All other countries	Low-income countries	Lower-middle-income countries	Upper-middle-income countries
Adolescent and adult vaccine												
Base-case												
Averted cases before 2050, millions	44·0 (37·2–51·6)	13·9 (11·7–16·7)	0·5 (0·5–0·6)	3·9 (3·1–4·8)	0·3 (0·3–0·4)	19·5 (15·9–23·1)	5·9 (5·0–6·9)	39·8 (33·7–46·7)	4·1 (3·4–4·9)	5·0 (4·1–6·0)	34·3 (28·6–40·3)	4·7 (4·1–5·4)
Averted deaths before 2050, millions	5·0 (4·6–5·4)	2·1 (1·9–2·3)	0·04 (0·03–0·04)	0·3 (0·2–0·4)	0·03 (0·03–0·03)	2·2 (2·0–2·6)	0·3 (0·2–0·3)	4·5 (4·2–4·9)	0·5 (0·4–0·5)	0·6 (0·5–0·6)	4·1 (3·7–4·4)	0·4 (0·3–0·5)
Averted treatment before 2050, millions	24·9 (21·9–27·3)	6·3 (5·7–6·8)	0·4 (0·3–0·4)	2·4 (2·0–2·8)	0·2 (0·2–0·3)	11·7 (10·1–13·4)	3·8 (3·3–4·2)	22·6 (19·9–24·8)	2·3 (2·0–2·6)	2·9 (2·5–3·2)	19·0 (16·6–21·2)	2·9 (2·7–3·2)
Incidence rate reduction in 2050, %	25·4% (23·9–27·7)	27·0% (25·7–31·3)	15·9% (15·2–16·9)	26·7% (23·7–31·6)	20·2% (18·6–22·6)	25·4% (23·3–28·2)	19·8% (18·3–22·2)	25·4% (23·8–27·9)	25·1% (24·1–26·6)	27·3% (26·0–29·1)	26·1% (24·3–28·9)	16·7% (15·8–18·0)
Mortality rate reduction in 2050, %	27·1% (25·6–30·1)	27·7% (26·3–33·3)	17·7% (16·8–18·7)	28·1% (25·0–32·8)	19·9% (18·6–21·6)	26·5% (24·3–29·4)	23·1% (21·2–25·8)	27·3% (25·5–30·6)	25·9% (25·0–27·1)	27·8% (26·6–29·4)	27·6% (25·8–31·3)	19·4% (18·1–21·3)
Accelerated scale-up												
Averted cases before 2050, millions	65·5 (55·6–76·0)	19·5 (16·7–23·1)	0·8 (0·7–1·0)	5·4 (4·3–6·7)	0·6 (0·5–0·7)	31·0 (25·8–36·4)	8·1 (6·9–9·5)	58·6 (49·9–67·9)	7·0 (5·8–8·2)	7·5 (6·2–9·0)	51·7 (43·6–60·2)	6·4 (5·6–7·2)
Averted deaths before 2050, millions	7·9 (7·3–8·5)	3·1 (2·9–3·4)	0·1 (0·1–0·1)	0·5 (0·4–0·6)	0·1 (0·1–0·1)	3·8 (3·3–4·3)	0·4 (0·4–0·4)	7·0 (6·4–7·6)	0·8 (0·8–0·9)	0·9 (0·8–1·0)	6·5 (5·9–7·0)	0·5 (0·4–0·6)
Averted treatment before 2050, millions	38·6 (34·4–42·3)	9·2 (8·5–9·9)	0·6 (0·5–0·7)	3·4 (2·9–4·0)	0·4 (0·4–0·5)	19·5 (16·8–22·2)	5·3 (4·8–5·9)	34·6 (30·7–37·9)	4·0 (3·5–4·4)	4·5 (4·0–5·0)	30·0 (26·5–33·3)	4·1 (3·7–4·4)
Incidence rate reduction in 2050, %	25·2% (23·9–27·5)	27·6% (26·3–32·1)	15·2% (14·4–16·2)	27·1% (24·5–31·4)	18·4% (16·4–21·6)	24·7% (22·8–27·3)	19·4% (18·1–21·3)	25·2% (23·8–27·6)	25·3% (24·5–26·8)	27·5% (26·3–29·2)	25·9% (24·3–28·6)	16·3% (15·5–17·3)
Mortality rate reduction in 2050, %	26·7% (25·2–29·9)	28·2% (26·8–34·6)	16·2% (15·3–17·3)	27·9% (25·2–32·3)	18·1% (16·5–20·7)	25·3% (23·2–28·2)	21·8% (20·2–24·3)	26·8% (25·1–30·4)	26·1% (25·3–27·2)	27·7% (26·6–29·2)	27·2% (25·5–31·0)	18·4% (17·3–20·0)
Routine-only												
Averted cases before 2050, millions	8·8 (7·6–10·1)	3·5 (3·0–3·9)	0·04 (0·03–0·05)	0·9 (0·7–1·2)	0·02 (0·02–0·03)	3·4 (2·6–4·4)	1·0 (0·8–1·2)	8·1 (7·0–9·3)	0·7 (0·6–0·8)	1·1 (0·9–1·3)	7·2 (6·2–8·3)	0·5 (0·4–0·7)
Averted deaths before 2050, millions	1·1 (0·9–1·2)	0·5 (0·4–0·6)	0·003 (0·003–0·004)	0·1 (0·1–0·1)	0·002 (0·002–0·003)	0·4 (0·3–0·5)	0·1 (0·0–0·1)	1·0 (0·8–1·1)	0·1 (0·1–0·1)	0·1 (0·1–0·1)	0·9 (0·7–1·0)	0·1 (0·0–0·1)
Averted treatment before 2050, millions	4·1 (3·7–4·6)	1·2 (1·1–1·4)	0·03 (0·02–0·03)	0·5 (0·4–0·6)	0·01 (0·01–0·02)	1·8 (1·4–2·2)	0·6 (0·5–0·7)	3·8 (3·4–4·2)	0·3 (0·3–0·4)	0·6 (0·5–0·6)	3·3 (2·9–3·8)	0·3 (0·2–0·3)
Incidence rate reduction in 2050, %	9·9% (9·0–11·6)	11·2% (10·3–14·7)	3·4% (3·1–3·9)	11·9% (9·9–15·3)	4·1% (3·4–5·2)	9·1% (7·8–11·1)	7·7% (6·5–9·5)	10·2% (9·1–12·0)	8·0% (7·3–9·2)	10·5% (9·6–11·9)	10·4% (9·2–12·5)	5·2% (4·4–6·3)
Mortality rate reduction in 2050, %	9·9% (8·9–12·3)	10·7% (9·7–15·2)	3·7% (3·3–4·2)	11·9% (9·9–15·1)	3·8% (3·3–4·5)	8·7% (7·3–10·7)	9·2% (7·5–11·7)	10·2% (9·1–12·9)	7·2% (6·5–8·1)	9·6% (8·8–10·7)	10·2% (9·0–13·1)	6·2% (5·2–7·8)

(Table 2 continues on next page)

	All modelled countries	WHO region						WHO tuberculosis burden level		World Bank income group		
		African region	Region of the Americas	Eastern Mediterranean region	European region	South-East Asian region	Western Pacific region	High-burden countries	All other countries	Low-income countries	Lower-middle-income countries	Upper-middle-income countries
(Continued from previous page)												
Infant vaccine												
Base-case												
Averted cases before 2050, millions	6·7 (5·8–7·7)	2·9 (2·5–3·4)	0·03 (0·02–0·03)	0·8 (0·6–1·1)	0·02 (0·01–0·02)	2·2 (1·6–2·8)	0·8 (0·6–1·0)	6·2 (5·3–7·1)	0·5 (0·4–0·6)	0·9 (0·7–1·1)	5·4 (4·7–6·2)	0·4 (0·3–0·5)
Averted deaths before 2050, millions	0·9 (0·8–1·0)	0·5 (0·4–0·6)	0·003 (0·002–0·003)	0·1 (0·1–0·1)	0·002 (0·002–0·002)	0·3 (0·2–0·4)	0·1 (0·0–0·1)	0·8 (0·7–1·0)	0·1 (0·1–0·1)	0·1 (0·1–0·1)	0·7 (0·6–0·9)	0·1 (0·0–0·1)
Averted treatment before 2050, millions	2·7 (2·4–2·9)	0·9 (0·8–0·9)	0·02 (0·01–0·02)	0·4 (0·3–0·5)	0·009 (0·008–0·01)	1·0 (0·8–1·2)	0·4 (0·3–0·5)	2·4 (2·2–2·7)	0·2 (0·2–0·3)	0·4 (0·4–0·5)	2·1 (1·9–2·3)	0·2 (0·1–0·2)
Incidence rate reduction in 2050, %	8·8% (7·9–10·4)	11·0% (10·0–14·5)	2·7% (2·4–3·1)	12·0% (9·7–15·6)	2·9% (2·5–3·4)	6·9% (5·8–8·6)	7·2% (5·9–9·2)	9·0% (8·1–10·7)	7·1% (6·4–8·2)	9·8% (8·9–11·1)	9·1% (8·1–11·1)	4·7% (3·9–5·9)
Mortality rate reduction in 2050, %	9·8% (8·7–12·0)	11·3% (10·1–15·7)	3·7% (3·2–4·3)	13·4% (10·5–18·1)	3·3% (2·9–3·9)	7·2% (5·9–9·6)	11·2% (8·5–15·4)	10·1% (8·9–12·5)	7·1% (6·4–8·0)	9·9% (9·0–11·2)	10·0% (8·7–12·5)	6·6% (5·4–8·5)
Accelerated scale-up												
Averted cases before 2050, millions	16·3 (14·0–18·8)	6·3 (5·4–7·2)	0·1 (0·1–0·1)	1·7 (1·3–2·2)	0·1 (0·1–0·1)	6·6 (5·1–8·6)	1·5 (1·2–1·9)	14·7 (12·6–17·1)	1·6 (1·3–1·9)	2·2 (1·8–2·8)	13·3 (11·4–15·5)	0·8 (0·6–0·9)
Averted deaths before 2050, millions	2·3 (2·0–2·6)	1·1 (0·9–1·2)	0·007 (0·006–0·008)	0·2 (0·1–0·2)	0·007 (0·006–0·009)	0·9 (0·7–1·2)	0·1 (0·1–0·2)	2·0 (1·8–2·3)	0·2 (0·2–0·3)	0·3 (0·2–0·3)	1·9 (1·6–2·2)	0·1 (0·1–0·1)
Averted treatment before 2050, millions	7·7 (6·9–8·6)	2·2 (2·0–2·4)	0·04 (0·04–0·05)	0·9 (0·8–1·2)	0·04 (0·04–0·05)	3·6 (2·9–4·3)	0·9 (0·7–1·0)	6·9 (6·2–7·8)	0·7 (0·7–0·8)	1·1 (1·0–1·3)	6·2 (5·5–7·0)	0·4 (0·3–0·4)
Incidence rate reduction in 2050, %	14·3% (13·0–16·7)	16·7% (15·4–21·6)	4·6% (4·2–5·2)	17·6% (14·5–22·3)	7·5% (6·2–9·8)	12·9% (11·0–15·8)	10·3% (8·7–12·6)	14·4% (13·0–17·0)	13·4% (12·4–14·9)	16·3% (15·1–18·1)	14·9% (13·3–17·9)	6·5% (5·6–7·8)
Mortality rate reduction in 2050, %	15·9% (14·2–19·3)	17·5% (15·9–24·1)	5·8% (5·2–6·6)	19·2% (15·5–24·7)	7·7% (6·5–9·5)	13·4% (11·2–17·0)	15·0% (12·0–19·3)	16·1% (14·3–19·9)	14·1% (13·1–15·3)	16·8% (15·6–18·5)	16·3% (14·4–20·3)	8·9% (7·5–11·1)

Data are median estimates (95% uncertainty range). Cumulative cases, treatments, and deaths averted are calculated for each vaccine scenario compared with the estimated number predicted by 2050 with the status quo no-new-vaccine baseline. Incidence and mortality rate reductions are calculated relative to the incidence and mortality rate predicted in 2050 relative to the status quo no-new-vaccine baseline. See appendix 5 for all scenarios (pp 55–68).

Table 2: **Cumulative cases, treatments, and deaths averted between vaccine introduction and 2050, and incidence and mortality rate reductions in 2050 by WHO region, WHO tuberculosis burden level, and World Bank income group for select vaccine scenarios (all 10-year duration of protection and medium coverage targets)**

incidence and mortality rate reductions by 2050 and 0·1–0·3 times the number of cases, treatments, and deaths averted (table 2).

Under the accelerated scale-up scenario, a 50% efficacy of the vaccine for adolescents and adults could prevent 7·9 million (7·3–8·5) deaths—2·9 million more than the base-case—and avert 65·5 million (55·6–76·0) cases and 38·6 million (34·4–42·3) treatments (table 2, figure 2). By contrast, by only routinely vaccinating those aged 9 years (ie, the routine-only scenario), 8·8 million (7·6–10·1) cases, 4·1 million (3·7–4·6) treatments, and 1·1 million (0·9–1·2) deaths would be averted compared with the status quo no-new-vaccine baseline scenario (table 2, figure 2).

Assuming non-vaccine interventions do not improve in the future (ie, the status quo no-new-vaccine baseline), the outcomes of the base-case scenario of introducing the vaccine for adolescents and adults suggest we would reach 34% of the 2035 global target to reduce tuberculosis cases by 90% compared with 2015 levels, and under the accelerated scale-up scenario, we would reach 41% of the target. Assuming the 2025 End TB target of reducing the incidence by 50% compared with 2015 levels is met (ie, the 2025 End TB no-new-vaccine baseline), progress would be increased further, with the base-case and accelerated scale-up scenarios reaching 82% of the target.

Impact results from scenarios with lifelong protection, 75% efficacy, and low-coverage and high-coverage targets are provided in appendix 5 (pp 55–68). Assuming lower coverage targets or the 2025 End TB no-new-vaccine baseline led to reduced vaccine impact compared with vaccines with medium coverage or the status quo no-new-vaccine baseline, and vaccines with higher coverage, 75% efficacy, or lifelong protection led to increased vaccine impact compared with vaccines with medium coverage, 50% efficacy, or 10 years protection.

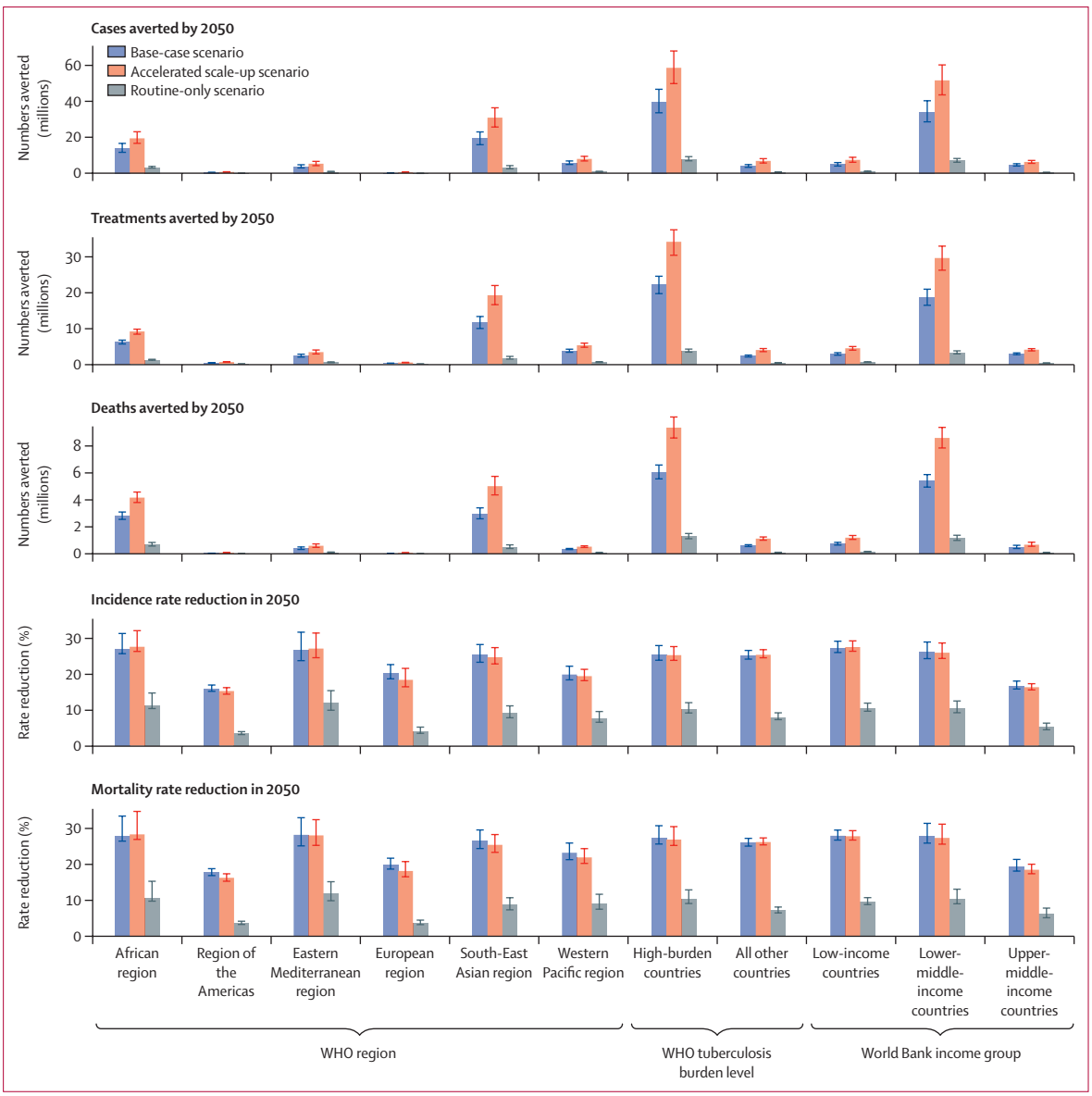

Figure 2: **Cumulative cases, treatments, and deaths averted between vaccine introduction and 2050, and incidence and mortality rate reductions in 2050 for the vaccine for adolescents and adults with varying delivery scenarios (50% efficacy vaccine, medium coverage, 10-year duration of protection), by WHO region, WHO tuberculosis burden level, and World Bank income group, expressed relative to a baseline scenario with no new vaccine**

Cumulative cases, treatments, and deaths averted are calculated for each vaccine scenario compared with the estimated number predicted by 2050 with the status quo no-new-vaccine baseline. Incidence and mortality rate reductions are calculated relative to the incidence and mortality rate predicted in 2050 by the status quo no-new-vaccine baseline. Base-case scenario: routine vaccination of those aged 9 years and a one-off campaign for those aged 10 years and older, introduced in country-specific years between 2028 and 2047 and scaled up over 5 years. Accelerated scale-up scenario: routine vaccination of those aged 9 years and a one-off campaign for those aged 10 years and older, introduced in 2025 and scaled up instantly in all countries. Routine-only scenario: routine vaccination of those aged 9 years, introduced in country-specific years between 2028 and 2047 and scaled up over 5 years.

Discussion

Our results suggest that novel tuberculosis vaccines could substantially reduce the tuberculosis burden in the coming decades. Relative to the status quo no-new-vaccine baseline, the base-case scenario—in which a tuberculosis vaccine for adolescents and adults with 50% efficacy was introduced during 2028–47—could prevent 44·0 million cases and 5·0 million deaths before 2050, including 2·2 million deaths in the WHO South-East Asian region and 2·1 million deaths in the African region. The more ambitious accelerated scale-up scenario could prevent 65·5 million cases and 7·9 million deaths relative to baseline (which is around 60% more deaths than the base-case scenario). The less ambitious routine-only scenario could prevent 8·8 million cases and 1·1 million deaths relative to

baseline (which is around a fifth of the base-case scenario).

Impact estimates for vaccine introduction varied by region in our results. Although incidence and mortality rate reductions achievable by 2050 were similar between high-tuberculosis-burden countries and all other countries, the number of cases, treatments, and deaths averted were around ten times higher than those averted in all other countries, emphasising the need to focus on high-burden countries to maximise health impact. Large numbers of averted cases, treatments, and deaths were predicted in the African region and South-East Asian region, and in lower-middle-income countries, which are arguably populations in the greatest need.

Our modelling suggests that campaigns will be important to expedite health gains from vaccination. The base-case and routine-only scenarios offer a direct comparison of implementing vaccination with and without a campaign for those 10 years and older. The base-case scenario averted up to six times as many cases, deaths, and treatments as the routine-only scenario, supporting the need to include a campaign in any future delivery strategy to maximise health impact.

A new vaccine will be an important tool to accelerate progress towards the 2035 End TB targets. Conservatively assuming non-vaccine interventions do not improve in the future (status quo no-new-vaccine baseline) and roll out from 2028 in line with the pace of historical vaccine uptake, the base-case scenario suggests we could reach around a third of the 2035 global target. More optimistic assumptions, in which the 2025 End TB targets are met before vaccine roll-out (2025 End TB no-new-vaccine baseline), combined with the accelerated scale-up scenario, suggest more than 80% of the global 2035 target could be met.

Two systematic reviews have highlighted potential health impacts of novel tuberculosis vaccines.[20,21] Our study expands on their findings, and it addresses some identified gaps. We showed that a vaccine for adolescents and adults would have greater and more rapid health impacts than a vaccine for infants before 2050. The largest burden of pulmonary tuberculosis disease is often found in adults;[1] and in our modelling the vaccine for adolescents and adults was delivered to ages with a higher burden of tuberculosis compared with the vaccine for infants. Because health outcomes are estimated for 2050, the maximum follow-up time between vaccine delivery and impact calculation is 25 years. Therefore, even with the duration of protection increased, the infant vaccine is unlikely to protect those at highest risk of progressing to active disease in most countries during our simulation.

Meeting the End TB target to develop and license a vaccine for adolescents and adults by 2025, and introducing this vaccine at a pace similar to that of COVID-19 vaccines (accelerated scale-up) could avert around 60% more deaths compared with introduction at a historical pace (base-case). The pace of COVID-19 vaccine introduction in LMICs, which was albeit slower than in high-income countries, was much faster than our base-case introduction assumption. As of February, 2023, more than 10% of the population in almost 95% of LMICs (ie, 122 of 129 countries reporting data) have been fully vaccinated since COVID-19 vaccines have been available, showing that faster vaccine introduction in LMICs is possible with high political will and financial resources.[22] This situation is more similar to our accelerated scale-up scenario, which averted up to 2·9 million more deaths, than our base-case scenario. Although the benefits of rolling out a vaccine from 2028 at a pre-COVID-19 pace are predicted to be large, the increase in deaths shows the consequences of failing to rapidly introduce a vaccine. Unlike COVID-19, tuberculosis is a disease of those on low-incomes, which does not have the associated novelty, nor the same effect on high-income countries. Therefore, tuberculosis vaccines need concerted, sustained policy attention to overcome these barriers.

We successfully calibrated 105 of 135 LMICs, representing 93% of global tuberculosis incidence. Excluding 30 countries will underestimate the number of cases, deaths, and treatments averted, and could bias the generalisability of the relative impact results if the epidemic in the excluded countries is substantially different than those included. Model misspecification and structural uncertainty is possible if country-specific epidemiology does not align with our structure. We used the best available estimates from literature, combined with previous knowledge and expert opinion, to substantiate the prior distributions. Therefore, our results reflect the inherent uncertainty in our knowledge of tuberculosis natural history. For newer discoveries in the field (eg, subclinical disease and self-clearance) data are sparse, and uncertainty is wide, which could bias our vaccine impact estimates. We made assumptions on parameters (eg, assuming the same amount of protection against reinfection in the infection and resolved compartments), which might slightly underestimate vaccine impact. We predicted tuberculosis declining across time, but the projected declines are unlikely to match actual declines, primarily affecting estimates of reaching End TB strategy goals, and numbers averted.

Because there are no new vaccines for tuberculosis, we assumed the characteristics of the modelled vaccines aligned with the recommendations in the WHO preferred product characteristics. Our impact results could be overestimated or underestimated if values for efficacy and duration of protection are lower or higher than the actual characteristics of a new vaccine. We assumed the vaccine for adolescents and adults would be efficacious in all individuals, because testing for tuberculosis infection before vaccination would be costly and logistically difficult. However, most trials

have only enrolled individuals who are either positive for interferon-gamma release assay or negative for interferon-gamma release assay.[6,7] If the vaccine will only be efficacious in those who are positive for interferon-gamma release assay or those who are negative, our results will be overestimates, as shown previously.[8] We assumed equivalent vaccine efficacy in people living with HIV and those who are HIV-naive, but vaccines are not always as efficacious in individuals who are immunocompromised,[23,24] which would reduce impact in countries classified as having a high tuberculosis burden associated with HIV.

For vaccine delivery, we attempted to represent a reasonable breadth of possibilities by speaking to experts and evaluating low and high coverage, efficacy, and introduction scenarios. Should there be rapid developments in tuberculosis diagnostics and treatments, or if funding were substantially increased, the impacts could be overestimates or underestimates. Our more ambitious scenario, accelerated scale-up, is less realistic than the base-case scenario, particularly in some LMICs. The scenario assumes a vaccine candidate would be ready for licensure, the supply exists, and that countries are positioned to make an introduction decision resulting in immediate uptake, all within the next 2–3 years, which is unlikely to be attainable by all countries. No specific risk groups were vaccinated in our model; however, initial delivery within countries could be through a targeted approach, which was previously shown to have a large population impact per vaccinated individual.[25–29] Some countries could initially vaccinate groups at the highest risk of developing disease or who contribute the most to transmission, whereas others could focus on vulnerable ages or those who have had contact with an individual with confirmed tuberculosis disease. Understanding how a new tuberculosis vaccine could be introduced in different settings is an important area for future research.

There are remaining gaps that modelling can address to provide evidence for investing in tuberculosis vaccine development and delivery to inform the Full Value of Vaccine Assessment.[30] Estimates of the cost-effectiveness, budget effect, and wider benefits of specific tuberculosis vaccine candidates would support research investment decision making. Future modelling research can help to better understand potential vaccine effectiveness considering a variety of factors, such as age, sex, and specific risk groups. We included an access-to-care structure to account for differences in tuberculosis burden and health-care access, which could be used to investigate differential vaccine targeting. To maximise the potential evidence available to countries, creating detailed individual country models to inform vaccine introduction decision making would be beneficial.

Our results suggest that novel tuberculosis vaccines could have a substantial impact on cases of and deaths from tuberculosis, which would vary depending on vaccine and delivery characteristics. Vaccination campaigns will be crucial for rapid impact, and an accelerated introduction that is done at a similar pace to that of COVID-19 vaccine introduction could save around 60% more lives before 2050 than the same vaccine introduced and scaled up across 20 years. The COVID-19 pandemic has shown the advantages that billions of dollars of investment can have on vaccine research and development, and it provides an illustration of what is possible to achieve with novel tuberculosis vaccines. Continued investment in tuberculosis vaccine research is required to strengthen vaccine development, trials, and manufacturing, and to support prompt introduction and scale-up.

Contributors

RGW, NAM, MJ, RCH, and CKW contributed to the conception of the paper. AD, RAC, CM, CKW, DS, AP, and SM contributed to the data acquisition and preparation. RAC, CM, DS, and CKW contributed to the data analysis. RAC, RGW, NAM, CKW, CM, and AP contributed to the interpretation of results. RAC, RGW, AP, NAM, CKW, CM, RCH, MJ, SM, DS, RB, NG, MZ, RCWH, BG, MQ, AD, and AI contributed to the manuscript drafting and revisions. RAC, CM, CKW, AD, DS, AP, SM, NAM, and RGW had the opportunity to access and verify the data. All authors were responsible for the decision to submit the manuscript for publication.

Declaration of interests

SM reports employment by the International AIDS Vaccine Initiative, a non-profit product development partnership supporting the access-oriented development of vaccines for several disease areas, including tuberculosis, and grant funding from WHO. MJ is funded by the Bill & Melinda Gates Foundation, Gavi the Vaccine Alliance, the UK Research Institute, the National Institute for Health Research, the European Commission, and the Wellcome Trust, and reports leadership or fiduciary roles in the board, society, committee, or advocacy groups for WHO and Gavi. RCH reports employment by Sanofi Pasteur, unrelated to tuberculosis and outside the submitted work. NAM received consulting fees from The Global Fund to Fight AIDS, Tuberculosis and Malaria and WHO, and reports funding to their institution from the US Centers for Disease Control and Prevention, the Gates Foundation, the National Institute of Health, and the US Council of State and Territorial Epidemiologists. RGW is funded for other work by the Wellcome Trust (218261/Z/19/Z), the National Institute of Health (1R01AI147321–01), EDCTP (RIA208D-2505B), the UK's Medical Research Council (CCF17–7779 via SET Bloomsbury), the Economic and Social Research Council (ES/P008011/1), the Gates Foundation (OPP1084276, OPP1135288, and INV-001754), and WHO. All other authors declare no competing interests.

Data sharing

No individual level participant data were used for this modelling study. Epidemiological data used are available from the WHO Global Tuberculosis Report and are summarised in appendix 5 (pp 41–49). Population estimates and projections are available from the UN Department of Economic and Social Affairs World Population Prospects 2019. The analytic code will be available immediately following publication, indefinitely, for anyone who wishes to access the data for any purpose.

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For more on the **WHO Global Tuberculosis Report** see https://www.who.int/teams/global-tuberculosis-programme/data

For more on the **UN Department of Economic and Social Affairs World Population Prospects 2019** see https://population.un.org/wpp/Download/Standard/Population/

For more on the **analytic code** see https://doi.org/10.5281/zenodo.6421372

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3.3 Supplementary Material – The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study

The Supplementary Material for Research Paper 1 was published online at *The Lancet Global Health*. It is reproduced here with no modifications or adaptations from the published version.

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Supplementary appendix 5

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2023; **11:** e546–55.

Supplementary Material for *The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study*

Rebecca A. Clark et al.

Table of Contents

SUPPLEMENTAL METHODS:

1. Model structure and equations

We created a compartmental tuberculosis vaccine model, which includes separate structures to account for key modelling components required. The structures, or "dimensions" we incorporated into the low- and middle-income country (LMIC) modelling are age, tuberculosis natural history, HIV and ART, and access to care.

1.1 Tuberculosis natural history dimension

1.1.1 Tuberculosis natural history structure

The core natural history model is specified in Figure S1.1. Model parameters used in the tuberculosis natural history dimension and their definitions are provided in Table S3.1.

Those with no previous exposure or infection with *Mtb* [Uninfected-Naive (U_N)] could become infected at rate λ_j and progress to an Infection-Fast (I_F) class following initial infection. From Infection-Fast, three possible pathways were possible: (i) Fast progression to Subclinical Disease (D_S), where individuals are infectious with a reduced infectiousness compared to clinical tuberculosis, but display no symptoms of tuberculosis disease;[1] (ii) self-clearance to Uninfected-Cleared (U_C), where individuals are no longer infected with *Mtb* and therefore are not at risk of progression to tuberculosis disease without reinfection;[2] or (iii) continue to remain latently infected with a risk of reactivation and progression to disease, albeit at a lower rate than Infection-Fast, by transitioning to the Infection-Slow (I_S) class. Those in the Infection-Slow class could self-clear to the Uninfected-Cleared class, be reinfected and return to the Infection-Fast class, or reactivate their infection and progress to Subclinical Disease.

Once in the Subclinical Disease class, individuals could naturally cure (*without* treatment) to the Resolved (R) class, or progress to Clinical Disease (D_C), where individuals are infectious and display symptoms of tuberculosis disease. Treatment initiation from Clinical Disease to On-Treatment (T) began in 1960 and increased following a sigmoid curve to 2019, with average treatment duration assumed to be 6 months.[3,4] Treatment completions transitioned to the Resolved class and treatment non-completions returned to Clinical Disease. Deaths occurring on-treatment and in clinical disease counted toward the total number of tuberculosis deaths during the year. Those with clinical disease could also naturally cure to the resolved class. Individuals in the Resolved class could be reinfected or relapse to Subclinical Disease but could *not* enter Infection-Fast or Infection-Slow directly. We assumed that the infection and resolved classes are partially protected against reinfection.[5,6] In those who have self-cleared, we assumed the level of protection against reinfection is half of the protection against reinfection for the infection and resolved classes.

Age was modelled in single years from ages 0 to 79 and aggregated into two categories for ages 80 to 89, and ages 90 to 99. Births and ageing occurred at the beginning of each year.

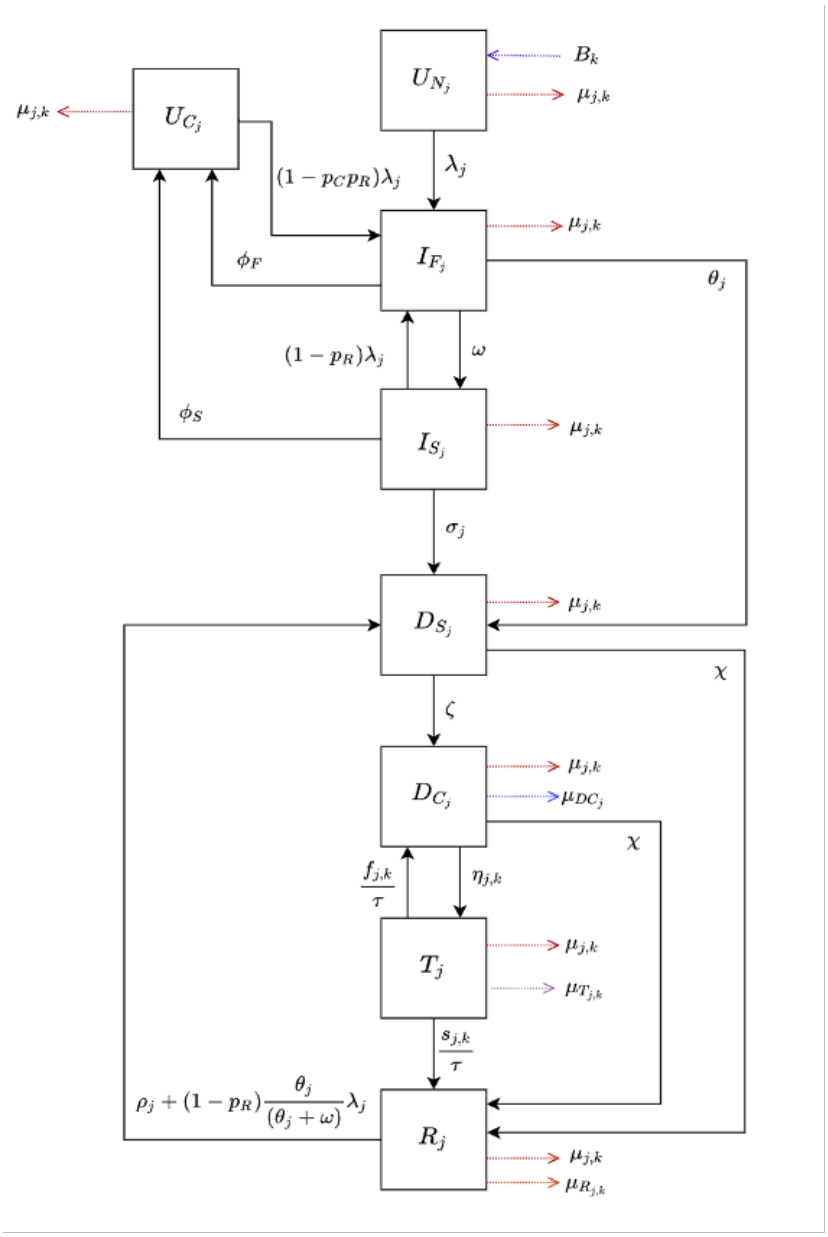

Figure S1.1 Tuberculosis natural history model

Abbreviations: D_C = Clinical Disease; D_S = Subclinical Disease; I_F = Infection-Fast; I_S = Infection-Slow; R = Resolved; T = On-Treatment; U_C = Uninfected-Cleared; U_N = Uninfected-Naive.

Subscript *j* represents parameters that vary by age, and subscript *k* represents parameters that vary over time.

1.1.2 Tuberculosis natural history equations

$Age\ j = 0$

$$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$$

$Age\ j \neq 0$

$$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_j}$$

$$\frac{dU_{C_j}}{dt} = \phi_F I_{F_j} + \phi_S I_{S_j} - [(1 - p_C p_R)\lambda_j + \mu_{j,k}]U_{C_j}$$

$$\frac{dI_{F_j}}{dt} = \lambda_j U_{N_j} + (1 - p_C p_R)\lambda_j U_{C_j} + [(1 - p_R)\lambda_j]I_{S_j} - (\phi_F + \omega + \theta_j + \mu_{j,k})I_{F_j}$$

$$\frac{dI_{S_j}}{dt} = \omega I_{F_j} - (\phi_S + \sigma_j + (1 - p_R)\lambda_j + \mu_{j,k})I_{S_j}$$

$$\frac{dD_{S_j}}{dt} = \theta_j I_{F_j} + \sigma_j I_{S_j} + [\rho_j + (1 - p_R)\frac{\theta_j}{\theta_j + \omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_j} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + \mu_{DC_j} + \mu_{j,k})D_{C_j}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k} + f_{j,k}}{\tau} + \mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [\rho_j + (1 - p_R)\frac{\theta_j}{\theta_j + \omega}\lambda_j + \mu_{R_j} + \mu_{j,k}]R_j$$

1.1.3 Force of infection equation

The equation for the age-specific force of infection (λ_j), or the rate at which Uninfected-Naïve individuals acquire *Mtb* infection in the population, is given below. Clinically, infection with *Mtb* can present as pulmonary tuberculosis which impacts the lungs, and extrapulmonary tuberculosis (EPTB) which occurs in sites other than the lungs.[7,8] EPTB is not infectious, and as we are modelling *Mtb* transmission we would want to exclude it. However, the WHO tuberculosis estimates which we calibrated to include both EPTB and pulmonary tuberculosis. Therefore, instead of excluding EPTB from the model, we discounted the force of infection by the proportion of incident cases that are EPTB to account for the fact that they are not infectious and calibrated to the targets that include both EPTB and pulmonary tuberculosis. We also discounted the force of infection to account for the relative reduced infectiousness of subclinical disease compared to clinical disease.

$$\lambda_j = p_T \times \sum_{y=1}^{n_{ygroups}} C[m,y] \times \left(\frac{(1-ep)(TD_{C_y} + rTD_{S_y})}{N_y} \right)$$

where:

$$N_y = \sum_{j=j_{min}}^{j_{max}} U_{N_j} + U_{C_j} + I_{F_j} + I_{S_j} + D_{S_j} + D_{C_j} + T_j + R_j$$

$$TD_{C_y} = \sum_{j=j_{min}}^{j_{max}} D_{C_j} \qquad TD_{S_y} = \sum_{j=j_{min}}^{j_{max}} D_{S_j}$$

Parameter	Definition
j	Age of individual (in years)
y	Age group of contact
$n_{ygroups}$	Number of contact age groups
p_T	Accounting for the probability of transmission per infectious contact
m	Age group of individual
$C[m,y]$	Contact rate between individual of age group m and contact of age group y from Prem et al.[9]
ep	Average proportion of tuberculosis cases that are extrapulmonary
r	Relative infectiousness of subclinical disease compared to clinical disease
TD_{C_y}	Total population in a clinical disease class in age group y
TD_{S_y}	Total population in a subclinical disease class in age group y
N_y	Total population alive in age group y
j_{min}	Minimum age j within age group y
j_{max}	Maximum age j within age group y

1.2 HIV and ART structure

1.2.1 HIV and ART description

In order to account for the influences of human immunodeficiency virus (HIV) and antiretroviral therapy (ART) on the risk of infection with *Mtb* and progression to tuberculosis disease,[10,11] we have implemented an HIV structure composed of 3 compartments: HIV uninfected [HIV_0], people living with HIV (PLHIV) not on ART [HIV_1], and PLHIV on ART [ART]. HIV uninfected individuals acquired HIV and moved from the HIV_0 compartment to the HIV_1 compartment with rate λ_H. Within the HIV_1 compartment, there is a higher risk of tuberculosis progression and an increased tuberculosis mortality rate compared to the HIV_0 compartment. PLHIV are initiated on treatment with ART from HIV_1 following a sigmoid trend which increases over time. The HIV incidence rate decreases over time following a sigmoid trend which depends on ART coverage (as ART coverage increases over time, the HIV incidence rate decreases). The increases in tuberculosis mortality rate and tuberculosis progression are reduced while in ART compared to HIV_1, but still higher than in HIV_0. ART also reduces the HIV mortality rate. Model parameters used in the HIV and ART structure and their definitions are provided in Table S3.1.

1.2.2 HIV and ART diagram

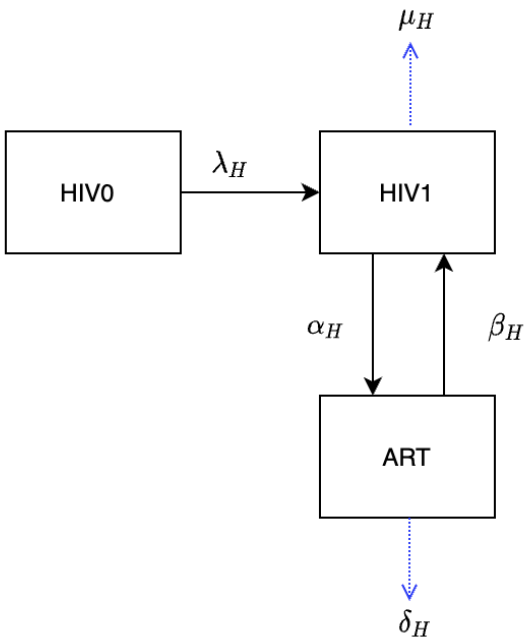

Figure S1.2 HIV and ART structure

1.2.3 HIV and ART equations

$$\frac{d\ \mathrm{HIV}_0}{dt} = -\lambda_H \mathrm{HIV}_0$$

$$\frac{d\ \mathrm{HIV}_1}{dt} = \lambda_H \mathrm{HIV}_0 + \beta_H \mathrm{ART} - (\alpha_H + \mu_H)\mathrm{HIV}_1$$

$$\frac{d\ \mathrm{ART}}{dt} = \alpha_H \mathrm{HIV}_1 - (\beta_H + \delta_H)\mathrm{ART}$$

1.2.4 Natural history equations incorporating HIV and ART

Let $p_{adj} = (1 + th1(\theta_{mul} - 1))$

$Age\ j = 0$	$Age\ j \neq 0$
$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$	$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_i}$

$$\frac{dU_{C_j}}{dt} = \phi_F I_{F_i} + \phi_S I_{S_i} - [(1 - p_C p_R)\lambda_j + \mu_{j,k}]U_{C_i}$$

$$\frac{dI_{F_j}}{dt} = \lambda_j U_{N_i} + (1 - p_C p_R)\lambda_j U_{C_i} + [(1 - p_R)\lambda_j]I_{S_i} - (\phi_F + \omega + p_{adj}\theta_j + \mu_{j,k})I_{F_i}$$

$$\frac{dI_{S_j}}{dt} = \omega I_{F_i} - (\phi_S + p_{adj}\sigma_j + (1 - p_R)\lambda_j + \mu_{j,k})I_{S_i}$$

$$\frac{dD_{S_j}}{dt} = p_{adj}\theta_j I_{F_j} + p_{adj}\sigma_j I_{S_j} + [p_{adj}\rho_j + (1 - p_R)\frac{p_{adj}\theta_j}{p_{adj}\theta_j + \omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_i} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + m_{adj}\mu_{DC_i} + \mu_{j,k})D_{C_i}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k} + f_{j,k}}{\tau} + m_{adj}\mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [p_{adj}\rho_j + (1 - p_R)\frac{p_{adj}\theta_j}{p_{adj}\theta_j + \omega}\lambda_j + m_{adj}\mu_{R_j} + \mu_{j,k}]R_j$$

1.3 Access to Care Dimension

1.3.1 Access to care description

The access to care dimension is incorporated to allow for the negative correlation between tuberculosis burden and health care access to prevent the overestimation of vaccine impact, as well as to facilitate future analyses of equity implications of vaccine introduction. The access to care dimension contains 2 classes: high-access-to-care, representing the top 3 quintiles (60% of the population) and low-access-to-care, representing the bottom 2 quintiles (40% of the population). We assumed that there was no transition between the high- and low-access-to-care classes, as well as assuming random mixing between the high-access-to-care and low-access-to-care classes.

To constrain relative burden between access-to-care classes, we calibrated the relative tuberculosis prevalence in the high-access-to-care class to the low-access-to-care class in 2019. The calibration target, 0·674, was calculated as a weighted average from eleven studies, with lower and upper bounds (0·575–0·801) representing the 25th and 75th percentiles of the datasets.[12–22] Specifically, a weighted simple linear regression was performed on the log of the prevalence rate ratio of the upper 60% of the population relative to the lower 40% of the population by socioeconomic status (calculations performed by the authors), with weights representing the suspected overlap between potential duplicate observations (0·5 for Philippines and 0·7 for Zambia observations).

Table S1.1 TB prevalence study data

Source	Country	Prevalence rate ratio of upper 60% vs. lower 40% of population by socioeconomic status	Weight
[14]	Bangladesh	0·394	1
[17]	India	0·386	1
[18]	India	0·467	1
[20]	Kenya	0·588	1
[19]	Malawi	0·867	1
[19]	Mongolia	0·716	1
[19]	Myanmar	0·807	1
[19]	Philippines	0·755	0·5
[20]	Philippines	0·608	0·5
[16]	Rwanda	1·081	1
[19]	Rwanda	0·774	1
[12]	South Africa	0·486	1
[21]	South Africa	0·896	1
[19]	Tanzania	0·648	1
[13]	Vietnam	0·701	1
[22]	Vietnam	0·799	1
[19]	Vietnam	0·672	1
[15]	Zambia	0·534	0·7
[19]	Zambia	1·312	0·7
[21]	Zambia	0·728	0·7

To incorporate access to care into our model, we assume that the differences in tuberculosis burden between strata are due to differences in the force of infection, the rate of care-seeking (i.e., tuberculosis treatment initiation), and the rate of tuberculosis progression. We assume relative to the low-access-to-care stratum, the high-access-to-care stratum has a reduced force of infection per contact, an increased rate of treatment initiation, and a reduced rate of tuberculosis progression. Differential burden was implemented by introducing a new parameter p_E, such that $p_E \in [0, 1]$ for the high-access-to-care and $p_E = 0$ for low access-to-care. p_E was included within the model natural history structure as described in Table S1.1. This new parameter was fitted during calibration.

Table S1.2 Implementing the access-to-care parameter

	Access-to-Care
Force of infection	$p_T \times \sum_{y=1}^{n_{ygroups}} (1 - p_E) \times C[m, y] \times \left(\frac{(1-ep)(TD_{C_y} + rTD_{S_y})}{N_y} \right)$
Treatment Initiation Rate	$\frac{\eta_{j,k}}{(1-p_E)}$
Rate of Tuberculosis Progression	$(1 - p_E) \times \theta_j$ $(1 - p_E) \times \sigma_j$ $(1 - p_E) \times \rho_j$

2. Model Parameters and Data Sources

2.1 Model Parameters and Data Sources

Parameters used in the natural history model structure and the HIV and ART model structure are provided in Table S2.1 below, along with their definitions, sources, and information on whether the parameter is fixed or varied (as well as whether they are varied by age or time) during calibration. Further details about how the age varying parameters are implemented are provided in section 2.2. The parameter ranges provided for the tuberculosis natural history parameters are priors fitted during calibration in a Bayesian analysis. We assume that all values within the prior range are equally likely. The prior ranges were pre-specified based on literature review and were reviewed as new data became available.

Table S2.1 Demographic and tuberculosis natural history parameters and definitions

Description	Units	Symbol	Prior	Fixed or Varying During Calibration	Age Varying	Time Varying	Source
Births and deaths (excluding on-treatment mortality)							
Birth rate	Per year	B_k	United Nations World Population Prospects population estimates and projections	Fixed	No	Yes	[23]
Background mortality rate	Per year	$\mu_{j,k}$	Calculated in the model from United Nations population estimates and projections	Fixed	Yes, age specific mortality rates from demographic dataset	Yes	[23]
Mortality rate for clinical tuberculosis disease	Per person per year	μ_{DC_j}	(0–0·178)	Varying	Yes, value for children is greater than value for adults	No	[24]
Mortality rate post-tuberculosis disease	Per person per year	μ_{R_j}	$0.22\mu_{j,k}$	Fixed relationship	Yes, because $\mu_{j,k}$ varies	Yes, because $\mu_{j,k}$ varies	[25]
Natural history							
Force of infection	Per year	λ_j	Fitted	Fixed equation	Yes, age specific contact rates[9]	No	*Calculated*

Probability of transmission per infectious contact	-	p_T	(0–0·0068)	Varying	No	No	*Assumed*
Fraction of total tuberculosis disease that is extrapulmonary	-	ep	Country-specific average of previous 3 years	Fixed	No	No	[26,27]
Infectiousness of subclinical relative to clinical tuberculosis	-	r	0·80	Fixed	No	No	[28]
Rate of self-clearance from I_F to U_C	Per person per year	ϕ_F	0·00000140	Fixed	No	No	[2]
Rate of self-clearance from I_S to U_C	Per person per year	ϕ_S	(0·0254–0·0467)	Varying	No	No	[2]
Rate of fast progression to disease, by age	Per person per year	θ_j	(0·0696–0·111)	Varying	Yes, value for children is less than value for adults	No	[2]
Rate from I_F to I_S	Per person per year	ω	0·5	Fixed	No	No	*Defined*
Rate of reactivation from I_S, by age	Per person per year	σ_j	(0·000135–0·00113)	Varying	Yes, value for children is less than value for adults	No	[2]
Rate of progression from D_S to D_C	Per person per year	ζ	(0–12)	Varying	No	No	*Assumed*
Rate of natural cure from D_C and D_S	Per person per year	χ	(0·1–0·25)	Varying	No	No	[29,30]
Rate of relapse from R, by age	Per person per year	ρ_j	(0·0001–0·07)	Varying	Yes, value for children is less than value for adults	No	[31–33]
Treatment outcome parameters							
Treatment duration	Number of years	τ	0·5	Fixed	No	No	[3,4]
Rate of on-treatment mortality	Per person per year	$\mu_{T_j} = \frac{\kappa_j}{\tau}$	Country-specific	Varying	Yes, value for children greater than value for adults	Yes	[34]

Rate of treatment completion	Per person per year	$\frac{s_j}{\tau}$	Country-specific	Fixed equation	Yes, indirectly scaled by s_{Age}	Yes	[34]
Rate of treatment non-completion	Per person per year	$\frac{f_j}{\tau}$	Country-specific	Fixed equation	Yes, indirectly scaled by s_{Age}	Yes	[34]
Protection parameters							
Protection from reinfection for I_S, I_F, R	-	p_R	(0·6–0·85)	Varying	No	No	[5,6,29,30,35]
Relative protection from reinfection for self-clearance compared to p_R	-	p_C	0·50	Fixed	No	No	*Assumed*
SES parameter	-	p_E	(0–1)	Varying	No	No	*Assumed*
HIV parameters							
HIV incidence rate fitting factor	-	$\lambda_{H\text{fit}}$	(0–300)	Varying	No	No	*Fitted*
Rate of ART initiation fitting factor	-	$\alpha_{H\text{fit}}$	(0–7000)	Varying	No	No	*Fitted*
Rate of ART discontinuation	Per year	β_H	0·074	Fixed	No	No	[36,37]
Mortality rate from HIV not on ART	Per year	μ_H	0·10	Fixed	No	No	[38]
Mortality rate from HIV on ART	Per year	δ_H	0·026	Fixed	No	No	[39]
Relative increase in progression rate for HIV_1	-	θ_{mul}	(3·94–14·45)	Varying	No	No	[40]
Relative reduction in θ_{mul} for HIV and ART compartments	-	$th1$	HIV_0 = 0 HIV_1 = 1·00 ART = 0·35	Fixed	No	No	[11]
Relative mortality rate adjustment for HIV and ART compartments	-	m_{adj}	HIV_0 = 1·00 HIV_1 = 1·50 ART = 1·15	Fixed	No	No	[11,24,41,42]

2.2 Operationalising Age Varying Parameters

We assume that aspects of tuberculosis natural history and mortality vary by age. This is implemented by stratifying certain natural history parameters by age and applying age-specific prior ranges and relative constraints during calibration.[43] The following table describes the method used to operationalise the age varying differences in parameters between adults, defined as all ages greater than and equal to 15, and children, defined as all ages less than 15. For the rate per year of reactivation, relapse, and fast progression to tuberculosis disease, we assume that the rate for children is less than that for adults. For the clinical tuberculosis and on-treatment mortality rates, we assume the opposite: the rate for children is higher than that for adults. Age varying for the treatment initiation rate is described in section 3.

Table S2.2 How age varying parameters are operationalised

Parameter	Parameter prior range	Age-specific constraints during calibration	Sample the corresponding age scaling parameter	Adults (θ_{A15})	Children (θ_{A0})
θ_j Rate per year of fast progression	Sample from $(0.0696, 0.111)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_1 from $(0, 1)$	Sample θ_{A15} from $(0.0696, 0.111)$	$\max(0.0696, \theta_{A15} \times j_1)$
σ_j Rate per year of reactivation	Sample from $(0.000135, 0.00113)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_2 from $(0, 1)$	Sample σ_{A15} from $(0.000135, 0.00113)$	$\max(0.000135, \sigma_{A15} \times j_2)$
ρ_j Rate per year of relapse	Sample from $(0.0001, 0.07)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_3 from $(0, 1)$	Sample ρ_{A15} from $(0.0001, 0.07)$	$\max(0.0001, \rho_{A15} \times j_3)$
μ_{DC_j} Clinical tuberculosis mortality rate per year	Sample from $(0, 0.178)$	Retain if value for children is greater than value for adults	Sample S_{Age} from $(0, 1)$	$\mu_{DC_{A0}} \times S_{Age}$	Sample $\mu_{DC_{A0}}$ from $(0, 0.178)$
$\mu_{T_j} = \frac{\kappa_j}{\tau}$ On-treatment mortality rate per year	Sample from $(0, \frac{\kappa_{max}}{\tau})$	Retain if value for children is greater than value for adults	Sample S_{Age} from $(0, 1)$	$\frac{\kappa_{A0}}{\tau} \times S_{Age}$	Sample κ_{A0} from $(0, \kappa_{max})$

3. Tuberculosis treatment

3.1 Tuberculosis treatment initiation

Tuberculosis treatment was assumed to start in 1960, aligned roughly with the discovery and widespread use of rifampicin, and increase following a sigmoid curve (Figure S3.1) to 2019. The treatment initiation rate parameter, η_j, represents the age specific rate of treatment initiation from the clinical disease compartment to the on-treatment compartment. During calibration, a country-specific value for η_j was sampled between 0 and 1. η_j was multiplied by an age scaling parameter for children, j_4, also sampled between 0 and 1, to ensure that the treatment initiation rate in children was less than in adults. This was then multiplied by the value of the sigmoid curve at each year. The treatment initiation rate was calibrated to the country-specific notification rate in 2019 overall and by age reported by the WHO.[26] Due to inconsistencies in the availability of private sector treatment notification data, the contribution of the private sector was not explicitly represented in our model aside from where it had already been incorporated in WHO estimates.

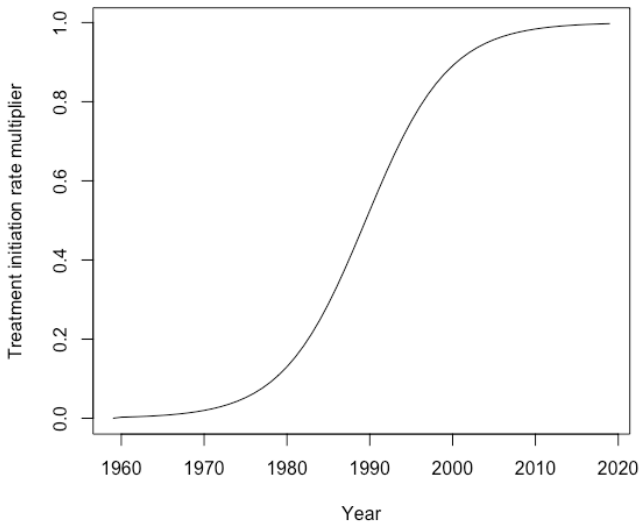

Figure S3.1 Sigmoid curve representing the scale-up in tuberculosis treatment from 1960-2019

3.2 Tuberculosis treatment outcomes

There are three possible exits from the on-treatment compartment: treatment completion, which progresses to the resolved compartment, treatment non-completion, which returns to the clinical disease compartment, and on-treatment mortality, which counts toward tuberculosis mortality. To account for the variability in tuberculosis treatment outcomes and possible underreporting of on-treatment mortality, we used the following country-specific process:

1. For each country separately, the proportion of treatment completions out of the sum of the number of treatment completions and non-completions (previously called "treatment failures") was calculated and averaged over the years of available data from WHO.

Let s_R = Reported number of treatment completions, f_R = Reported number of treatment non-completions

Note: reported number of treatment non-completions included 0·5 × (reported number lost to follow up)

$$\mathrm{SFR} = \frac{s_R}{s_R + f_R}$$

Ex. In India, averaged over 2012–2018, SFR = 0·96. This can be interpreted as of the sum of treatment completions and non-completions, on average, 96% are completions and 4% non-completions.

2. A value for child treatment mortality (κ_{A0}) was sampled between 0 and $(2 \times \text{Average Reported Treatment Mortality})$. The average reported treatment mortality is multiplied by 2 to give an upper bound in the case of unreported data.

   Ex. For India, $\kappa_{A0} \in (0, 0.135)$

3. The age multiplier, S_{Age}, was sampled from $(0, 1)$, and multiplied by κ_{A0} to calculate the adult treatment mortality

$$\kappa_{A15} = \kappa_{A0} \times S_{Age}$$

4. The success and failure rates per year were calculated as in Table S3.1

Table S3.1 Calculating treatment outcome parameter values for adults and children

Parameter	Adults	Children
κ_j On-treatment mortality fraction	$\kappa_{A0} \times S_{Age}$	Sample κ_{A0} from 0 to 2 x Average mortality on-treatment
s_j On-treatment completion fraction	$(1 - \kappa_{A15})\mathrm{SFR}$	$(1 - \kappa_{A0})\mathrm{SFR}$
f_j On-treatment non-completion fraction	$(1 - \kappa_{A15})(1 - \mathrm{SFR})$	$(1 - \kappa_{A0})(1 - \mathrm{SFR})$

5. Each of the parameters in Table S3.1 were divided by τ to obtain the on-treatment mortality rate per year, on-treatment completion rate per year, and on-treatment non-completion rate per year.

4. Model simulation and calibration methodology

4.1 Model simulation

For each country-specific model, we specified a system of ordinary differential equations defining the derivatives with respect to time of a set of state variables, to simulate the country-specific tuberculosis epidemic between 1900 and 2050. We initialised the simulation by distributing the population between the eight tuberculosis natural history states using a fitted parameter representing the proportion of the population uninfected at the start of the simulation. For each year of the simulation (1900–2050), our models are designed to exactly match the age and country specific UN population estimates and projections.[23] Forty percent of the population was assigned to the low access-to-care stratum and the remaining 60% of the population was assigned to the high access-to-care stratum. For countries we classified as having a higher tuberculosis burden due to HIV, the entire population began as HIV uninfected in 1900. As the simulation progresses, the HIV incidence rate is applied and transitions occur to the PLHIV not on ART compartment, and (once ART is introduced in 2000) to the PLHIV on ART compartment.

4.2 Model calibration

Broadly, our modelling approach was as follows:

1. Construct a mechanistic model(s)
2. Calibrate the model(s) by identifying areas of the input parameter space where the output of the mechanistic model was consistent with the historical epidemiologic data
3. Use the calibrated model to simulate and predict future tuberculosis epidemiology and model new vaccines

In the context of this analysis, step 1 was achieved by creating the compartment differential equation model as specified in Section 1. For step 2, we independently calibrated one model for each country by identifying areas of the parameter space that made the output of each country-specific model match the corresponding calibration targets. The model was fitted to calibration targets using history matching with emulation, a relatively new calibration method that allows us to explore high-dimensional parameter spaces efficiently and robustly.[44–47] History matching progresses as a series of iterations, called waves, where implausible areas of the parameter space, i.e., areas that are unable to give a match between the model output (e.g., the predicted incidence rate by the model) and the empirical data (e.g., the incidence rate calibration target from the WHO data), are found and discarded. In order to identify implausible parameter sets, emulators are used. Emulators are statistical approximations of model outputs that are built using a modest number of model runs. Emulators provide an estimate of the value of the model at any parameter set of interest, with the advantage that they are orders of magnitude faster than the model.

History matching with emulation, implemented through the *hmer* package in R,[48] considerably reduced the size of the parameter space to investigate. Rejection sampling was then performed on the reduced space to identify at least 1000 parameter sets that matched all targets for each country.

If countries were unable to find at least 1000 fully fitted parameter sets using history matching with emulation, they were subsequently assessed using an Approximate Bayesian Computation using Markov Chain Monte Carlo method (ABC-MCMC). ABC-MCMC was conducted using the *easyABC* package in R, modified by the Sebastian Funk, Gwenan Knight, and the Tuberculosis Modelling group at LSHTM for adaptive sampling and to accept seeded parameter values.[49,50] We used parameter sets with the maximum number of targets fitted using history matching with emulation as starting seeds for multiple MCMC chains per country, with the ABC-MCMC algorithm continuously adapting using the last 1000 points, a burn in of 1000 samples, and the noise factor set to 0·0001.

Once we had obtained 1000 parameter sets that produced output consistent with the calibration targets, we used those parameter sets with the mechanistic model to simulate the future (step 3) for each country.

5. Low- and middle-income countries

5.1 Eligible countries

To decide which low- and middle-income countries (LMICs) to model on, we used the 135 LMICs indicated on the 2019 World Bank Income Level classifications.[51] The 135 countries were broken down into 29 low-income countries (LICs), 50 lower middle-income countries (LMICs), and 56 upper middle-income countries (UMICs). Distribution by World Bank Income and WHO region are shown below in Table S5.1.

Table S5.1 LMICs by WHO Region and World Bank Income Level 2019

WHO Region	World Bank Income Level 2019			*Total*
	LIC	LMIC	UMIC	
AFR	21	19	5	45
AMR	1	4	20	25
EMR	5	6	5	16
EUR	1	4	15	20
SEAR	1	7	3	11
WPR	0	10	8	18
Total	29	50	56	135

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

5.2 Countries excluded from attempting calibration

Of the 135 LMIC countries, 20 countries were excluded from attempting calibration due to missing data for calibration. We considered imputing data for countries where it was missing but wanted to keep consistent methods and data sources across the included countries. We do not believe that this omission will have a large impact on our conclusions, given that the excluded countries represented only 3.7% of the total LMIC TB incidence and 5% of the total LMIC TB mortality in 2019. Countries excluded and reasons for exclusion from attempting calibration are provided in Table S5.2 below.

Table S5.2 Countries excluded from attempting calibration and reasons for exclusion

Country	Reason for Exclusion
American Samoa	Missing critical epidemiological data for calibration, no contact matrices available
Belize	No case notification or incidence data for children
Comoros	No case notification data
Democratic Republic of the Congo	No case notification data by age
Republic of the Congo	No population estimates
Democratic People's Republic of Korea	Missing critical epidemiological data for calibration
Djibouti	No case notification data by age
Dominica	Missing critical epidemiological data for calibration, no contact matrices available
Federated States of Micronesia	Missing critical epidemiological data for calibration, no contact matrices available
Grenada	Missing critical epidemiological data for calibration, no contact matrices available
Haiti	Missing 2020 contact matrix
Kiribati	Missing 2020 contact matrix
Kosovo	Missing critical epidemiological data for calibration
Lebanon	Missing 2020 contact matrix
Marshall Islands	Missing critical epidemiological data for calibration, no contact matrices available
Samoa	No case notification or incidence data for children
Somalia	No contact matrices available
St. Lucia	No case notification or incidence data for children
Tuvalu	No contact matrices available
West Bank and Gaza	Missing critical epidemiological data for calibration

5.3 Countries classified as having a higher tuberculosis burden due to HIV

We classified countries as having a higher tuberculosis burden due to HIV if at least 15% of the total tuberculosis cases were in people living with HIV (PLHIV) and if the HIV prevalence in the country was greater than 1%, and included a separate stratum to dynamically model the tuberculosis-HIV co-epidemic. Our definition resulted in 23 of the 115 worth running countries classified as having a higher tuberculosis burden due to HIV (Table S5.3).

Table S5.3 HIV prevalence and proportion of total tuberculosis cases that were in PLHIV for countries classified as having a higher tuberculosis burden due to HIV

Country	HIV Prevalence in 2019 (%)[23,52]	Proportion of total tuberculosis cases that were PLHIV in 2019 (%)[26]
Botswana	16·5 (14·8–17·8)	48·6 (39·0–59·0)
Central African Republic	2·1 (1·8–2·7)	25·4 (20·0–30·0)
Côte d'Ivoire	1·7 (1·4–1·9)	17·5 (15·0–21·0)
Cameroon	2·0 (1·7–2·2)	26·8 (21·0–32·0)
Gabon	2·3 (1·7–3·0)	32·8 (19·3–44·0)
Ghana	1·1 (0·8–1·5)	20·8 (17·0–26·0)
The Gambia	1·2 (0·9–1·5)	17·7 (14·0–22·0)
Guinea-Bissau	2·1 (1·8–2.4)	31·3 (25·0–38·0)
Equatorial Guinea	4·8 (3·5–6·5)	26·5 (25·8–26·8)
Guyana	1·1 (1·0–1.2)	19·0 (18·0–20·0)
Kenya	2·9 (2·5–3·2)	26·2 (21·0–32·0)
Lesotho	16·0 (15·1–16·9)	61·6 (50·0–74·0)
Mozambique	7·2 (5·9–9·2)	33·8 (27·0–41·0)
Malawi	5·9 (5·2–5·9)	46·6 (46·2–56·0)
Namibia	8·4 (7·6–8·8)	32·5 (32·5–39·0)
Rwanda	1·8 (1·6–2·0)	21·1 (17·0–25·0)
Eswatini	17·4 (16·5–19·2)	60·1 (56·6–62·4)
Togo	1·5 (1·2–1·7)	16·2 (13·0–20·0)
Tanzania	2·9 (2·6–3·1)	23·6 (19·0–29·0)

Uganda	3·4 (3·2–3·6)	39·0 (31·0–47·0)
South Africa	12·8 (11·8–13·7)	58·0 (46·0–70·0)
Zambia	6·7 (5·4–7·3)	46·2 (35·0–56·0)
Zimbabwe	9·6 (8·2–10·9)	59·8 (48·0–72·0)

6. No-New-Vaccine baselines

6.1 *Status Quo No-New-Vaccine* baseline

The primary no-new-vaccine simulated was the "*Status Quo No-New-Vaccine*" baseline, which assumed non-vaccine tuberculosis interventions continue at current levels into the future. As reported country-level data includes the high coverage levels of neonatal BCG vaccination, this was not explicitly modelled. We assumed that BCG vaccination would not be discontinued over the model time horizon.

All countries were fitted to nine calibration targets in 2019:

- The country-specific tuberculosis incidence rate per 100,000 population (all ages, ages 0–14, and ages 15+)
- The country-specific tuberculosis case notification rate per 100,000 population (all ages, ages 0–14, and ages 15+)
- The country-specific tuberculosis mortality rate per 100,000 population (all ages)
- The global estimate of the ratio of the prevalence of subclinical tuberculosis with the prevalence of active tuberculosis (subclinical + clinical tuberculosis)[1]
- The global estimate of the ratio of the prevalence of active tuberculosis in the high access-to-care class relative to low access-to-care[12–22]

In addition to the targets above, countries classified as having a higher tuberculosis burden due to HIV were fitted to four HIV specific calibration targets for all ages in 2019:

- HIV prevalence (%)
- ART coverage (%)
- Tuberculosis incidence rate in PLHIV per 100,000 population (all ages)
- Tuberculosis mortality rate in PLHIV per 100,000 population (all ages)

For the country-specific calibration targets, Table S6.1 indicates where the data to inform the targets was sourced and which variables were used.

For the data obtained from the WHO, we subset the data sets to the 135 LMICs and excluded countries if they were missing key variables indicated in Table S6.1 used to calculate calibration targets. For the data obtained from the UN population division and Prem et al.,[9] we subset the data sets to the 135 LMICs and excluded countries if they were missing population estimates and projections or contact matrices. Countries excluded and reasons for exclusion from further analysis are detailed in Table S5.2.

Data manipulation to create incidence and case notification rate calibration targets

The age-specific and case notification data required further manipulation to a usable form for calibration targets. The best estimate, as well as low and high estimates for the number of incident cases by age were transformed to rates per 100,000 population. We aggregated the UN population data in 2019 into the required age groups (children = 0–14, adults 15–99), and calculated the targets as follows:

$$\frac{\text{Number of incident tuberculosis cases in age group}}{\text{Total population of age group}} \times 100,000$$

Only one estimate of the number of case notifications per age group was provided. Once we calculated the estimate of the age specific case notification rate following the same method as used for the number of incident tuberculosis cases in the age group, we manually added 20% uncertainty bounds.

Data manipulation for simulation age groups

We simulated the model with 82 age groups (single ages from 0–79, and then aggregated groups for ages 80–89 and 90–99). We aggregated age specific data from the UN population estimates and projection by year to create the two age groups used for ages 80–99.

Table S6.1 Sources and variables used for calculations of country-specific calibration targets

Calibration target description	Source	Variables used
All countries		
The country-specific tuberculosis incidence rate per 100,000 population (all ages, ages 0–14, and ages 15+)	WHO TB incidence estimates disaggregated by age group, sex and risk factor (Retrieved 28 October 2020)[53] UN population estimates and projections[23]	best lo hi
The country-specific tuberculosis case notification rate per 100,000 population (all ages, ages 0–14, and ages 15+)	Case Notifications (Retrieved 28 October 2020)[27] - Number of notified TB cases reported by countries and territories to the WHO UN population estimates and projections[23] The Case Notifications dataset downloaded from the WHO website provides the number of estimated case notifications. We added 20% uncertainty on the calculated target to create upper and lower bounds for calibration.	newrel_f014 newrel_m014 newrel_f15plus newrel_m15plus c_newinc
The country-specific tuberculosis mortality rate per 100,000 population (all ages)	WHO TB burden estimates (Retrieved 28 October 2020)[26] - Estimates generated by WHO	e_mort_100k e_mort_100k_lo e_mort_100k_hi
Countries classified as having a higher tuberculosis burden due to HIV		
HIV prevalence (%)	HIV estimates with uncertainty bounds 1990-Present (Retrieved 28 October 2020)[52] - Sheet 2: HIV estimates – by Area UN population estimates and projections[23]	Estimated adults and children living with HIV Estimate, Low, High
ART coverage (%)	HIV estimates with uncertainty bounds 1990-Present (Retrieved 28 October 2020)[52] - Sheet 4: HIV Test & Treat – by Area	Among people who know their HIV status, the percent on ART (All Ages) Estimate, Low, High
Tuberculosis incidence rate in PLHIV per 100,000 population (all ages)	WHO TB burden estimates (Retrieved 28 October 2020)[26] - Estimates generated by WHO	e_inc_tbhiv_100k e_inc_tbhiv_100k_lo e_inc_tbhiv_100k_hi
Tuberculosis mortality rate in PLHIV per 100,000 population (all ages)	WHO TB burden estimates (Retrieved 28 October 2020)[26] - Estimates generated by WHO	e_mort_tbhiv_100k e_mort_tbhiv_100k_lo e_mort_tbhiv_100k_hi

6.2 *2025 End TB No-New-Vaccine* baseline

To provide conservative estimates on absolute vaccine impact, we simulated an alternative *No-New-Vaccine* baseline assuming scale-up between 2019 and 2025 in order to meet the End TB incidence target in 2025 of a reduction in 50% of the tuberculosis incidence rate in 2015 by 2025 for all ages.[54] To implement this, an additional parameter, p_F (equal to 1 up to and including 2019 and sampled between 0 and 1 afterwards), was included in the model as a contact rate multiplier within the force of infection equation, and as a multiplier on the progression to disease flows. Using the fully fitted parameter sets for each country from the *Status Quo No-New-Vaccine baseline*, we then varied p_F during calibration to hit the country-specific target of a reduction in 50% of the tuberculosis incidence rate in 2015 in 2025.

7. Vaccination

7.1 Vaccine profile

The vaccine profile for an adult/adolescent vaccine and infant vaccine were based on the WHO Preferred Product Characteristics for New Tuberculosis vaccines,[55] and are outlined in Table S7.1 below.

Table S7.1 WHO Preferred Product Characteristics for New Tuberculosis Vaccines

Vaccine	Host infection status at time of vaccination required for efficacy	Effect type	Vaccine efficacy	Duration of protection
Adolescent / Adult	Pre- and post-infection	Prevention of disease	50%	Lifelong
				10 years
Infant	Pre-infection	Prevention of disease	80%	Lifelong
				10 years

Vaccine efficacy was assumed to be the same in both PLHIV and HIV-naïve recipients in countries classified as having a higher tuberculosis burden due to HIV, and in both younger age groups and older adults. The vaccine was assumed to have the same impact on preventing drug-susceptible and drug-resistant tuberculosis as specified in the WHO PPCs,[55] and as we were modelling a prevention of disease vaccine, there was no direct impact on *Mtb* transmission or the force of infection.

7.2 Vaccine delivery scenarios

The infant vaccine was implemented in two scenarios, and, separately, the adolescent/adult vaccine was implemented in three scenarios. The *Basecase* and *Accelerated Scale-up* scenarios included routine neonatal vaccination for the infant vaccine (85% coverage), and routine vaccination of 9-year-olds (80% coverage) with a one-time vaccination campaign for ages ten and older (70% coverage) for the adolescent/adult vaccine. The *Routine Only* scenario (adolescent/adult vaccine only) was introduced through routine 9-year-old vaccination only (i.e., no campaign). Specifics of the infant and adolescent/adult vaccine scenarios are provided in Table S7.5.

7.2.1 Country-specific introduction years

In the *Basecase* and *Routine Only* scenarios, vaccines were introduced in country-specific introduction years between 2028 and 2047. To calculate the specific year of introduction, countries were divided into two general categories: those procuring with support from Gavi, the Vaccine Alliance, and those self-procuring. Determination of country status was based on eligibility information posted on Gavi's website.[56] Countries transitioning from Gavi support are able to benefit from Gavi pricing and incremental financing for a period of 5-10 years. For countries that have already initiated the period of transition by 2019, this window will have largely ended by the time of tuberculosis vaccine availability through Gavi. As such, these countries were categorised as self-procuring

countries. Countries that have not yet commenced transition, including India and Nigeria, were categorised as Gavi supported countries, given the long grace period post-commencement of transition. For more information, please see Gavi, https://www.gavi.org/types-support/sustainability/transition (last accessed 2 November 2022).

Through a consultative process with experts from WHO, Gavi, PATH, PDVAC, CHAI, and industry partners, factors influencing likelihood of being an early or late adopter were identified for both Gavi and self-procuring countries. Identified factors include disease burden, immunization capacity, and early adopter status. Country-specific registration timelines and commercial prioritization were also deemed important determinants of introduction timing for self-procuring countries.

Additional factors for Gavi countries: For countries procuring through Gavi, timelines for introduction are also influenced by Gavi processes. Prior to offering a new vaccine, Gavi requires that products be licensed, included in Gavi's Vaccine Investment Strategy, reviewed by SAGE, recommended in a WHO position paper, WHO prequalified, and approved for procurement by Gavi (Table S7.2). In addition, time for country application processing, contracting, and delivery must be factored. Through consultations, it was determined that a baseline time of roughly two years post licensure would be needed for Gavi processes prior to first country introduction, assuming several steps advance in parallel.

Table S7.2 Timelines for Gavi processes post licensure

	Cumulative additional time (years)		
Activities post licensure	**Low End**	**High End**	**Average**
WHO PQ	0·25	1·00	0·63
SAGE Policy Review & WHO Position Paper	0·25	0·50	0·38
Gavi Decision	0·25	0·50	0·38
National review & Country applications	0·25	0·75	0·50
Contracting & delivery	0·25	0·50	0·38
Years	**1·25**	**3·25**	**2·25**

Weight of criteria, indicators, and scoring: Differential weight was assigned to criteria based on their relative impact on the order of country adoption. This weight varied for self-procuring and Gavi countries (Table S7.3).

Table S7.3 Weight of criteria influencing order of country adoption

Criteria	**Self-procuring countries**	**Gavi countries**
Disease burden	30%	45%
Immunization capacity	15%	30%
Early adopter/leader	15%	25%
Lack of regulatory barriers	15%	NA
Commercial prioritization	25%	NA

The following indicators were used to measure each of the variables identified in Table S7.3.

Table S7.4 Indicators of criteria influencing order of country adoption

Criteria	Indicator
Disease burden	Tuberculosis incidence
Immunization capacity	% receiving 3 doses DPT3 among infants 1 years of age (The percent of infants receiving 3 doses DPT3 is commonly used as a proxy for assessing immunization infrastructure)
Lack of regulatory barriers	Signatories to WHO PQ or SRA collaborative registration scheme Lack of requirements for additional local clinical trial data
Early adopter/leader	Time to policy adoption of universal Xpert MTB/RIF screening for presumed tuberculosis cases Time to adoption of HPV
Commercial prioritization	
Ability to finance vaccines	GDP per capita
Political will to address tuberculosis	Spending per tuberculosis case
Market potential	Population

To standardise across these varied metrics, a point value ranging from 1–5 per criteria was assigned, with a score of 1 correlating with an earlier adopter and score of 5 correlating with a later adopter.

*Continuous variable*s such as disease burden or population were divided into quintiles. Those in the highest quintile were assigned a score of 1, those in the second highest quintile received a score of 2, and so forth. *Categorical variables* such as registration or early adopter status were scored based on whether countries met fixed criteria. For instance, countries that are signatories of WHO PQ or SRA collaborative registration schemes were assigned a score of 1. Those that are not signatories and have requirements for additional clinical trial data in local populations received a score of 5.

Scores were then weighted as reflected in Table S7.3 and aggregated into a composite score to determine countries' relative position in the queue of introductions. Composite scores for each of the 135 countries are provided in the SupplementaryMaterial_CountryTimelines.xls.

Assumptions for the pace of introduction—i.e., how many countries per year would introduce the product and what the scale up curve might look like— was informed with data from pneumococcal vaccine (PCV) scale-up.[57] The percent of countries adopting each year (year 1 to year 12) for PCV was calculated. These annual percentages were then applied to tuberculosis vaccine scale up (based on a total n=135 countries: 78 self-procuring countries and 57 Gavi countries). The first year of tuberculosis vaccine scale up was estimated to be 2028, with Gavi countries following a similar scale up trajectory but delayed by two years due to required Gavi lead time for processing new vaccines (Table S7.2). Because PCV data is only available for 12 years, data was extrapolated for years 13 to 20 of tuberculosis vaccine roll out at a steady state. Country introduction timelines were adjusted—where applicable—to group countries with the same composite score in the same year of adoption. The cumulative number of countries introducing the vaccine by year is shown in Figure S7.1, and the country-specific introduction year for each country is in Table S8.1.

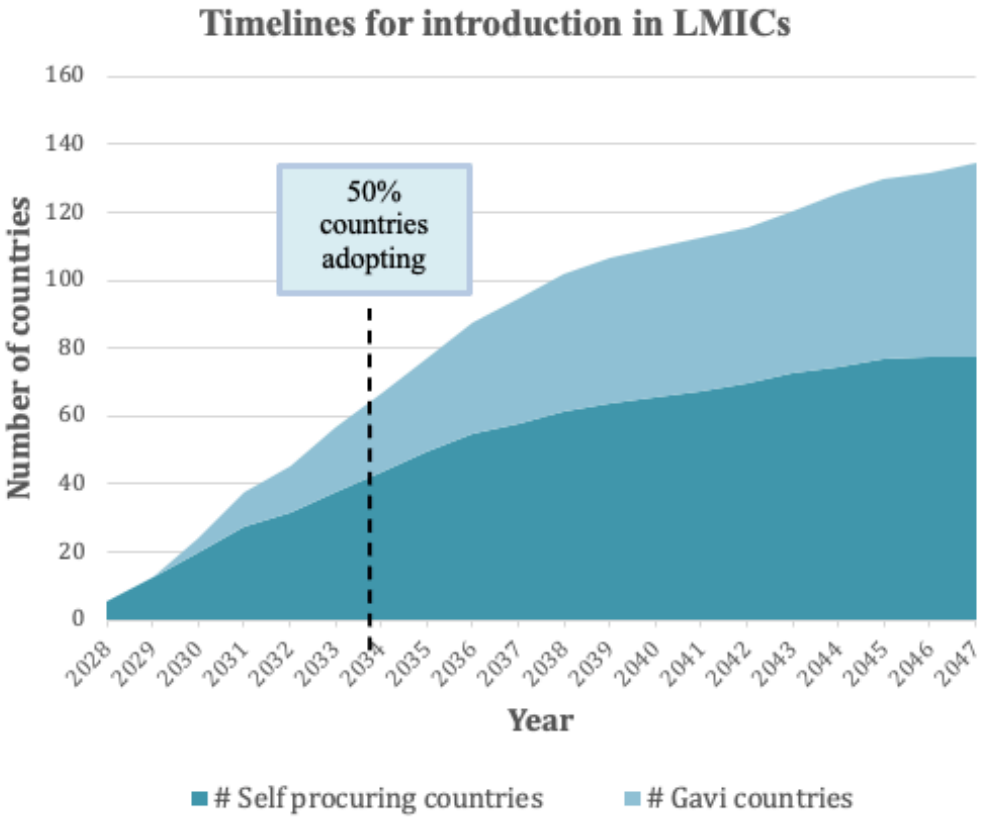

Figure S7.1 Assumed cumulative number of countries introducing a novel vaccine per year

7.2.2 Vaccine coverage targets

For each vaccine implementation scenario, low, medium, and high coverage targets for 5 years post-introduction were evaluated. The medium coverage target for the routine infant vaccination was 85%, based on the 2019 DTP3 (diphtheria, tetanus toxoid, and pertussis) average coverage level according to the WHO and UNICEF estimates of national immunisation coverage, with 10% uncertainty (low coverage = 75%, high coverage = 95%).[57] Routine adolescent vaccination assumed a medium coverage target of 80% aligning with HPV coverage in South Africa combined with aggregated secondary school enrolment in China and India as assumed in Harris 2020,[58] also with 10% uncertainty targets (low coverage = 70%, high coverage = 90%). The medium coverage target for the adolescent/adult campaign was 70% aligning with the lower bound of the MenAfriVac campaigns in sub-Saharan Africa as assumed in Harris 2020,[58] with a wider uncertainty of 20% (low coverage = 50%, high coverage = 90%). In the *Accelerated Scale-up* implementation, the 5-year coverage targets are achieved instantly in year 1, while in the *Basecase* and *Routine Only* implementations, the scale-up to coverage occurs linearly over 5 years.

Table S7.5 Vaccine scenarios for the infant and adolescent/adult vaccines

Characteristics	Infant Vaccine Scenarios		Adolescent/Adult Vaccine Scenarios		
	Basecase	***Accelerated Scale-up***	***Basecase***	***Accelerated Scale-up***	***Routine Only***
Ages Targeted	*Neonatal:* Routine	*Neonatal:* Routine	*Age 9:* Routine *Ages 10+:* One-time vaccination campaign over 5 years	*Age 9:* Routine *Ages 10+:* One-time vaccination campaign in 2025	*Age 9:* Routine
Introduction Year	Country-specific	2025	Country-specific	2025	Country-specific
Vaccine Rollout Trend	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage
Target Coverage *(Low/Med/High)*	75% / 85% / 95%		Age 9: 70% / 80% / 90% Ages 10+: 50% / 70% / 90%		

7.3 Vaccine implementation

7.3.1 Vaccine structure

To simplify accounting for the number of vaccinees and vaccinations in the model, we included vaccines through an additional "vaccine structure" with three compartments (Figure S7.2) with the influences of vaccines on tuberculosis natural history parameters occurring separately in the natural history structure (Figure S7.3). Each compartment in the vaccine structure is replicated for all tuberculosis natural history compartments, access-to-care strata, HIV statuses, and ages.

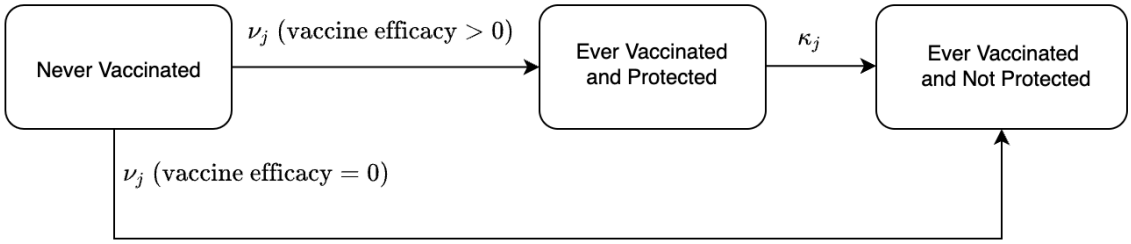

Figure S7.2 Vaccine structure

Before vaccination, all individuals in the model begin in the *Never Vaccinated* compartment, with no vaccine protection. Upon vaccination, individuals either transition to the *Ever Vaccinated and Protected* compartment (with vaccine protection) or *Ever Vaccinated and Not Protected* compartment (with no vaccine protection), depending on vaccine specific host infection status at time of vaccination required for vaccine to be efficacious and their infection status at the time of vaccination, summarised in Table S7.6.

In this work, we modelled the infant vaccine as a pre-infection (PRI) vaccine, meaning the individual must be uninfected at the time of vaccination for the vaccine to be efficacious. We modelled the adolescent/adult vaccine as a pre- and post-infection (PPI) vaccine, which means that it will be efficacious in any infection status at time of vaccination aside from active disease. We assumed that the effect of disease on the immune response is likely to be substantially larger than any additional benefit from the vaccine, and therefore would not be efficacious in those compartments. For example, the Phase 2b M72/AS01$_E$ trial saw a small number of cases in each arm within the first 6 months after ruling out those who were XPERT positive on the day they were tested. Assuming those cases were individuals who were subclinical but not XPERT positive on the day they were tested, the vaccine had no impact on their disease progression.[59]

The arrow directly from *Never Vaccinated* to *Ever Vaccinated and Not Protected* was included to account for individuals who may be accidentally administered a vaccine which would not be efficacious (i.e., vaccine efficacy is zero) given their infection status at the time of vaccination. As individuals with subclinical disease present with no symptoms, it is possible that they may be accidentally vaccinated, as seen in the Phase 2b M72/AS01$_E$ trial. Similarly, with a PRI vaccine, if no pre-vaccination testing is available, it is possible that individuals who are not uninfected may be vaccinated. By including the flow directly to *Ever Vaccinated and Not Protected*, we could easily identify and track these individuals, and ensure they received no protection from the vaccine in the model.

Table S7.6 Transitions within the vaccine structure following vaccination based on natural history state and host infection status at time of vaccination required for vaccine to be efficacious

	Host infection status at the time of vaccination required for vaccine to be efficacious	
Natural History State (Infection Status) at time of vaccination	**Pre-infection vaccine** (i.e., the infant vaccine)	**Pre- and post-infection vaccine** (i.e., the adolescent/adult vaccine)
Uninfected – Naïve	*Ever Vaccinated and Protected*	*Ever Vaccinated and Protected*
Uninfected – Cleared	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Infection – Fast	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Infection – Slow	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Subclinical Disease	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Not Protected*
Clinical Disease	*NA*	*NA*
On-treatment	*NA*	*NA*
Resolved	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*

Waning, or loss of vaccine protection, moved individuals from the *Ever Vaccinated and Protected* compartment to the *Ever Vaccinated and Not Protected* compartment. We assumed duration of protection was 10 years on average, in addition to a sensitivity analysis with lifelong duration of protection. The shape of waning immunity was modelled as an exponential distribution, based on similar shapes for waning vaccine immunity of BCG[60] and other vaccines.[61,62]

7.3.1 Vaccine implementation in the tuberculosis natural history model

Vaccines are incorporated in the tuberculosis natural history structure as indicated with the orange boxes in Figure S7.3 by reducing the rate of progression to disease parameters into the subclinical disease compartment from the infection-fast, infection-slow, and resolved compartments by (1-p_V), where p_V is the vaccine efficacy. Vaccine efficacy was modelled as "degree", also known as "leaky". Degree vaccines assume that everyone who has been vaccinated receives some protection from the vaccine equivalent to the value of the vaccine efficacy.

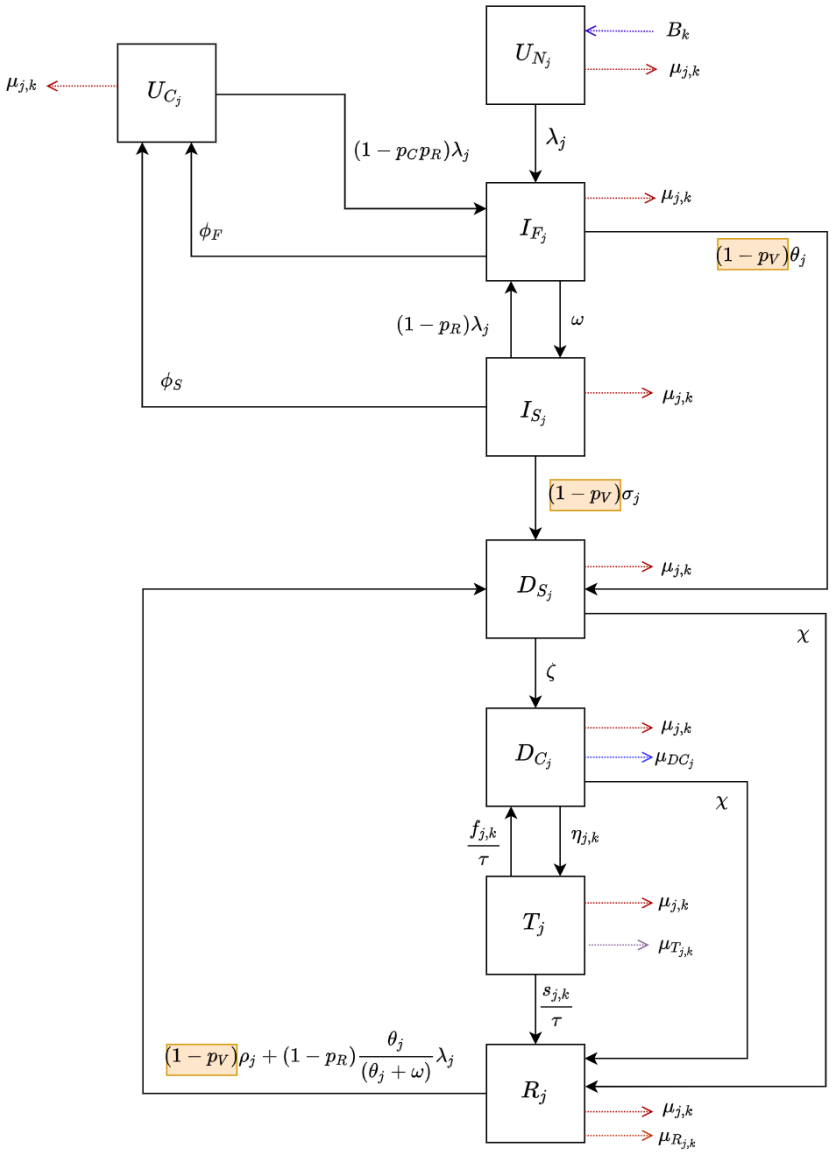

Figure S7.3 Tuberculosis natural history model incorporating vaccination

Abbreviations: D_C = Clinical Disease; D_S = Subclinical Disease; I_F = Infection-Fast; I_S = Infection-Slow; R = Resolved; T = On-Treatment; U_C = Uninfected-Cleared; U_N = Uninfected-Naive.

Subscript *j* represents parameters that vary by age, and subscript *k* represents parameters that vary over time.

8. Model outcomes

8.1 Epidemiological impact measures

The following measures were calculated for each vaccine scenario as the median and 95% uncertainty range

- Percent incidence rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Incidence rate per 100,000 population in 2035 for each vaccine scenario
- Percent mortality rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Cumulative cases averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative deaths averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative treatments averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years

8.2 Groupings for reporting model outcomes

The epidemiological impact measures were calculated and reported for the calibrated countries by WHO region, World Bank Income Group, for tuberculosis burden, and overall. Countries are divided into the six WHO regions,[63] [African region (AFR), region of the Americas (AMR), Eastern-Mediterranean region (EMR), South-East Asian region (SEAR), and Western-Pacific region (WPR)], three income groups based on the 2021 World Bank Income Groups[51] for low- and middle-income countries [low-income countries (LIC), lower-middle-income countries (LMIC) or upper-middle-income countries (UMIC)], and by whether they were or were not included on the WHO high TB burden list[64] (*High TB Burden* vs *Other* respectively). Groups for each of the LMICs are in Table S8.1.

Table S8.1 Country-specific introduction year, WHO region, 2021 World Bank income group, and WHO TB burden level for LMICs

Country	Gavi/Self Procuring	Introduction Year	WHO Region	2021 World Bank Income Group	WHO High TB Burden
Afghanistan	Gavi	2031	EMR	LIC	Other
Albania	Self-Procuring	2035	EUR	UMIC	Other
Algeria	Self-Procuring	2032	AFR	LMIC	Other
American Samoa	Self-Procuring	2044	WPR	UMIC	Other
Angola	Self-Procuring	2032	AFR	LMIC	High TB Burden
Argentina	Self-Procuring	2031	AMR	UMIC	Other
Armenia	Self-Procuring	2033	EUR	UMIC	Other
Azerbaijan	Self-Procuring	2028	EUR	UMIC	Other
Bangladesh	Gavi	2035	SEAR	LMIC	High TB Burden
Belarus	Self-Procuring	2028	EUR	UMIC	Other
Belize	Self-Procuring	2034	AMR	UMIC	Other
Benin	Gavi	2037	AFR	LMIC	Other
Bhutan	Self-Procuring	2034	SEAR	LMIC	Other
Bolivia	Self-Procuring	2037	AMR	LMIC	Other
Bosnia and Herzegovina	Self-Procuring	2039	EUR	UMIC	Other
Botswana	Self-Procuring	2028	AFR	UMIC	Other
Brazil	Self-Procuring	2030	AMR	UMIC	High TB Burden
Bulgaria	Self-Procuring	2029	EUR	UMIC	Other
Burkina Faso	Gavi	2039	AFR	LIC	Other
Burundi	Gavi	2044	AFR	LIC	Other
Cabo Verde	Self-Procuring	2043	AFR	LMIC	Other
Cambodia	Gavi	2036	WPR	LMIC	Other
Cameroon	Gavi	2031	AFR	LMIC	Other
Central African Republic	Gavi	2033	AFR	LIC	High TB Burden
Chad	Gavi	2033	AFR	LIC	Other
China	Self-Procuring	2029	WPR	UMIC	High TB Burden
Colombia	Self-Procuring	2030	AMR	UMIC	Other
Comoros	Gavi	2046	AFR	LMIC	Other
Congo	Gavi	2035	AFR	LMIC	High TB Burden
Costa Rica	Self-Procuring	2033	AMR	UMIC	Other
Côte d'Ivoire	Gavi	2034	AFR	LMIC	Other
Cuba	Self-Procuring	2035	AMR	UMIC	Other
Democratic People's Republic of Korea	Gavi	2035	SEAR	LIC	High TB Burden

Democratic Republic of the Congo	Gavi	2030	AFR	LIC	High TB Burden
Djibouti	Gavi	2043	EMR	LMIC	Other
Dominica	Self-Procuring	2031	AMR	UMIC	Other
Dominican Republic	Self-Procuring	2031	AMR	UMIC	Other
Ecuador	Self-Procuring	2033	AMR	UMIC	Other
Egypt	Self-Procuring	2033	EMR	LMIC	Other
El Salvador	Self-Procuring	2039	AMR	LMIC	Other
Equatorial Guinea	Self-Procuring	2042	AFR	UMIC	Other
Eritrea	Gavi	2047	AFR	LIC	Other
Ethiopia	Gavi	2030	AFR	LIC	High TB Burden
Fiji	Self-Procuring	2031	WPR	UMIC	Other
Gabon	Self-Procuring	2038	AFR	UMIC	High TB Burden
Gambia	Gavi	2039	AFR	LIC	Other
Georgia	Self-Procuring	2029	EUR	UMIC	Other
Ghana	Gavi	2040	AFR	LMIC	Other
Grenada	Self-Procuring	2035	AMR	UMIC	Other
Guatemala	Self-Procuring	2036	AMR	UMIC	Other
Guinea	Gavi	2033	AFR	LIC	Other
Guinea-Bissau	Gavi	2043	AFR	LIC	Other
Guyana	Self-Procuring	2030	AMR	UMIC	Other
Haiti	Gavi	2033	AMR	LIC	Other
Honduras	Self-Procuring	2037	AMR	LMIC	Other
India	Gavi	2033	SEAR	LMIC	High TB Burden
Indonesia	Self-Procuring	2034	SEAR	LMIC	High TB Burden
Iran	Self-Procuring	2031	EMR	LMIC	Other
Iraq	Self-Procuring	2033	EMR	UMIC	Other
Jamaica	Self-Procuring	2036	AMR	UMIC	Other
Jordan	Self-Procuring	2037	EMR	UMIC	Other
Kazakhstan	Self-Procuring	2028	EUR	UMIC	Other
Kenya	Gavi	2032	AFR	LMIC	High TB Burden
Kiribati	Self-Procuring	2041	WPR	LMIC	Other
Kosovo	Self-Procuring	2045	EUR	UMIC	Other
Kyrgyz Republic	Gavi	2044	EUR	LMIC	Other
Lao People's Democratic Republic	Gavi	2035	WPR	LMIC	Other
Lebanon	Self-Procuring	2038	EMR	UMIC	Other
Lesotho	Gavi	2039	AFR	LMIC	High TB Burden
Liberia	Gavi	2037	AFR	LIC	High TB Burden
Libya	Self-Procuring	2035	EMR	UMIC	Other

Madagascar	Gavi	2031	AFR	LIC	Other
Malawi	Gavi	2038	AFR	LIC	Other
Malaysia	Self-Procuring	2028	WPR	UMIC	Other
Maldives	Self-Procuring	2034	SEAR	UMIC	Other
Mali	Gavi	2037	AFR	LIC	Other
Marshall Islands	Self-Procuring	2041	WPR	UMIC	Other
Mauritania	Gavi	2042	AFR	LMIC	Other
Mexico	Self-Procuring	2029	AMR	UMIC	Other
Micronesia	Self-Procuring	2045	WPR	LMIC	Other
Mongolia	Self-Procuring	2032	WPR	LMIC	High TB Burden
Montenegro	Self-Procuring	2044	EUR	UMIC	Other
Morocco	Self-Procuring	2029	EMR	LMIC	Other
Mozambique	Gavi	2032	AFR	LIC	High TB Burden
Myanmar	Gavi	2031	SEAR	LMIC	High TB Burden
Namibia	Self-Procuring	2030	AFR	UMIC	High TB Burden
Nepal	Gavi	2036	SEAR	LMIC	Other
Nicaragua	Gavi	2047	AMR	LMIC	Other
Niger	Gavi	2036	AFR	LIC	Other
Nigeria	Gavi	2030	AFR	LMIC	High TB Burden
North Macedonia	Self-Procuring	2038	EUR	UMIC	Other
Pakistan	Gavi	2031	EMR	LMIC	High TB Burden
Papua New Guinea	Gavi	2032	WPR	LMIC	High TB Burden
Paraguay	Self-Procuring	2035	AMR	UMIC	Other
Peru	Self-Procuring	2029	AMR	UMIC	Other
Philippines	Self-Procuring	2030	WPR	LMIC	High TB Burden
Republic of Moldova	Self-Procuring	2034	EUR	UMIC	Other
Russian Federation	Self-Procuring	2030	EUR	UMIC	Other
Rwanda	Gavi	2045	AFR	LIC	Other
Samoa	Self-Procuring	2046	WPR	UMIC	Other
Sao Tome and Principe	Gavi	2044	AFR	LMIC	Other
Senegal	Gavi	2038	AFR	LMIC	Other
Serbia	Self-Procuring	2036	EUR	UMIC	Other
Sierra Leone	Gavi	2037	AFR	LIC	High TB Burden
Solomon Islands	Gavi	2047	WPR	LMIC	Other
Somalia	Gavi	2030	EMR	LIC	Other
South Africa	Self-Procuring	2029	AFR	UMIC	High TB Burden
South Sudan	Gavi	2034	AFR	LIC	Other
Sri Lanka	Self-Procuring	2028	SEAR	LMIC	Other

St. Lucia	Self-Procuring	2031	AMR	UMIC	Other
St. Vincent and the Grenadines	Self-Procuring	2032	AMR	UMIC	Other
Sudan	Gavi	2036	EMR	LIC	Other
Suriname	Self-Procuring	2040	AMR	UMIC	Other
Swaziland	Self-Procuring	2036	AFR	LMIC	Other
Syrian Arab Republic	Gavi	2036	EMR	LIC	Other
Tajikistan	Gavi	2045	EUR	LMIC	Other
Thailand	Self-Procuring	2031	SEAR	UMIC	High TB Burden
Timor-Leste	Self-Procuring	2031	SEAR	LMIC	Other
Togo	Gavi	2041	AFR	LIC	Other
Tonga	Self-Procuring	2040	WPR	UMIC	Other
Tunisia	Self-Procuring	2036	EMR	LMIC	Other
Turkey	Self-Procuring	2030	EUR	UMIC	Other
Turkmenistan	Self-Procuring	2034	EUR	UMIC	Other
Tuvalu	Self-Procuring	2043	WPR	UMIC	Other
Uganda	Gavi	2034	AFR	LIC	High TB Burden
Ukraine	Self-Procuring	2033	EUR	LMIC	Other
United Republic of Tanzania	Gavi	2031	AFR	LMIC	High TB Burden
Uzbekistan	Gavi	2038	EUR	LMIC	Other
Vanuatu	Self-Procuring	2042	WPR	LMIC	Other
Venezuela	Self-Procuring	2035	AMR	UMIC	Other
Vietnam	Self-Procuring	2038	WPR	LMIC	High TB Burden
West Bank and Gaza	Self-Procuring	2043	EMR	LMIC	Other
Yemen	Gavi	2036	EMR	LIC	Other
Zambia	Gavi	2034	AFR	LIC	High TB Burden
Zimbabwe	Gavi	2032	AFR	LMIC	Other

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

8.2 Calculating uncertainty

To appropriately represent the global uncertainty and remove inter-country variability in parameters that are likely to be the same across countries when generating impact estimates (e.g., those governing the underlying biology of *Mtb*), we used the following process:

1. We obtained 1000 fitted parameter sets for each country by thinning the total number of fitted parameter sets per country to 1000.

2. Within each country, the 1000 parameter sets were ordered and ranked from smallest to largest by 2019 tuberculosis incidence rate.

3. The parameter sets for all countries were then pairwise grouped on their rank value. For example, the rank 1 parameter sets were grouped together for all countries, the rank 2 parameter sets were grouped together for all countries, etc.

4. Within each pairwise rank group, we calculated the measure of interest by combining all information. For example, to calculate the incidence rate, we summed the number of cases from all countries with rank 1 and divided by the sum of the population for all countries with rank 1. This was continued for all ranks until there were 1000 estimates of the measure of interest.

5. We combined the 1000 estimates for the measure of interest, generated the distribution and calculated all country and group-level estimates.

SUPPLEMENTAL RESULTS:

9. Model Calibration

9.1 LMIC calibration

Of the 135 LMICs, there were 20 countries which were excluded from calibration due to missing crucial data for calibration (as described in Table S5.3). The 10 countries that did not calibrate out of the 115 worth running were: Algeria, Bosnia and Herzegovina, Cabo Verde, Guinea-Bissau, Guyana, Jamaica, North Macedonia, St. Vincent and the Grenadines, Tonga, and Turkmenistan. Reasons for why the ten countries were unable to be calibrated have been thoroughly explored by our colleagues Scarponi et al, where the authors provided strong evidence that the models were misspecified and could not be calibrated to the target ranges.[65] Of the 105 calibrated countries, 21 countries were classified as having a higher tuberculosis burden due to HIV.

9.2 WHO Region and 2021 World Bank Income Group for Calibrated LMICs

Table S9.1 WHO regions and 2021 World bank income groups for the 105 calibrated LMICs

WHO Region	World Bank Income Level 2019			*Total*
	LIC	LMIC	UMIC	
AFR	20	14	5	39
AMR	0	4	13	17
EMR	4	5	3	12
EUR	0	4	12	16
SEAR	0	8	2	10
WPR	0	8	3	11
Total	24	43	38	105

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

9.3 *Status Quo No-New-Vaccine* baseline calibration target values

Table S9.2 presents the common country-specific calibration targets for the 105 calibrated countries, and Table S9.3 highlights the HIV specific calibration targets for the 21 countries classified as having a higher tuberculosis burden due to HIV. Two additional calibration targets were assumed consistent across countries: the global fraction of subclinical tuberculosis among active tuberculosis in 2019 [50·4% (36·1%–79·7%)],[1] and the risk ratio of active tuberculosis in the high-access-to-care group relative to low-access-to-care in 2019 [0·674 (0·575, 0·801)].[12–22]

Table S9.2 Values for the seven country specific calibration targets for all calibrated countries in 2019. Point values represent the mean with 95% confidence intervals in brackets

Country	Tuberculosis Incidence Rate[23,53] (per 100,000 population per year)			Tuberculosis Notification Rate[23,27] (per 100,000 population per year)			Tuberculosis Mortality Rate[23,26] (per 100,000 population per year)
	Ages 0–14	Ages 15+	Ages 0–99	Ages 0–14	Ages 15+	Ages 0–99	Ages 0–99
Afghanistan	92·8 (48·9–136·2)	260·5 (137·1–383·8)	189·3 (115·7–262·9)	71·0 (56·8–85·2)	187·2 (149·7–224·6)	137·8 (110·3–165·4)	26 (16–39)
Albania	2·6 (2·2–3·0)	19·3 (16·4–22·3)	16·3 (13·9–18·7)	2·2 (1·8–2·6)	16·9 (13·5–20·2)	14·3 (11·4–17·2)	0·3 (0·2–0·5)
Angola	107·8 (58·6–155·0)	565·1 (312·0–818·2)	351·9 (213·7–487·0)	59·4 (47·5–71·3)	384·3 (307·5–461·2)	232·8 (186·3–279·4)	62 (39–89)
Argentina	9·1 (7·9–10·9)	35·5 (29·6–41·5)	29·0 (24·6–33·5)	8·1 (6·5–9·8)	31·2 (24·9–37·4)	25·6 (20·4–30·7)	1·6 (1·4–1·8)
Armenia	7·7 (5·7–9·8)	31·1 (23·0–39·3)	26·4 (19·6–32·8)	6·2 (4·9–7·4)	24·9 (19·9–29·9)	21·0 (16·8–25·2)	0·6 (0·4–0·8)
Azerbaijan	19·5 (14·0–24·6)	72·8 (53·3–92·3)	59·7 (44·8–74·6)	7·6 (6·1–9·1)	44·6 (35·7–53·6)	48·0 (38·4–57·6)	6·1 (5·6–6·6)
Bangladesh	74·4 (49·6–96·9)	276·4 (187·9–364·9)	221·4 (156·4–285·8)	27·8 (22·2–33·3)	235·3 (188·3–282·4)	178·8 (143·1–214·6)	24 (15–35)
Belarus	4·3 (3·2–5·3)	34·4 (25·5–43·4)	29·6 (22·2–36·0)	0·5 (0·4–0·6)	28·0 (22·4–33·6)	23·3 (18·7–28·0)	3·3 (3·1–3·5)
Benin	11·4 (6·6–16·3)	86·5 (49·9–124·6)	55·1 (33·9–77·1)	4·6 (3·7–5·6)	59·2 (47·3–71·0)	36·1 (28·9–43·4)	11 (7·2–15)
Bhutan	32·1 (23·8–40·9)	210·6 (154·5–263·3)	170·4 (123·2–209·7)	14·5 (11·6–17·4)	171·5 (137·2–205·8)	131·7 (105·4–158·0)	18 (12–26)

Bolivia	25·8 (15·3–36·9)	137·7 (82·6–200·3)	104·2 (65·1–147·7)	6·9 (5·6–8·3)	90·3 (72·3–108·4)	64·8 (51·8–77·8)	11 (8·1–15)
Botswana	74·6 (55·3–93·9)	340·8 (249·0–432·5)	251·8 (191·0–312·5)	29·8 (23·9–35·8)	187·2 (149·8–224·7)	134·1 (107·3–160·9)	78 (61–96)
Brazil	7·0 (5·9–8·1)	55·8 (47·4–64·2)	45·5 (38·9–52·1)	6·0 (4·8–7·3)	48·5 (38·8–58·2)	39·6 (31·7–47·5)	3·2 (2·9–3·4)
Bulgaria	8·8 (6·4–10·7)	21·8 (16·6–28·5)	20·0 (15·7–25·7)	5·3 (4·2–6·3)	20·7 (16·5–24·8)	18·4 (14·7–22·1)	1·6 (1·6–1·7)
Burkina Faso	9·8 (5·6–14·3)	77·4 (44·5–106·7)	47·2 (28·5–64·0)	1·5 (1·2–1·8)	42·0 (33·6–50·4)	24·2 (19·4–29·0)	11 (7·2–16)
Burundi	24·8 (13·8–34·4)	174·7 (100·1–254·1)	104·1 (65·0–147·4)	6·2 (5·0–7·4)	102·1 (81·7–122·5)	58·6 (46·9–70·3)	24 (15–35)
Cambodia	68·3 (39·0–97·5)	387·3 (220·1–545·8)	285·1 (175·9–400·3)	36·1 (28·9–43·3)	247·0 (197·6–296·4)	181·4 (145·1–217·7)	20 (13–28)
Cameroon	43·8 (24·6–62·0)	274·9 (154·2–395·6)	177·8 (108·2–247·3)	11·4 (9·2–13·7)	154·6 (123·7–185·6)	94·0 (75·2–112·8)	48 (34–65)
Central African Republic	182·3 (100·8–263·9)	826·7 (450·9–1202·5)	547·9 (337·2–758·7)	79·1 (63·3–94·9)	391·2 (313·0–469·5)	253·9 (203·1–304·6)	158 (111–215)
Chad	36·2 (20·1–52·2)	235·8 (129·7–342·0)	144·2 (87·8–194·4)	14·0 (11·2–16·8)	148·5 (118·8–178·2)	85·5 (68·4–102·6)	31 (21–42)
China	14·9 (12·5–16·8)	67·5 (57·4–77·6)	58·1 (49·7–66·5)	2·6 (2·1–3·1)	61·2 (49·0–73·5)	50·8 (40·6–61·0)	2·3 (2·1–2·6)
Colombia	7·2 (5·4–8·8)	43·6 (33·4–53·9)	35·8 (25·8–43·7)	3·5 (2·8–4·2)	35·7 (28·5–42·8)	28·4 (22·7–34·1)	3·4 (3–3·9)
Costa Rica	1·7 (1·2–2·1)	12·3 (9·0–15·6)	10·1 (7·5–12·5)	1·3 (1·1–1·6)	9·8 (7·9–11·8)	8·0 (6·4–9·6)	0·8 (0·7–0·9)
Cote d'Ivoire	30·8 (17·7–43·8)	213·5 (120·1–306·9)	136·1 (81·7–190·5)	9·5 (7·6–11·4)	134·7 (107·8–161·6)	82·5 (66·0–99·0)	30 (20–41)
Cuba	0·4 (0·3–0·5)	7·6 (6·4–8·7)	6·4 (5·5–7·4)	0·3 (0·2–0·4)	6·6 (5·3–7·9)	5·6 (4·5–6·7)	0·4 (0·3–0·5)
Dominican Republic	6·7 (5·0–8·4)	55·4 (41·2–69·6)	41·9 (31·7–52·1)	2·7 (2·2–3·2)	45·2 (36·2–54·3)	33·4 (26·8–40·1)	4 (2·4–6)
Ecuador	8·7 (6·4–11·0)	59·7 (43·8–75·6)	45·5 (34·5–57·0)	3·9 (3·1–4·7)	49·1 (39·2–58·9)	36·5 (29·2–43·8)	4·6 (3·9–5·3)
Egypt	2·6 (2·3–2·9)	16·6 (14·2–18·1)	12·0 (10·0–12·9)	1·4 (1·1–1·7)	11·4 (9·1–13·7)	8·0 (6·4–9·6)	0·5 (0·4–0·5)

El Salvador	18·5 (13·3–23·7)	72·0 (53·0–93·2)	58·9 (43·4–72·8)	7·8 (6·2–9·3)	53·7 (43·0–64·5)	46·6 (37·3–56·0)	1·7 (1·4–2)
Equatorial Guinea	45·9 (39·9–53·9)	257·3 (222·3–292·4)	184·4 (154·9–206·5)	19·2 (15·3–23·0)	169·0 (135·2–202·8)	114·3 (91·4–137·2)	39 (31–48)
Eritrea	29·6 (7·6–51·6)	127·3 (32·8–220·3)	85·8 (31·5–143·0)	15·8 (12·7–19·0)	78·2 (62·6–93·9)	52·3 (41·8–62·7)	17 (8–29)
Ethiopia	37·6 (24·3–53·1)	207·9 (133·1–282·6)	140·1 (94·6–184·7)	24·4 (19·5–29·3)	149·6 (119·7–179·5)	99·1 (79·3–118·9)	22 (14–30)
Fiji	57·5 (38·4–76·7)	69·9 (47·7–92·2)	66·3 (49·4–83·2)	47·2 (37·7–56·6)	55·5 (44·4–66·6)	53·0 (42·4–63·6)	5·3 (4·9–5·7)
Gabon	160·9 (92·8–235·2)	732·7 (410·3–1025·8)	506·3 (317·6–736·5)	45·4 (36·3–54·5)	368·7 (295·0–442·4)	248·5 (198·8–298·2)	110 (66–165)
Gambia	37·6 (26·1–50·2)	251·6 (175·3–327·8)	157·6 (115·0–200·2)	12·5 (10·0–15·1)	189·8 (151·8–227·7)	111·6 (89·2–133·9)	27 (20–35)
Georgia	20·0 (16·2–23·7)	87·6 (72·0–103·2)	75·1 (62·6–87·6)	9·0 (7·2–10·8)	65·6 (52·5–78·7)	54·3 (43·4–65·1)	4·2 (3·8–4·6)
Ghana	55·4 (16·7–96·8)	194·2 (57·7–335·9)	144·7 (55·9–230·1)	7·2 (5·8–8·7)	72·8 (58·2–87·3)	48·3 (38·6–58·0)	50 (29–77)
Guatemala	10·9 (7·9–14·1)	34·4 (24·1–43·9)	26·2 (19·9–33·0)	7·4 (5·9–8·9)	28·0 (22·4–33·6)	21·1 (16·9–25·4)	2·4 (2·1–2·6)
Guinea	37·8 (21·6–54·1)	276·9 (166·2–401·5)	172·3 (109·6–242·7)	20·9 (16·7–25·0)	210·9 (168·7–253·1)	128·3 (102·7–154·0)	29 (20–39)
Honduras	4·3 (3·2–5·3)	43·2 (31·3–55·1)	30·8 (23·6–39·0)	1·6 (1·3–1·9)	35·4 (28·3–42·5)	24·9 (19·9–29·8)	5·0 (4·2–5·8)
India	91·6 (55·8–127·6)	229·4 (139·6–320·1)	193·2 (125·9–259·8)	40·0 (32·0–48·0)	201·1 (160·9–241·4)	158·2 (126·6–189·9)	33 (30–35)
Indonesia	200·2 (179·0–221·3)	352·1 (314·5–389·6)	312·2 (284·2–340·3)	98·8 (79·0–118·6)	245·5 (196·4–294·6)	207·7 (166·1–249·2)	36 (33–38)
Iran	3·0 (2·3–3·9)	16·0 (11·8–20·8)	13·3 (9·6–15·7)	1·6 (1·2–1·9)	13·1 (10·5–15·8)	10·3 (8·2–12·3)	1·2 (1·1–1·2)
Iraq	12·7 (10·7–14·7)	57·5 (49·3–65·7)	40·7 (35·6–45·8)	3·8 (3·0–4·6)	24·8 (19·9–29·8)	16·8 (13·5–20·2)	2·1 (1·9–2·3)
Jordan	1·1 (0·8–1·4)	7·7 (5·7–9·8)	5·5 (4·2–6·9)	0·9 (0·7–1·0)	6·2 (5·0–7·5)	4·4 (3·5–5·3)	0·1 (0·1–0·2)
Kazakhstan	6·7 (3·9–9·3)	91·0 (56·1–128·9)	70·1 (41·5–97·0)	6·6 (5·2–7·9)	92·1 (73·7–110·5)	67·4 (53·9–80·9)	1·9 (1·4–2·4)

Kenya	87·4 (43·2–126·2)	384·8 (193·9–572·4)	266·3 (150·3–382·3)	40·3 (32·2–48·3)	237·9 (190·3–285·5)	160·4 (128·3–192·5)	62 (42–85)
Kyrgyz Republic	16·8 (14·4–19·7)	154·7 (131·6–180·1)	110·7 (93·5–126·2)	14·6 (11·7–17·6)	134·7 (107·8–161·6)	95·7 (76·5–114·8)	5·9 (5·4–6·3)
Lao PDR	47·5 (25·9–64·8)	206·0 (119·5–288·5)	153·4 (94·8–209·2)	4·1 (3·3–4·9)	138·5 (110·8–166·2)	95·1 (76·1–114·1)	30 (19–44)
Lesotho	137·7 (75·4–202·9)	905·8 (494·7–1323·8)	658·7 (376·4–941·1)	41·2 (32·9–49·4)	472·0 (377·6–566·4)	332·1 (265·7–398·6)	224 (153–309)
Liberia	129·2 (69·6–188·9)	444·4 (232·5–615·3)	303·8 (188·4–425·3)	70·2 (56·2–84·3)	234·8 (187·8–281·7)	167·9 (134·3–201·4)	74 (49–103)
Libya	15·8 (8·4–23·1)	75·9 (41·0–110·8)	59·0 (33·9–84·1)	5·4 (4·3–6·5)	43·2 (34·6–51·8)	32·7 (26·1–39·2)	12 (7·1–19)
Madagascar	69·8 (38·6–101·0)	342·0 (192·8–497·4)	233·6 (140·9–322·6)	28 (22·4–33·6)	212·4 (169·9–254·9)	138·0 (110·4–165·6)	46 (27–68)
Malawi	48·2 (18·5–77·8)	218·4 (85·5–360·8)	144·9 (69·8–225·5)	18·9 (15·1–22·6)	146·0 (116·8–175·2)	90·7 (72·6–108·9)	37 (24–53)
Malaysia	12·9 (11·0–14·5)	114·9 (98·4–135·4)	90·8 (78·2–106·4)	11·2 (9·0–13·5)	101·4 (81·1–121·7)	80·0 (64·0–96·0)	4·8 (4·3–5·3)
Maldives	3·8 (2·8–4·7)	44·7 (32·9–56·4)	35·8 (26·4–45·2)	2·8 (2·3–3·4)	35·5 (28·4–42·6)	29·0 (23·2–34·8)	2·1 (1·9–2·3)
Mali	9·8 (5·7–14·0)	90·7 (53·1–125·5)	50·9 (32·6–71·2)	3·7 (3·0–4·4)	63·4 (50·7–76·1)	35·2 (28·1–42·2)	9·1 (6–13)
Mauritania	22·2 (12·7–31·6)	132·3 (77·2–191·1)	88·4 (55·2–123·7)	8·6 (6·9–10·4)	85·4 (68·3–102·5)	55·1 (44·1–66·1)	17 (10–25)
Mexico	3·9 (3·0–5·1)	29·7 (22·3–38·2)	23·5 (17·2–29·0)	2·0 (1·6–2·4)	24·5 (19·6–29·4)	18·6 (14·9–22·3)	2 (1·9–2·2)
Mongolia	201·3 (70·5–332·2)	537·7 (183·7–851·3)	434·1 (186–682·1)	40·9 (32·7–49·0)	173·4 (138·8–208·1)	132·6 (106·1–159·1)	10 (9·2–12)
Montenegro	0·9 (0·7–1·1)	17·7 (15·0–19·5)	14·6 (12·4–17·5)	0·9 (0·7–1·1)	15·4 (12·3–18·4)	12·7 (10·2–15·3)	0·2 (0·2–0·2)
Morocco	24·4 (20·3–28·5)	123·9 (105·1–142·7)	96·0 (82·3–112·4)	21·2 (17·0–25·5)	107·6 (86·1–129·2)	84·3 (67·5–101·2)	8·1 (5–12)
Mozambique	259·8 (111·3–400·8)	444·0 (189·4–692·6)	362·2 (207·5–517·0)	95·4 (76·3–114·5)	492·3 (393·9–590·8)	316·2 (253·0–379·5)	37 (25–52)
Myanmar	271·3 (142·8–392·7)	339·7 (182·3–497·0)	322·0 (199·8–442·2)	169·2 (135·4–203·1)	276·7 (221·3–332·0)	248·9 (199·1–298·6)	41 (27–59)

Namibia	152·1 (99·9–206·4)	698·9 (444·8–889·5)	481·1 (336·7–641·4)	79·6 (63·7–95·5)	449·1 (359·3–538·9)	312·7 (250·2–375·3)	107 (80–137)
Nepal	60·3 (30·7–89·9)	312·6 (158·8–466·4)	237·7 (129·3–346·0)	20·4 (16·3–24·5)	147·2 (117·8–176·7)	110·1 (88·1–132·1)	59 (32–92)
Nicaragua	13·8 (10·2–17·9)	54·5 (39·2–69·7)	42·8 (32·1–53·5)	8·9 (7·1–10·6)	45·2 (36·2–54·2)	34·3 (27·5–41·2)	2·3 (1·9–2·6)
Niger	17·2 (9·5–24·1)	153·9 (85·5–213·8)	85·8 (51·5–115·8)	4·6 (3·6–5·5)	93·9 (75·1–112·7)	49·3 (39·4–59·1)	17 (10–25)
Nigeria	94·5 (51·3–137·8)	316·3 (170·5–461·3)	218·9 (134·9–303·0)	10·8 (8·6–12·9)	95·2 (76·1–114·2)	58·4 (46·7–70·1)	77 (49–110)
Pakistan	100·1 (64·5–137·0)	351·2 (224·7–477·8)	263·2 (180·1–346·3)	59·9 (47·9–71·8)	200·9 (160·7–241·0)	151·6 (121·3–181·9)	20 (16–25)
Papua New Guinea	353·2 (256·9–417·4)	476·9 (353·2–600·5)	433·0 (353·2–512·8)	220·2 (176·2–264·3)	402·2 (321·8–482·7)	342·6 (274·1–411·1)	50 (34–70)
Paraguay	11·2 (9·2–12·6)	60·1 (50·1–70·2)	46·8 (39·7–52·5)	9·6 (7·7–11·5)	52·9 (42·3–63·4)	40·2 (32·2–48·3)	4·5 (3·8–5·2)
Peru	26·8 (19·5–34·1)	148·1 (111·1–189·3)	120·0 (89·2–147·6)	16·6 (13·3–19·9)	123·4 (98·7–148·0)	97·7 (78·2–117·2)	8·8 (7·2–11)
Philippines	209·4 (91·0–324·7)	705·1 (310·0–1101·5)	554·0 (276·6–831·5)	129·5 (103·6–155·4)	487·5 (390·0–585·1)	378·4 (302·8–454·1)	26 (22–29)
Republic of Moldova	18·7 (15·3–20·2)	91·2 (76·5–105·9)	79·1 (66·8–91·5)	15·7 (12·6–18·9)	79·6 (63·7–95·6)	69·5 (55·6–83·4)	6·2 (5·4–7·1)
Russian Federation	7·6 (4·5–10·6)	59·5 (35·2–82·9)	50·0 (30·2–69·2)	7·7 (6·1–9·2)	59·2 (47·4–71·1)	50·3 (40·2–60·3)	6·7 (6–7·4)
Rwanda	12·3 (9·0–15·7)	86·8 (63·1–110·4)	57·0 (42·8–71·3)	8·6 (6·9–10·4)	72·0 (57·6–86·4)	45·7 (36·5–54·8)	7·5 (5·5–9·7)
Sao Tome and Principe	21·0 (4·4–38·6)	184·9 (36·2–329·5)	116·3 (29·8–200·0)	12·1 (9·7–14·6)	103·7 (82·9–124·4)	65·1 (52·1–78·1)	26 (13–44)
Senegal	21·5 (14·3–30·1)	182·5 (128·8–246·9)	116·6 (79·8–153·4)	8·5 (6·8–10·2)	137·0 (109·6–164·4)	82·0 (65·6–98·4)	18 (12–25)
Serbia	1·3 (1·1–1·5)	17·5 (14·8–18·9)	14·8 (12·5–17·1)	1·1 (0·9–1·3)	14·4 (11·5–17·2)	12·6 (10·1–15·1)	0·5 (0·5–0·6)
Sierra Leone	100·6 (56·6–147·7)	431·8 (237·5–626·2)	294·4 (179·2–409·6)	73·9 (59·1–88·6)	333·4 (266·7–400·0)	227·7 (182·2–273·3)	40 (26–56)
Solomon Islands	24·6 (17·5–31·6)	94·8 (67·3–122·2)	65·7 (49·3–82·1)	19·7 (15·8–23·7)	75·1 (60·0–90·1)	52·8 (42·3–63·4)	7·3 (4·7–10)

South Africa	224·0 (141·5–306·5)	774·1 (488·0–1060·2)	614·8 (409·8–818)	97·0 (77·6–116·4)	464·2 (371·4–557·0)	357·8 (286·3–429·4)	99 (59–150)
South Sudan	106·6 (56·5–158·8)	309·4 (170·2–464·1)	226·0 (135·6–316·4)	72·8 (58·2–87·3)	200·8 (160·6–240·9)	147·6 (118·0–177·1)	42 (28–60)
Sri Lanka	15·5 (10·8–19·6)	80·2 (54·9–104·8)	65·7 (45·5–79·7)	4·6 (3·7–5·6)	49·1 (39·3–59·0)	38·5 (30·8–46·2)	3·6 (2·9–4·4)
Sudan	19·8 (12·2–27·3)	97·6 (58·5–136·6)	67·7 (44·4–88·8)	11·3 (9·1–13·6)	68·3 (54·6–81·9)	46·2 (37·0–55·5)	10 (6·6–15)
Suriname	4·5 (3·8–5·8)	37·7 (28·2–47·1)	29·2 (20·6–36·1)	3·8 (3·1–4·6)	29·9 (23·9–35·9)	22·9 (18·3–27·5)	4·5 (3·7–5·4)
Swaziland	80·6 (43·7–117·4)	532·4 (294·2–770·6)	365·8 (209·0–513·9)	40·5 (32·4–48·6)	378·3 (302·6–453·9)	250·5 (200·4–300·6)	84 (55–118)
Syrian Arab Republic	6·6 (4·7–8·3)	24·6 (17·8–31·4)	18·7 (14·1–23·4)	4·2 (3·4–5·1)	20·1 (16·1–24·1)	15·2 (12·1–18·2)	0·1 (0·1–0·1)
Tajikistan	18·2 (13·3–22·9)	121·0 (88·7–153·4)	82·6 (62·2–103·0)	11·7 (9·4–14·0)	91·2 (73–109·5)	61·7 (49·4–74·1)	8·5 (7·6–9·4)
Thailand	28·2 (20·5–35·9)	174·4 (127·8–221·0)	150·8 (112·0–188·1)	7·5 (6·0–9·0)	147·5 (118·0–177·0)	126·1 (100·9–151·3)	16 (13–21)
Timor-Leste	157·6 (89·2–228·1)	702·9 (394·6–1011·2)	494·9 (301·6–696·0)	75·5 (60·4–90·6)	454·6 (363·6–545·5)	313·2 (250·6–375·8)	90 (54–134)
Togo	5·7 (4·5–6·6)	58·7 (46·1–71·3)	37·1 (29·7–44·5)	2·6 (2·1–3·1)	52·2 (41·8–62·7)	31·9 (25·5–38·2)	3·6 (2·5–5)
Tunisia	11·3 (8·1–14·1)	42·9 (31·6–54·2)	35·1 (26·5–44·5)	7·5 (6·0–9·0)	34·8 (27·8–41·8)	28·2 (22·6–33·8)	1·3 (0·9–1·6)
Turkey	2·8 (2·4–3·3)	19·0 (15·8–22·2)	15·6 (13·2–18·0)	2·4 (2·0–2·9)	17·0 (13·6–20·4)	13·5 (10·8–16·2)	0·4 (0·3–0·4)
Uganda	77·7 (35·0–121·4)	304·0 (135·1–472·9)	198·8 (106·2–293·7)	39·9 (31·9–47·9)	238·1 (190·5–285·7)	148·9 (119·1–178·6)	35 (24–48)
Ukraine	18·5 (10·7–25·7)	89·2 (51·4–124·4)	77·3 (47·7–106·8)	8·3 (6·7–10·0)	67·0 (53·6–80·5)	57·7 (46·2–69·2)	12 (9·9–13)
United Republic of Tanzania	82·6 (22·8–145·5)	356·1 (98·2–617·1)	236·2 (89·6–384·4)	48·1 (38·5–57·8)	211·7 (169·4–254·1)	140·0 (112·0–168·0)	55 (32–84)
Uzbekistan	33·7 (21·1–46·3)	80·9 (51·1–110·7)	66·7 (45·5–91·0)	23·1 (18·4–27·7)	60·0 (48·0–72·0)	49·3 (39·5–59·2)	5·4 (5·0–5·8)
Vanuatu	16·4 (11·2–20·7)	59·8 (40·3–76·2)	40·0 (30·7–53·4)	12·1 (9·6–14·5)	43·0 (34·4–51·6)	31·0 (24·8–37·2)	5·4 (3·5–7·7)

Venezuela	11·5 (8·4–14·1)	58·0 (42·5–72·5)	45·6 (34·0–56·1)	7·2 (5·8–8·7)	47·0 (37·6–56·4)	36·1 (28·9–43·3)	3·4 (2·7–4·2)
Vietnam	35·7 (20·5–49·1)	218·7 (126·9–311·9)	176·2 (105·7–247·8)	7·6 (6·1–9·1)	136·0 (108·8–163·2)	106·3 (85·0–127·5)	12 (8·0–16)
Yemen	15·7 (14·0–18·4)	67·7 (56·4–79·0)	48·0 (41·1–54·9)	10·8 (8·7–13·0)	50·7 (40·5–60·8)	35·1 (28·0–42·1)	6·6 (4·7–8·9)
Zambia	80·6 (45·3–114·6)	534·3 (302·4–766·2)	330·3 (201·6–459·1)	31·1 (24·9–37·4)	339·5 (271·6–407·4)	202·4 (161·9–242·9)	86 (62–114)
Zimbabwe	43·7 (30·8–56·7)	306·9 (212·5–413·2)	198·0 (143·4–252·6)	19·0 (15·2–22·8)	234·2 (187·3–281·0)	143·4 (114·8–172·1)	43 (33–54)

Table S9.3 HIV specific calibration targets for countries classified as having a higher tuberculosis burden due to HIV for 2019 and for ages 0–99. Point values represent the mean with 95% confidence intervals in brackets

Country	HIV Prevalence[23,52] (%)	ART Coverage[52] (%)	Tuberculosis Incidence Rate in PLHIV[26] (per 100,000 population per year)	Tuberculosis Mortality Rate in PLHIV[26] (per 100,000 population per year)
Botswana	16·5 (14·8–17·8)	82 (74–89)	123 (95–155)	49 (23–81)
Central African Republic	2·1 (1·8–2·7)	46 (37–59)	137 (88–195)	61 (17–115)
Côte d'Ivoire	1·7 (1·4–1·9)	63 (54–74)	24 (16–35)	8·5 (2·3–15·5)
Cameroon	2·0 (1·7–2·2)	62 (54–68)	48 (31–69)	19 (5–37)
Gabon	2·3 (1·7–3·0)	51 (38–66)	171 (65–327)	26 (0–194)
Ghana	1·1 (0·8–1·5)	45 (32–61)	30 (15–52)	16 (0–40)
Gambia	1·2 (0·9–1·5)	29 (23–37)	28 (21–37)	7·9 (3·3–12·1)
Equatorial Guinea	4·8 (3·5–6·5)	35 (27–48)	48 (41–55)	16 (8–24)
Kenya	2·9 (2·5–3·2)	74 (65–86)	70 (43–104)	24 (6–48)
Lesotho	16·0 (15·1–16·9)	65 (61–70)	403 (250–591)	168 (38–328)
Mozambique	7·2 (5·9–9·2)	60 (48–74)	122 (75–180)	18 (4–38)
Malawi	5·9 (5·2–5·9)	79 (71–84)	68 (36–109)	23 (1·0 –49)
Namibia	8·4 (7·6–8·8)	85 (79–91)	158 (113–210)	50 (20–88)
Rwanda	1·8 (1·6–2·0)	87 (77–95)	12 (9·2–15)	2·5 (1·1–4·3)
Swaziland	17·4 (16·5–19·2)	96 (88–100)	218 (129–329)	61 (11–125)

Togo	1·5 (1·2–1·7)	64 (54–79)	6 (4·8–7·4)	1·0 (0·3–1·8)
United Republic of Tanzania	2·9 (2·6–3·1)	75 (67–81)	56 (27–97)	20 (0·0 –48)
Uganda	3·4 (3·2–3·6)	84 (78–92)	78 (46–119)	19 (3·0 –39)
South Africa	12·8 (11·8–13·7)	70 (64–74)	357 (248–486)	62 (0·0 –168)
Zambia	6·7 (5·4–7·3)	85 (80–92)	154 (100–220)	53 (15–99)
Zimbabwe	9·6 (8·2–10·9)	85 (74–97)	119 (88–154)	31 (13–53)

9.4 Calibrated *Status-Quo No-New-Vaccine* baseline trends

Each country was calibrated individually to either the nine or thirteen calibration targets as in section 9.3. We investigated the trends in incidence, mortality, and case notifications throughout the entire simulation period (1900–2050) when just fitting to 2019 targets. We observed declining trends in incidence and mortality aligning with the declining incidence and mortality rates predicted by the WHO.

Here we show the tuberculosis incidence and mortality rates plotted from 2000–2050 for the selected grouping for reporting model outcomes. In Figure S9.1, looking by WHO region, we see the incidence rates are highest in AFR and SEAR, and lowest in AMR and EUR. In Figure S9.2, we see that correspondingly, the mortality rates are highest in AFR and SEAR, and lowest in AMR, EUR, and WPR. The estimated model medians for all WHO regions demonstrate decreasing trends from 2000 to 2050.

In Figure S9.3 and Figure S9.4, we show the incidence and mortality rate trends by income group. Both incidence and mortality rates follow a trend with the highest estimated medians in lower-middle-income countries, followed by low-income countries and high-income countries, which aligns with the expectation of burden within each region.

In Figure S9.5 and S9.6, we compare incidence and mortality rates between countries included on the WHO high TB burden list and all other countries modelled, and as expected, higher values are predicted for countries on the high TB burden list.

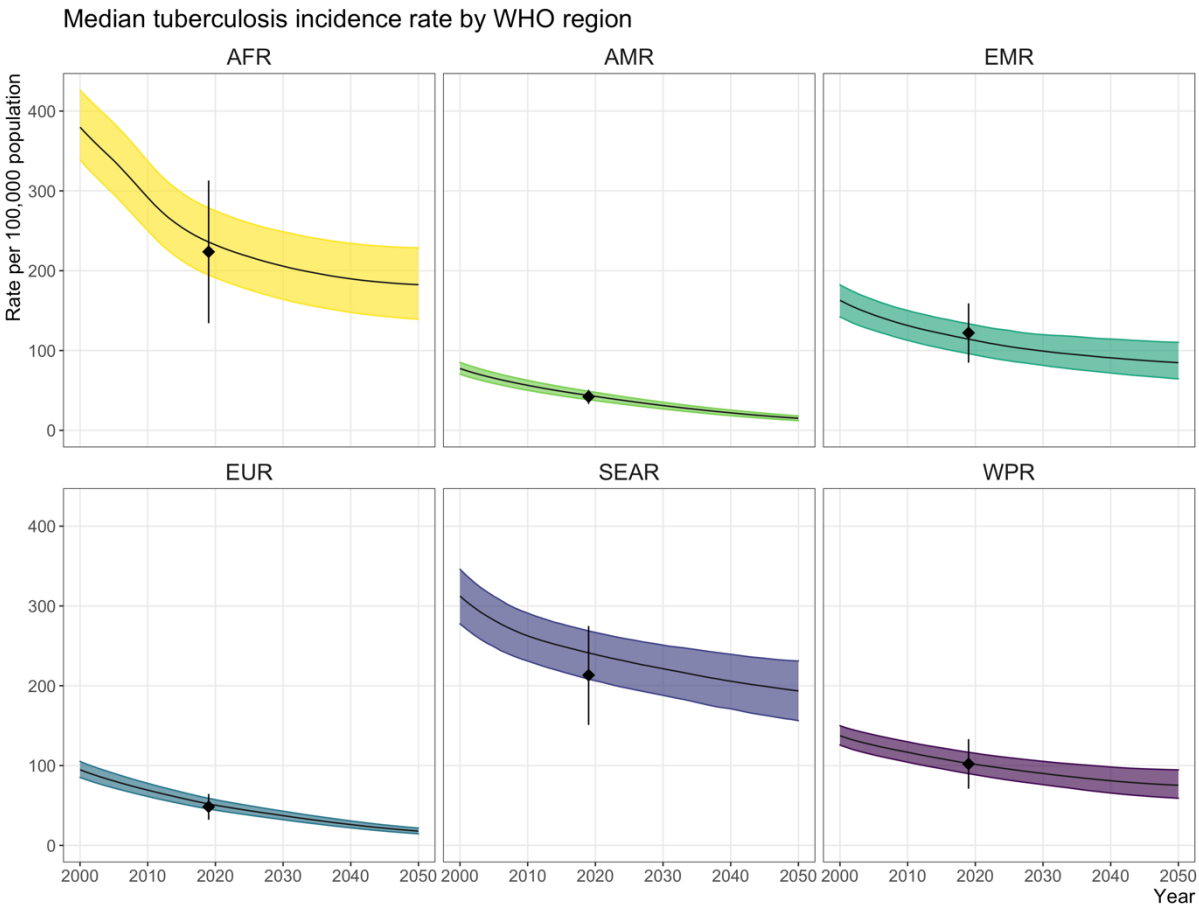

Figure S9.1 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline by WHO region

The black diamond is the WHO median estimate of the incidence in 2019 for the 105 modelled LMICs by WHO region with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, SEAR = WHO South-East Asian Region, WPR = WHO Western Pacific Region

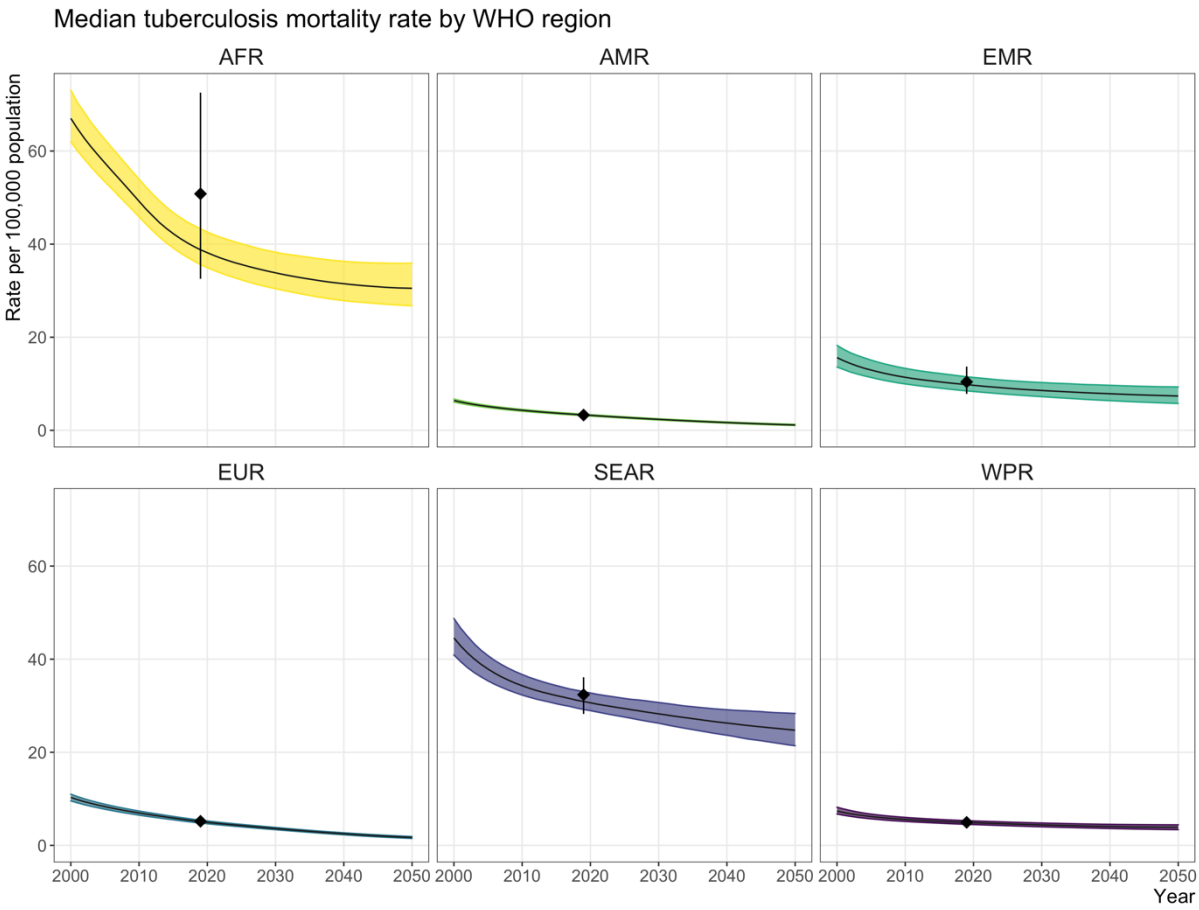

Figure S9.2 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline by WHO region

The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by WHO region with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, SEAR = WHO South-East Asian Region, WPR = WHO Western Pacific Region

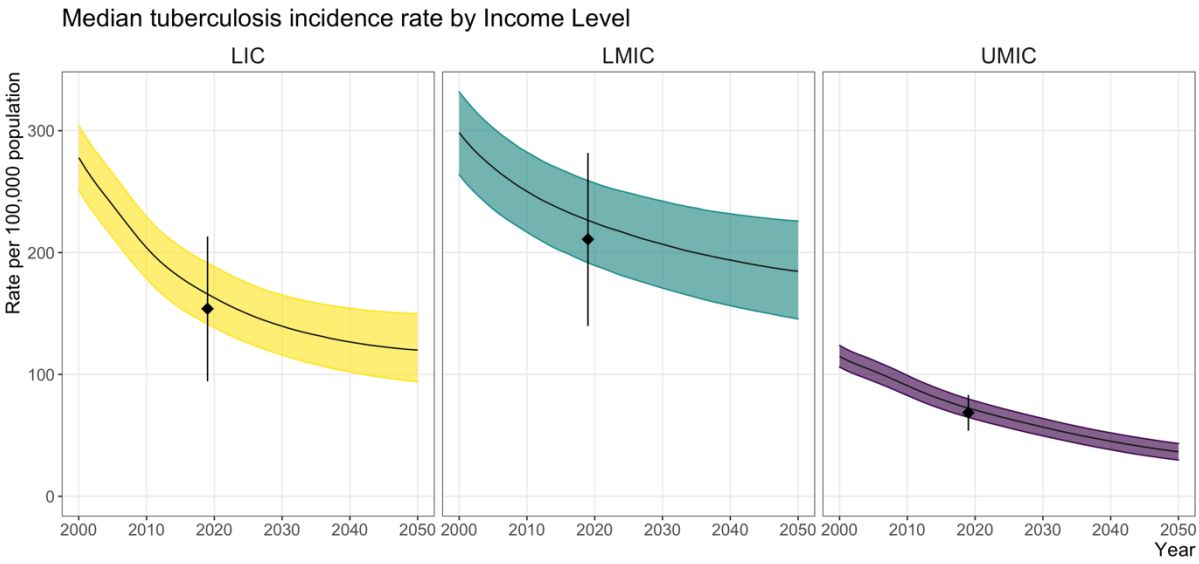

Figure S9.3 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline by income group

The black diamond is the WHO median estimate of the incidence rate in 2019 for the 105 modelled LMICs by income group with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

LIC = low-income countries, LMIC = lower-middle income countries, UMIC = upper-middle income countries

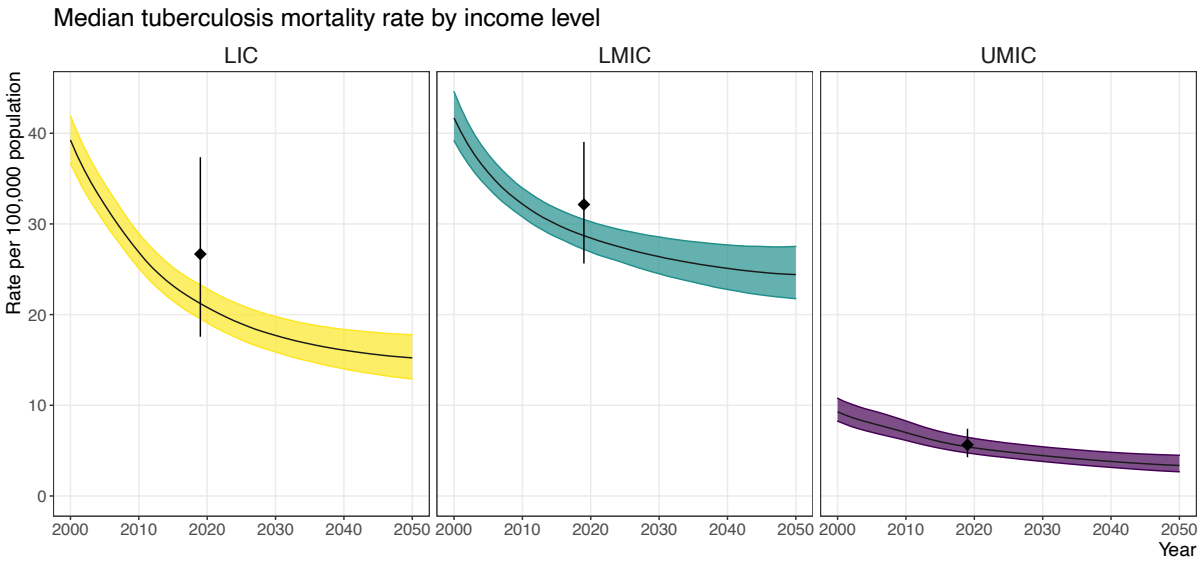

Figure S9.4 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline by income group

The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by income group with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

LIC = low-income countries, LMIC = lower-middle income countries, UMIC = upper-middle income countries

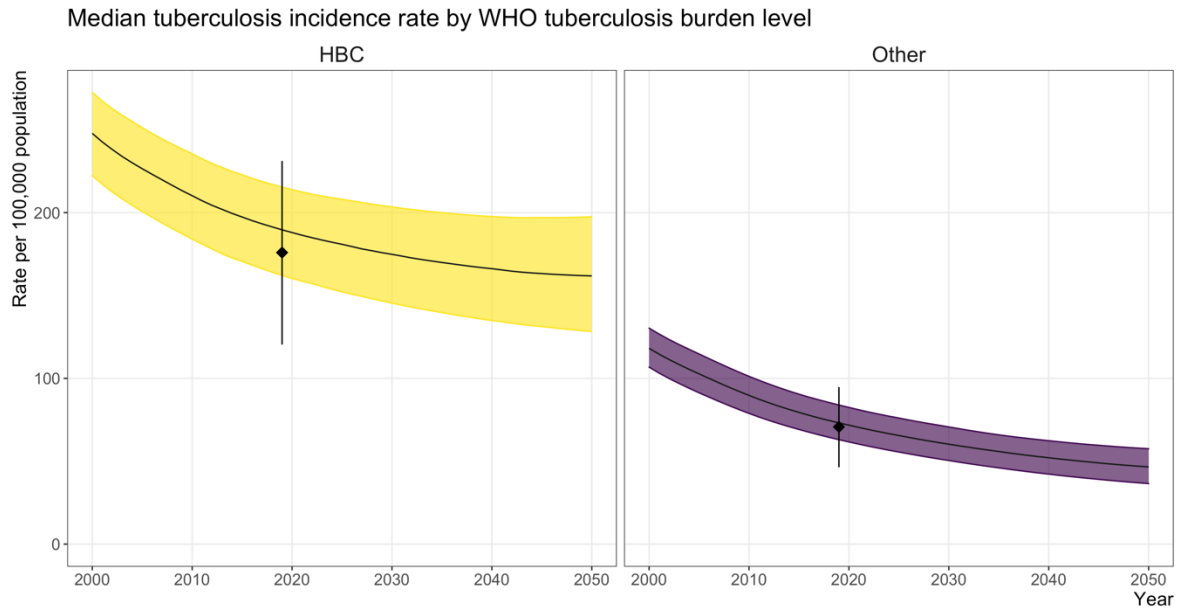

Figure S9.5 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline for the countries included on the WHO high-TB-burden list and for all other countries modelled

The black diamond is the WHO median estimate of the incidence rate in 2019 for the 105 modelled LMICs by burden level with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

HBC = high burden countries

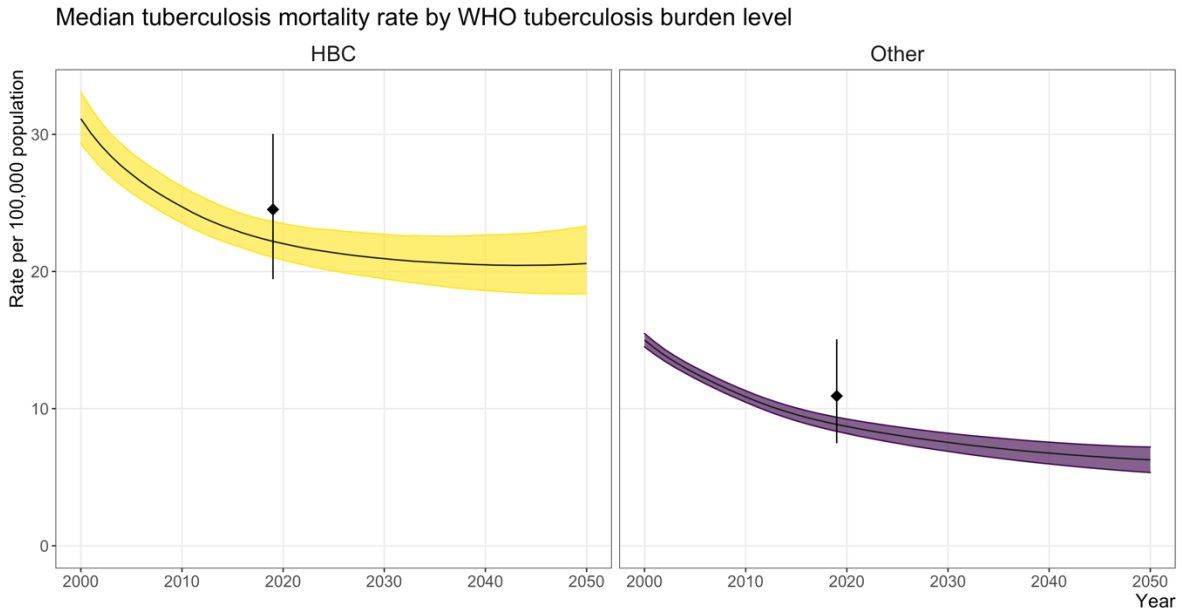

Figure S9.6 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline for the countries included on the WHO high-TB-burden list and for all other countries modelled

The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by burden level with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

HBC = high burden countries

10. Vaccine Health Impact Results

10.1 Incidence and mortality rate reductions and cumulative cases, treatments, and deaths averted

As stated in the main text, delivery of a 50% efficacy vaccine with an average of 10-years protection and medium coverage will have a substantial impact, which varies based on delivery and vaccine characteristics. For the adolescent/adult vaccine, compared to the *Basecase* implementation, the *Accelerated Scale-up* scenario averted approximately 60% more cases, treatments, and deaths by 2050, and almost ten times as many as the *Routine Only* scenario, demonstrating the benefits of instantly introducing and scaling-up to coverage, as well as including a campaign for ages ten and over. We performed scenario analyses by varying certain vaccine and delivery characteristics, the results of which are presented in Table S10.1 (adolescent/adult vaccine) and Table S10.2 (infant vaccine) below, as the median estimate and 95% uncertainty range. Decreasing the target vaccine coverage correspondingly decreased the health impact estimates, and increasing the target vaccine coverage, increasing the duration of protection to lifelong, or increasing the vaccine efficacy increases the health impact estimates. The order of vaccine scenario health impact results within each table is as follows:

Primary scenarios (as in main text)

- *Basecase*, medium coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, medium coverage, 50% efficacy, 10-years protection
- *Routine Only*, medium coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)

Low and high coverage targets

- *Basecase*, low coverage, 50% efficacy, 10-years protection
- *Basecase*, high coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, low coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, high coverage, 50% efficacy, 10-years protection
- *Routine Only*, low coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)
- *Routine Only*, high coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)

Lifelong duration of protection

- *Basecase*, medium coverage, 50% efficacy, lifelong protection
- *Accelerated Scale-up*, medium coverage, 50% efficacy, lifelong protection
- *Routine Only*, medium coverage, 50% efficacy, lifelong protection (adolescent/adult vaccine only)

75% efficacy (adolescent/adult vaccine only)

- *Basecase*, medium coverage, 75% efficacy, 10-years protection
- *Accelerated Scale-up*, medium coverage, 75% efficacy, 10-years protection

2025 End TB No-New-Vaccine baseline (adolescent/adult vaccine only)

- *Basecase*, medium coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, medium coverage, 50% efficacy, 10-years protection

Table S10.1 Estimated health impact in 2050 by WHO region, income level, and tuberculosis burden level for the adolescent and adult vaccine scenarios

	Health Impact Measure	All modelled countries	WHO region						WHO tuberculosis burden level		World Bank income group		
Vaccine Scenario			AFR	HBC	All other countries	EUR	SEAR	WPR	HBC	All other countries	LIC	LMIC	UMIC
Primary scenarios													
Basecase Medium coverage, 50% efficacy, 10 years protection	Averted cases before 2050	44·0m (37·2–51·6)	13·9m (11·7–16·7)	0·5m (0·5–0·6)	3·9m (3·1–4·8)	0·3m (0·3–0·4)	19·5m (15·9–23·1)	5·9m (5·0–6·9)	39·8m (33·7–46·7)	4·1m (3·4–4·9)	5·0m (4·1–6·0)	34·3m (28·6–40·3)	4·7m (4·1–5·4)
	Averted tx before 2050	24·9m (21·9–27·3)	6·3m (5·7–6·8)	0·4m (0·3–0·4)	2·4m (2·0–2·8)	0·2m (0·2–0·3)	11·7m (10·1–13·4)	3·8m (3·3–4·2)	22·6m (19·9–24·8)	2·3m (2·0–2·6)	2·9m (2·5–3·2)	19·0m (16·6–21·2)	2·9m (2·7–3·2)
	Averted deaths before 2050	5·0m (4·6–5·4)	2·1m (1·9–2·3)	0·04m (0·03–0·04)	0·3m (0·2–0·4)	0·028m (0·026–0·031)	2·2m (2·0–2·6)	0·3m (0·2–0·3)	4·5m (4·2–4·9)	0·5m (0·4–0·5)	0·6m (0·5–0·6)	4·1m (3·7–4·4)	0·4m (0·3–0·5)
	IRR in 2050 (%)	25·4% (23·9–27·7)	27·0% (25·7–31·3)	15·9% (15·2–16·9)	26·7% (23·7–31·6)	20·2% (18·6–22·6)	25·4% (23·3–28·2)	19·8% (18·3–22·2)	25·4% (23·8–27·9)	25·1% (24·1–26·6)	27·3% (26·0–29·1)	26·1% (24·3–28·9)	16·7% (15·8–18·0)
	MRR in 2050 (%)	27·1% (25·6–30·1)	27·7% (26·3–33·3)	17·7% (16·8–18·7)	28·1% (25·0–32·8)	19·9% (18·6–21·6)	26·5% (24·3–29·4)	23·1% (21·2–25·8)	27·3% (25·5–30·6)	25·9% (25·0–27·1)	27·8% (26·6–29·4)	27·6% (25·8–31·3)	19·4% (18·1–21·3)
Accelerated Scale-up Medium coverage, 50% efficacy, 10 years protection	Averted cases before 2050	65·5m (55·6–76·0)	19·5m (16·7–23·1)	0·8m (0·7–1·0)	5·4m (4·3–6·7)	0·6m (0·5–0·7)	31·0m (25·8–36·4)	8·1m (6·9–9·5)	58·6m (49·9–67·9)	7·0m (5·8–8·2)	7·5m (6·2–9·0)	51·7m (43·6–60·2)	6·4m (5·6–7·2)
	Averted tx before 2050	38·6m (34·4–42·3)	9·2m (8·5–9·9)	0·6m (0·5–0·7)	3·4m (2·9–4·0)	0·4m (0·4–0·5)	19·5m (16·8–22·2)	5·3m (4·8–5·9)	34·6m (30·7–37·9)	4·0m (3·5–4·4)	4·5m (4·0–5·0)	30·0m (26·5–33·3)	4·1m (3·7–4·4)
	Averted deaths before 2050	7·9m (7·3–8·5)	3·1m (2·9–3·4)	0·06m (0·05–0·06)	0·5m (0·4–0·6)	0·06m (0·05–0·06)	3·8m (3·3–4·3)	0·40m (0·36–0·45)	7·0m (6·4–7·6)	0·8m (0·8–0·9)	0·9m (0·8–1·0)	6·5m (5·9–7·0)	0·5m (0·4–0·6)
	IRR in 2050 (%)	25·2% (23·9–27·5)	27·6% (26·3–32·1)	15·2% (14·4–16·2)	27·1% (24·5–31·4)	18·4% (16·4–21·6)	24·7% (22·8–27·3)	19·4% (18·1–21·3)	25·2% (23·8–27·6)	25·3% (24·5–26·8)	27·5% (26·3–29·2)	25·9% (24·3–28·6)	16·3% (15·5–17·3)
	MRR in 2050 (%)	26·7% (25·2–29·9)	28·2% (26·8–34·6)	16·2% (15·3–17·3)	27·9% (25·2–32·3)	18·1% (16·5–20·7)	25·3% (23·2–28·2)	21·8% (20·2–24·3)	26·8% (25·1–30·4)	26·1% (25·3–27·2)	27·7% (26·6–29·2)	27·2% (25·5–31·0)	18·4% (17·3–20·0)
Routine Only Medium coverage, 50% efficacy, 10 years protection	Averted cases before 2050	8·8m (7·6–10·1)	3·5m (3·0–3·9)	0·04m (0·03–0·05)	0·9m (0·7–1·2)	0·02m (0·02–0·03)	3·4m (2·6–4·4)	1·0m (0·8–1·2)	8·1m (7·0–9·3)	0·7m (0·6–0·8)	1·1m (0·9–1·3)	7·2m (6·2–8·3)	0·5m (0·4–0·7)
	Averted tx before 2050	4·1m (3·7–4·6)	1·2m (1·1–1·4)	0·03m (0·02–0·03)	0·5m (0·4–0·6)	0·01m (0·01–0·02)	1·8m (1·4–2·2)	0·6m (0·5–0·7)	3·8m (3·4–4·2)	0·3m (0·3–0·4)	0·6m (0·5–0·6)	3·3m (2·9–3·8)	0·3m (0·2–0·3)
	Averted deaths before 2050	1·1m (0·9–1·2)	0·5m (0·4–0·6)	0·003m (0·003–0·004)	0·08m (0·06–0·10)	0·002m (0·002–0·003)	0·4m (0·3–0·5)	0·1m (0·0–0·1)	1·0m (0·8–1·1)	0·08m (0·07–0·09)	0·12m (0·10–0·14)	0·9m (0·7–1·0)	0·1m (0·0–0·1)

	IRR in 2050 (%)	9·9% (9·0–11·6)	11·2% (10·3–14·7)	3·4% (3·1–3·9)	11·9% (9·9–15·3)	4·1% (3·4–5·2)	9·1% (7·8–11·1)	7·7% (6·5–9·5)	10·2% (9·1–12·0)	8·0% (7·3–9·2)	10·5% (9·6–11·9)	10·4% (9·2–12·5)	5·2% (4·4–6·3)
	MRR in 2050 (%)	9·9% (8·9–12·3)	10·7% (9·7–15·2)	3·7% (3·3–4·2)	11·9% (9·9–15·1)	3·8% (3·3–4·5)	8·7% (7·3–10·7)	9·2% (7·5–11·7)	10·2% (9·1–12·9)	7·2% (6·5–8·1)	9·6% (8·8–10·7)	10·2% (9·0–13·1)	6·2% (5·2–7·8)
Low and high coverage													
Basecase Low coverage, 50% efficacy, 10 years protection	Averted cases before 2050	33·5m (28·5–39·2)	10·7m (9·1–12·8)	0·4m (0·3–0·5)	3·0m (2·4–3·7)	0·3m (0·2–0·3)	14·7m (12·1–17·5)	4·4m (3·8–5·2)	30·4m (25·7–35·5)	3·1m (2·6–3·7)	3·9m (3·2–4·6)	26·1m (22·0–30·7)	3·5m (3·0–4·0)
	Averted tx before 2050	18·8m (16·6–20·6)	4·8m (4·4–5·1)	0·3m (0·2–0·3)	1·8m (1·5–2·2)	0·2m (0·1–0·2)	8·8m (7·6–10·1)	2·8m (2·5–3·2)	17·0m (15·1–18·8)	1·7m (1·5–1·9)	2·2m (1·9–2·5)	14·4m (12·6–16·0)	2·2m (2·0–2·3)
	Averted deaths before 2050	3·8m (3·5–4·1)	1·6m (1·5–1·8)	0·03m (0·02–0·03)	0·2m (0·2–0·3)	0·021m (0·019–0·023)	1·7m (1·5–1·9)	0·21m (0·18–0·23)	3·5m (3·2–3·8)	0·3m (0·3–0·4)	0·4m (0·4–0·5)	3·1m (2·8–3·4)	0·3m (0·2–0·4)
	IRR in 2050 (%)	20·2% (19·0–22·2)	21·6% (20·5–25·4)	12·2% (11·6–13·0)	21·5% (19·0–25·8)	15·5% (14·2–17·5)	20·1% (18·3–22·6)	15·7% (14·4–17·7)	20·3% (18·9–22·5)	19·7% (18·9–21·0)	21·7% (20·6–23·4)	20·8% (19·3–23·3)	13·0% (12·2–14·1)
	MRR in 2050 (%)	21·5% (20·2–24·2)	22·0% (20·9–27·0)	13·5% (12·8–14·4)	22·5% (19·9–26·6)	15·2% (14·1–16·6)	20·9% (19·0–23·4)	18·3% (16·6–20·7)	21·7% (20·2–24·6)	20·1% (19·3–21·2)	22·0% (20·9–23·4)	22·0% (20·4–25·2)	15·1% (14·0–16·8)
Basecase High coverage, 50% efficacy, 10 years protection	Averted cases before 2050	54·2m (45·7–63·6)	17·0m (14·2–20·5)	0·7m (0·6–0·8)	4·8m (3·8–5·9)	0·4m (0·4–0·5)	24·1m (19·7–28·5)	7·3m (6·2–8·6)	49·1m (41·4–57·6)	5·1m (4·2–6·1)	6·2m (5·0–7·4)	42·1m (35·1–49·7)	6·0m (5·2–6·8)
	Averted tx before 2050	30·8m (27·1–33·9)	7·7m (7·0–8·4)	0·5m (0·4–0·5)	2·9m (2·4–3·4)	0·29m (0·26–0·33)	14·5m (12·5–16·6)	4·7m (4·2–5·3)	27·9m (24·6–30·7)	2·9m (2·5–3·2)	3·5m (3·1–4·0)	23·5m (20·5–26·2)	3·7m (3·4–4·0)
	Averted deaths before 2050	6·1m (5·7–6·7)	2·6m (2·3–2·9)	0·0m (0·0–0·1)	0·4m (0·3–0·5)	0·04m (0·03–0·04)	2·8m (2·4–3·2)	0·3m (0·3–0·4)	5·6m (5·1–6·1)	0·6m (0·5–0·6)	0·7m (0·6–0·8)	5·0m (4·6–5·4)	0·5m (0·4–0·6)
	IRR in 2050 (%)	30·3% (28·6–32·8)	32·1% (30·6–36·7)	19·5% (18·6–20·6)	31·6% (28·2–37·0)	24·6% (22·9–27·3)	30·3% (28·0–33·5)	23·9% (22·2–26·4)	30·3% (28·5–33·0)	30·2% (29·1–31·7)	32·5% (31·0–34·5)	31·1% (29·0–34·1)	20·2% (19·2–21·8)
	MRR in 2050 (%)	32·4% (30·7–35·7)	33·1% (31·6–39·1)	21·7% (20·7–22·9)	33·3% (29·9–38·5)	24·4% (22·9–26·4)	31·8% (29·3–35·1)	27·8% (25·6–30·8)	32·6% (30·6–36·2)	31·4% (30·4–32·7)	33·3% (32·0–35·1)	33·0% (31·0–37·0)	23·5% (22·0–25·7)
Accelerated Scale-up Low coverage, 50% efficacy, 10 years protection	Averted cases before 2050	50·9m (43·4–59·0)	15·3m (13·3–18·1)	0·6m (0·5–0·7)	4·3m (3·4–5·2)	0·5m (0·4–0·6)	24·0m (19·9–28·3)	6·2m (5·3–7·2)	45·6m (38·9–52·8)	5·4m (4·5–6·3)	5·9m (4·9–7·1)	40·2m (34·1–46·8)	4·8m (4·2–5·4)
	Averted tx before 2050	29·7m (26·6–32·6)	7·2m (6·6–7·7)	0·4m (0·4–0·5)	2·6m (2·2–3·1)	0·3m (0·3–0·4)	15·0m (13·0–17·2)	4·0m (3·6–4·5)	26·6m (23·8–29·3)	3·1m (2·7–3·4)	3·5m (3·1–3·9)	23·2m (20·6–25·8)	3·0m (2·8–3·3)
	Averted deaths before 2050	6·1m (5·7–6·6)	2·5m (2·2–2·7)	0·04m (0·04–0·05)	0·4m (0·3–0·4)	0·04m (0·04–0·05)	2·9m (2·5–3·4)	0·3m (0·3–0·3)	5·5m (5·0–6·0)	0·7m (0·6–0·7)	0·7m (0·6–0·8)	5·0m (4·6–5·5)	0·4m (0·3–0·5)

	IRR in 2050 (%)	20·8% (19·5–22·8)	22·7% (21·6–26·8)	12·0% (11·3–12·8)	22·4% (20·2–26·3)	14·9% (13·2–17·8)	20·3% (18·6–22·7)	15·7% (14·6–17·5)	20·8% (19·5–22·9)	20·7% (20·0–22·1)	22·7% (21·6–24·2)	21·4% (19·9–23·8)	13·0% (12·3–13·8)
	MRR in 2050 (%)	21·9% (20·6–24·8)	23·2% (21·9–28·9)	12·8% (12·0–13·7)	23·1% (20·7–27·0)	14·6% (13·2–16·9)	20·7% (18·9–23·4)	17·8% (16·4–20·0)	22·0% (20·6–25·2)	21·2% (20·5–22·3)	22·7% (21·8–24·2)	22·4% (20·9–25·9)	14·7% (13·8–16·1)
Accelerated Scale-up High coverage, 50% efficacy, 10 years protection	Averted cases before 2050	79·6m (67·5–92·6)	23·5m (20·0–28·0)	1·0m (0·9–1·2)	6·5m (5·2–8·1)	0·8m (0·7–0·9)	37·7m (31·4–44·1)	10·0m (8·5–11·7)	71·1m (60·4–82·7)	8·5m (7·1–10·1)	9·1m (7·5–10·8)	62·6m (52·7–73·1)	8·0m (7·0–9·0)
	Averted tx before 2050	47·0m (41·9–51·7)	11·2m (10·2–12·0)	0·7m (0·7–0·8)	4·1m (3·5–4·8)	0·6m (0·5–0·6)	23·7m (20·5–27·0)	6·6m (5·9–7·3)	42·2m (37·4–46·4)	4·9m (4·3–5·4)	5·4m (4·8–6·0)	36·5m (32·3–40·6)	5·1m (4·7–5·5)
	Averted deaths before 2050	9·5m (8·8–10·3)	3·8m (3·5–4·2)	0·1m (0·1–0·1)	0·5m (0·4–0·7)	0·07m (0·06–0·07)	4·6m (4·0–5·2)	0·5m (0·4–0·5)	8·5m (7·8–9·2)	1·0m (0·9–1·1)	1·1m (1·0–1·2)	7·8m (7·2–8·5)	0·6m (0·5–0·8)
	IRR in 2050 (%)	29·4% (28·0–31·9)	32·1% (30·7–37·0)	18·3% (17·2–19·4)	31·4% (28·6–36·1)	21·5% (19·5–25·0)	28·8% (26·7–31·7)	22·9% (21·5–25·0)	29·4% (27·9–32·0)	29·6% (28·7–31·2)	32·0% (30·7–33·9)	30·2% (28·4–33·1)	19·5% (18·6–20·6)
	MRR in 2050 (%)	31·2% (29·6–34·7)	33·0% (31·4–39·8)	19·4% (18·3–20·7)	32·4% (29·4–37·1)	21·4% (19·6–24·2)	29·6% (27·3–32·7)	25·7% (23·8–28·3)	31·3% (29·5–35·1)	30·6% (29·8–31·8)	32·3% (31·2–34·0)	31·8% (29·9–35·9)	21·9% (20·7–23·7)
Routine Only Low coverage, 50% efficacy, 10 years protection	Averted cases before 2050	7·8m (6·8–8·9)	3·1m (2·6–3·5)	0·04m (0·03–0·04)	0·8m (0·6–1·1)	0·02m (0·02–0·03)	3·0m (2·3–3·8)	0·9m (0·7–1·1)	7·2m (6·2–8·2)	0·6m (0·5–0·7)	1·0m (0·8–1·2)	6·3m (5·5–7·3)	0·5m (0·4–0·6)
	Averted tx before 2050	3·6m (3·3–4·0)	1·1m (1·0–1·2)	0·022m (0·019–0·025)	0·4m (0·4–0·6)	0·013m (0·011–0·015)	1·5m (1·3–1·9)	0·5m (0·4–0·6)	3·3m (3·0–3·7)	0·29m (0·26–0·33)	0·5m (0·4–0·6)	2·9m (2·6–3·3)	0·2m (0·2–0·3)
	Averted deaths before 2050	0·9m (0·8–1·1)	0·5m (0·4–0·6)	0·003m (0·002–0·003)	0·1m (0·0–0·1)	0·0019m (0·0017–0·0022)	0·3m (0·3–0·4)	0·1m (0·0–0·1)	0·9m (0·7–1·0)	0·07m (0·06–0·08)	0·1m (0·1–0·1)	0·8m (0·7–0·9)	0·0m (0·0–0·1)
	IRR in 2050 (%)	8·8% (7·9–10·3)	9·9% (9·2–13·1)	3·0% (2·7–3·5)	10·6% (8·7–13·6)	3·6% (3·0–4·6)	8·1% (6·9–9·9)	6·8% (5·8–8·5)	9·0% (8·1–10·6)	7·1% (6·4–8·1)	9·3% (8·5–10·5)	9·2% (8·1–11·1)	4·6% (3·9–5·6)
	MRR in 2050 (%)	8·8% (7·8–10·9)	9·5% (8·6–13·5)	3·3% (2·9–3·7)	10·6% (8·7–13·4)	3·3% (2·9–4·0)	7·7% (6·5–9·5)	8·1% (6·6–10·3)	9·1% (8·0–11·4)	6·3% (5·7–7·2)	8·5% (7·8–9·5)	9·1% (8·0–11·6)	5·5% (4·5–6·9)
Routine Only High coverage, 50% efficacy, 10 years protection	Averted cases before 2050	9·8m (8·5–11·3)	3·9m (3·3–4·4)	0·0m (0·0–0·1)	1·0m (0·8–1·3)	0·03m (0·02–0·03)	3·8m (2·9–4·9)	1·1m (0·9–1·4)	9·1m (7·8–10·4)	0·8m (0·6–0·9)	1·2m (1·0–1·5)	8·0m (6·9–9·3)	0·6m (0·5–0·7)
	Averted tx before 2050	4·6m (4·2–5·1)	1·4m (1·2–1·5)	0·03m (0·02–0·03)	0·6m (0·4–0·7)	0·02m (0·01–0·02)	2·0m (1·6–2·4)	0·6m (0·5–0·8)	4·2m (3·8–4·7)	0·4m (0·3–0·4)	0·6m (0·5–0·7)	3·6m (3·2–4·2)	0·3m (0·3–0·4)
	Averted deaths before 2050	1·2m (1·0–1·3)	0·6m (0·5–0·7)	0·004m (0·003–0·004)	0·08m (0·06–0·11)	0·002m (0·002–0·003)	0·4m (0·3–0·6)	0·07m (0·05–0·09)	1·1m (0·9–1·3)	0·09m (0·07–0·10)	0·1m (0·1–0·2)	1·0m (0·8–1·2)	0·1m (0·0–0·1)
	IRR in 2050 (%)	11·0% (10·0–12·9)	12·5% (11·5–16·3)	3·8% (3·4–4·4)	13·2% (11·0–17·0)	4·6% (3·8–5·8)	10·1% (8·6–12·3)	8·6% (7·3–10·6)	11·3% (10·1–13·3)	8·9% (8·1–10·2)	11·7% (10·7–13·2)	11·5% (10·2–13·8)	5·8% (4·9–7·0)

	MRR in 2050 (%)	11·0% (9·9–13·6)	12·0% (10·9–16·9)	4·1% (3·7–4·7)	13·3% (11·0–16·8)	4·2% (3·6–5·0)	9·7% (8·2–11·9)	10·3% (8·4–13·0)	11·4% (10·1–14·3)	8·0% (7·3–9·0)	10·7% (9·8–11·9)	11·4% (10·0–14·5)	6·9% (5·8–8·7)
Lifelong protection													
Basecase Medium coverage, 50% efficacy, lifelong protection	Averted cases before 2050	69·7m (58·3–82·0)	21·9m (18·1–26·6)	0·9m (0·8–1·0)	6·2m (4·9–7·7)	0·6m (0·5–0·6)	30·3m (24·7–35·8)	9·8m (8·3–11·7)	63·2m (52·9–74·5)	6·5m (5·3–7·7)	7·8m (6·4–9·4)	53·7m (44·5–63·7)	8·2m (7·1–9·4)
	Averted tx before 2050	38·4m (33·9–42·4)	9·7m (8·7–10·5)	0·6m (0·5–0·7)	3·7m (3·1–4·4)	0·4m (0·3–0·4)	17·8m (15·3–20·3)	6·2m (5·5–6·9)	34·9m (30·7–38·5)	3·5m (3·1–3·9)	4·4m (3·8–4·9)	29·1m (25·3–32·5)	5·0m (4·5–5·3)
	Averted deaths before 2050	7·5m (6·9–8·2)	3·2m (2·9–3·5)	0·06m (0·05–0·06)	0·5m (0·4–0·6)	0·04m (0·04–0·05)	3·3m (2·9–3·8)	0·4m (0·4–0·5)	6·8m (6·3–7·5)	0·7m (0·6–0·8)	0·8m (0·7–0·9)	6·1m (5·6–6·6)	0·6m (0·5–0·8)
	IRR in 2050 (%)	50·2% (48·1–53·2)	51·4% (49·4–56·5)	40·7% (39·2–42·4)	52·8% (48·4–59·2)	42·7% (40·8–45·2)	50·2% (47·1–53·8)	44·8% (41·9–48·7)	50·6% (48·2–53·8)	47·5% (46·0–49·4)	51·2% (49·2–53·6)	51·0% (48·4–54·7)	42·0% (40·0–44·9)
	MRR in 2050 (%)	49·5% (47·3–53·2)	49·5% (47·5–55·8)	40·8% (39·4–42·5)	52·2% (48·1–58·2)	40·8% (39·1–42·8)	49·3% (46·3–52·9)	45·7% (42·6–49·7)	50·1% (47·7–54·1)	45·1% (43·4–46·8)	48·9% (47·0–51·1)	50·2% (47·6–54·5)	42·9% (40·1–46·6)
Accelerated Scale-up Medium coverage, 50% efficacy, lifelong protection	Averted cases before 2050	116·7m (98·4–136·4)	34·1m (28·4–41·2)	1·6m (1·3–1·8)	9·5m (7·6–11·7)	1·2m (1·0–1·3)	55·3m (45·6–64·8)	15·0m (12·7–17·7)	104·2m (88·0–121·9)	12·4m (10·2–14·7)	13·2m (10·8–15·9)	91·4m (76·3–107·3)	12·1m (10·6–13·7)
	Averted tx before 2050	67·9m (60·1–74·7)	16·1m (14·5–17·3)	1·1m (1·0–1·2)	5·9m (5·0–6·9)	0·8m (0·7–0·9)	34·2m (29·5–38·9)	9·7m (8·6–10·8)	60·9m (53·8–67·2)	7·0m (6·2–7·7)	7·8m (6·8–8·6)	52·5m (46·1–58·5)	7·6m (6·9–8·1)
	Averted deaths before 2050	13·4m (12·4–14·5)	5·2m (4·8–5·8)	0·11m (0·10–0·12)	0·8m (0·6–0·9)	0·10m (0·09–0·11)	6·5m (5·7–7·4)	0·7m (0·6–0·8)	11·9m (11·0–13·0)	1·5m (1·3–1·6)	1·5m (1·4–1·7)	10·9m (10·1–11·9)	0·9m (0·8–1·2)
	IRR in 2050 (%)	55·6% (53·5–58·7)	57·7% (55·8–63·0)	43·4% (41·9–45·1)	57·4% (52·8–64·1)	47·1% (44·6–50·6)	55·7% (52·4–59·6)	47·9% (45·1–51·9)	55·7% (53·3–59·1)	54·9% (53·6–56·8)	58·0% (56·1–60·4)	56·6% (53·9–60·3)	44·4% (42·6–47·2)
	MRR in 2050 (%)	55·7% (53·4–59·8)	56·5% (54·5–63·5)	43·7% (42·2–45·4)	57·1% (52·7–63·3)	46·1% (43·7–49·0)	55·2% (51·8–59·3)	49·4% (46·3–53·5)	55·9% (53·4–60·4)	54·4% (53·1–56·0)	56·7% (54·9–58·9)	56·5% (53·7–61·2)	45·9% (43·3–49·5)
Routine Only Medium coverage, 50% efficacy, lifelong protection	Averted cases before 2050	13·4m (11·6–15·5)	5·3m (4·6–6·1)	0·06m (0·05–0·08)	1·4m (1·1–1·8)	0·04m (0·03–0·05)	5·0m (4·0–6·5)	1·6m (1·2–1·9)	12·4m (10·7–14·4)	1·1m (0·9–1·2)	1·7m (1·4–2·0)	10·9m (9·4–12·7)	0·9m (0·7–1·1)
	Averted tx before 2050	6·2m (5·6–6·9)	1·9m (1·7–2·1)	0·04m (0·03–0·05)	0·8m (0·6–1·0)	0·02m (0·02–0·03)	2·6m (2·1–3·2)	0·9m (0·7–1·1)	5·7m (5·1–6·4)	0·5m (0·4–0·6)	0·8m (0·7–1·0)	4·9m (4·4–5·6)	0·4m (0·4–0·5)
	Averted deaths before 2050	1·5m (1·3–1·7)	0·8m (0·6–0·9)	0·00m (0·00–0·01)	0·11m (0·08–0·15)	0·003m (0·003–0·004)	0·5m (0·4–0·7)	0·08m (0·07–0·11)	1·4m (1·2–1·6)	0·1m (0·1–0·1)	0·2m (0·1–0·2)	1·3m (1·1–1·5)	0·08m (0·06–0·12)
	IRR in 2050 (%)	16·8% (15·3–19·2)	19·2% (18·0–24·0)	6·5% (5·8–7·4)	20·4% (17·2–25·9)	6·8% (5·8–8·3)	15·1% (13·0–18·0)	13·5% (11·6–16·5)	17·2% (15·6–19·8)	13·3% (12·2–15·1)	17·6% (16·2–19·6)	17·5% (15·7–20·4)	9·9% (8·5–11·7)

	MRR in 2050 (%)	15·8% (14·2–19·2)	17·3% (15·9–23·7)	6·3% (5·7–7·1)	19·3% (16·2–24·0)	5·9% (5·2–6·9)	13·7% (11·7–16·5)	14·4% (12·0–17·6)	16·3% (14·7–20·0)	11·3% (10·2–12·7)	15·2% (14·0–16·8)	16·3% (14·5–20·3)	10·9% (9·1–13·5)
75% efficacy vaccine													
Basecase Medium coverage, 75% efficacy, 10 years protection	Averted cases before 2050	64·3m (54·0–75·6)	20·3m (17·0–24·6)	0·8m (0·7–0·9)	5·6m (4·5–7·0)	0·5m (0·4–0·6)	28·4m (23·2–33·5)	8·7m (7·3–10·3)	58·2m (49·0–68·5)	6·1m (5·0–7·2)	7·3m (6·0–8·9)	49·8m (41·4–58·9)	7·1m (6·2–8·1)
	Averted tx before 2050	36·4m (32·0–40·1)	9·2m (8·3–10·0)	0·6m (0·5–0·6)	3·4m (2·9–4·0)	0·3m (0·3–0·4)	17·1m (14·7–19·6)	5·6m (4·9–6·3)	33·0m (29·0–36·4)	3·4m (2·9–3·8)	4·2m (3·7–4·7)	27·7m (24·1–30·9)	4·4m (4·0–4·8)
	Averted deaths before 2050	7·3m (6·7–7·9)	3·1m (2·8–3·4)	0·1m (0·0–0·1)	0·4m (0·4–0·6)	0·04m (0·04–0·05)	3·3m (2·9–3·7)	0·04m (0·04–0·05)	6·6m (6·1–7·2)	0·7m (0·6–0·7)	0·8m (0·7–0·9)	5·9m (5·4–6·4)	0·6m (0·5–0·7)
	IRR in 2050 (%)	36·4% (34·5–39·1)	38·7% (37·1–44·0)	23·4% (22·4–24·7)	37·7% (34·1–43·8)	29·1% (27·1–32·1)	36·2% (33·6–39·7)	29·1% (27·2–32·1)	36·4% (34·4–39·4)	36·0% (34·9–37·8)	39·0% (37·4–41·2)	37·3% (35·0–40·7)	24·8% (23·7–26·6)
	MRR in 2050 (%)	38·8% (36·9–42·5)	39·8% (38·2–46·6)	26·0% (24·8–27·3)	39·7% (35·9–45·4)	28·9% (27·3–31·1)	37·9% (35·1–41·4)	33·7% (31·3–37·1)	39·0% (36·9–43·1)	37·4% (36·3–38·9)	39·9% (38·5–41·9)	39·5% (37·2–43·8)	28·9% (27·2–31·6)
Accelerated Scale-up Medium coverage, 75% efficacy, 10 years protection	Averted cases before 2050	95·0m (80·5–110·9)	28·2m (23·9–33·9)	1·2m (1·1–1·4)	7·8m (6·2–9·6)	0·9m (0·8–1·1)	44·8m (37·1–52·5)	12·0m (10·2–14·1)	84·8m (71·8–98·9)	10·1m (8·4–12·0)	10·9m (8·9–13·0)	74·5m (62·6–87·3)	9·6m (8·4–10·9)
	Averted tx before 2050	56·0m (49·7–61·6)	13·4m (12·2–14·5)	0·9m (0·8–1·0)	4·9m (4·1–5·7)	0·7m (0·6–0·7)	28·2m (24·3–32·1)	7·9m (7·0–8·8)	50·2m (44·5–55·3)	5·8m (5·1–6·4)	6·5m (5·7–7·2)	43·4m (38·2–48·2)	6·1m (5·6–6·6)
	Averted deaths before 2050	11·4m (10·5–12·3)	4·5m (4·1–5·0)	0·09m (0·08–0·10)	0·6m (0·5–0·8)	0·08m (0·07–0·09)	5·4m (4·8–6·2)	0·6m (0·5–0·7)	10·1m (9·3–11·0)	1·2m (1·1–1·4)	1·3m (1·2–1·5)	9·3m (8·5–10·1)	0·8m (0·6–1·0)
	IRR in 2050 (%)	35·8% (34·2–38·5)	39·2% (37·6–44·6)	22·0% (20·8–23·2)	37·9% (34·6–43·5)	25·6% (23·3–29·6)	34·9% (32·5–38·2)	28·2% (26·6–30·7)	35·9% (34·1–38·7)	35·8% (34·7–37·4)	38·9% (37·5–40·9)	36·7% (34·7–40·0)	24·1% (23·1–25·3)
	MRR in 2050 (%)	37·8% (36·0–41·7)	40·1% (38·4–47·7)	23·4% (22·1–24·9)	39·1% (35·6–44·5)	25·5% (23·6–28·6)	35·8% (33·2–39·3)	31·6% (29·5–34·8)	37·9% (35·9–42·3)	36·9% (36·0–38·3)	39·2% (37·9–41·1)	38·5% (36·3–43·1)	27·3% (25·9–29·4)
***2025 End TB No-New-Vaccine* baseline**													
Basecase Medium coverage, 50% efficacy, 10 years protection	Averted cases before 2050	10·1m (8·4–12·9)	2·9m (2·3–4·2)	0·19m (0·17–0·22)	0·8m (0·6–1·8)	0·1m (0·1–0·2)	4·0m (3·0–6·4)	1·7m (1·3–2·8)	1·0m (0·8–1·4)	7·1m (5·6–9·8)	1·9m (1·6–2·6)	9·0m (7·3–11·8)	1·1m (0·9–1·2)
	Averted tx before 2050	6·1m (5·0–7·8)	1·5m (1·2–2·0)	0·1m (0·1–0·2)	0·5m (0·4–1·1)	0·10m (0·08–0·13)	2·5m (1·8–4·0)	1·1m (0·9–1·9)	0·6m (0·5–0·8)	4·3m (3·2–5·9)	1·2m (1·0–1·6)	5·4m (4·3–7·2)	0·6m (0·6–0·7)
	Averted deaths before 2050	1·1m (0·8–1·5)	0·4m (0·3–0·7)	0·01m (0·01–0·02)	0·1m (0·0–0·1)	0·01m (0·01–0·02)	0·5m (0·3–0·8)	0·07m (0·05–0·13)	0·1m (0·1–0·2)	0·8m (0·6–1·2)	0·1m (0·1–0·2)	0·9m (0·7–1·4)	0·11m (0·10–0·14)

	IRR in 2050 (%)	12·2% (9·7–16·5)	14·2% (10·2–21·8)	7·8% (6·7–9·4)	11·1% (6·5–20·6)	10·8% (9·1–13·9)	11·7% (8·3–16·7)	9·1% (6·7–16·2)	13·4% (10·5–17·6)	12·4% (9·5–17·7)	9·3% (5·8–14·1)	12·1% (9·3–16·8)	12·9% (11·0–15·3)
	MRR in 2050 (%)	14·5% (11·6–20·1)	15·8% (11·6–25·5)	9·5% (8·2–11·4)	12·9% (7·9–22·2)	11·5% (9·5–14·3)	13·5% (9·9–18·5)	12·2% (9·2–19·4)	15·4% (12·7–19·2)	14·6% (11·2–21·2)	12·0% (7·0–18·0)	14·4% (11·2–20·6)	15·3% (13·3–17·7)
Accelerated Scale-up Medium coverage, 50% efficacy, 10 years protection	Averted cases before 2050	15·4m (12·8–20·0)	4·3m (3·4–6·1)	0·3m (0·3–0·3)	1·2m (0·8–2·6)	0·3m (0·2–0·3)	6·6m (4·8–10·5)	2·4m (1·9–3·8)	1·6m (1·3–2·1)	11·2m (8·8–15·5)	2·6m (2·1–3·5)	13·6m (10·9–18·1)	1·9m (1·6–2·1)
	Averted tx before 2050	9·6m (7·8–12·5)	2·3m (1·8–3·1)	0·2m (0·2–0·2)	0·8m (0·5–1·6)	0·19m (0·16–0·24)	4·3m (3·0–6·9)	1·7m (1·3–2·7)	1·0m (0·8–1·3)	6·9m (5·2–9·7)	1·7m (1·4–2·1)	8·5m (6·6–11·3)	1·1m (1·0–1·3)
	Averted deaths before 2050	1·7m (1·3–2·5)	0·7m (0·5–1·1)	0·02m (0·02–0·03)	0·1m (0·1–0·2)	0·02m (0·02–0·03)	0·8m (0·5–1·4)	0·1m (0·1–0·2)	0·2m (0·1–0·3)	1·3m (1·0–2·0)	0·2m (0·1–0·3)	1·5m (1·1–2·3)	0·2m (0·2–0·3)
	IRR in 2050 (%)	9·2% (6·5–14·0)	12·1% (7·7–21·0)	4·7% (3·4–6·6)	8·8% (3·6–19·5)	5·7% (3·8–9·2)	7·7% (4·1–13·6)	6·8% (4·0–14·7)	10·4% (6·9–15·4)	9·2% (5·8–15·3)	7·7% (4·0–12·6)	9·3% (6·2–14·5)	8·9% (6·5–11·9)
	MRR in 2050 (%)	10·6% (7·3–17·3)	13·0% (8·1–24·9)	5·5% (4·1–7·7)	9·7% (4·2–20·4)	6·3% (4·1–9·7)	8·3% (4·5–14·5)	8·5% (5·2–16·7)	11·3% (7·8–15·9)	10·4% (6·5–18·4)	10·0% (4·6–15·8)	10·7% (7·0–18·0)	10·1% (7·4–13·4)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

Table S10.2 Estimated health impact in 2050 by WHO region, income level, and tuberculosis burden level for the infant vaccine scenarios

			WHO Region						TB Burden Level		World Bank Income Group		
Vaccine Scenario	**Health Impact Measure**	**All modelled countries**	**AFR**	**AMR**	**EMR**	**EUR**	**SEAR**	**WPR**	**HBC**	**All other countries**	**LIC**	**LMIC**	**UMIC**
Basecase Medium coverage, 80% efficacy, 10 years protection	Averted cases before 2050	6·7m (5·8–7·7)	2·9m (2·5–3·4)	0·03m (0·02–0·03)	0·8m (0·6–1·1)	0·02m (0·01–0·02)	2·2m (1·6–2·8)	0·8m (0·6–1·0)	6·2m (5·3–7·1)	0·5m (0·4–0·6)	0·9m (0·7–1·1)	5·4m (4·7–6·2)	0·4m (0·3–0·5)
	Averted tx before 2050	2·7m (2·4–2·9)	0·9m (0·8–0·9)	0·02m (0·01–0·02)	0·4m (0·3–0·5)	0·009m (0·008–0·01)	1·0m (0·8–1·2)	0·4m (0·3–0·5)	2·4m (2·2–2·7)	0·2m (0·2–0·3)	0·4m (0·4–0·5)	2·1m (1·9–2·3)	0·2m (0·1–0·2)
	Averted deaths before 2050	0·9m (0·8–1·0)	0·5m (0·4–0·6)	0·003m (0·002–0·003)	0·08m (0·05–0·11)	0·0018m (0·0015–0·0021)	0·3m (0·2–0·4)	0·1m (0·0–0·1)	0·8m (0·7–1·0)	0·07m (0·06–0·08)	0·11m (0·09–0·13)	0·7m (0·6–0·9)	0·1m (0·0–0·1)
	IRR in 2050 (%)	8·8% (7·9–10·4)	11·0% (10·0–14·5)	2·7% (2·4–3·1)	12·0% (9·7–15·6)	2·9% (2·5–3·4)	6·9% (5·8–8·6)	7·2% (5·9–9·2)	9·0% (8·1–10·7)	7·1% (6·4–8·2)	9·8% (8·9–11·1)	9·1% (8·1–11·1)	4·7% (3·9–5·9)
	MRR in 2050 (%)	9·8% (8·7–12·0)	11·3% (10·1–15·7)	3·7% (3·2–4·3)	13·4% (10·5–18·1)	3·3% (2·9–3·9)	7·2% (5·9–9·6)	11·2% (8·5–15·4)	10·1% (8·9–12·5)	7·1% (6·4–8·0)	9·9% (9·0–11·2)	10·0% (8·7–12·5)	6·6% (5·4–8·5)
Accelerated Scale-up Medium coverage, 80% efficacy, 10 years protection	Averted cases before 2050	16·3m (14·0–18·8)	6·3m (5·4–7·2)	0·07m (0·06–0·08)	1·7m (1·3–2·2)	0·07m (0·06–0·09)	6·6m (5·1–8·6)	1·5m (1·2–1·9)	14·7m (12·6–17·1)	1·6m (1·3–1·9)	2·2m (1·8–2·8)	13·3m (11·4–15·5)	0·8m (0·6–0·9)
	Averted tx before 2050	7·7m (6·9–8·6)	2·2m (2·0–2·4)	0·04m (0·04–0·05)	0·9m (0·8–1·2)	0·04m (0·04–0·05)	3·6m (2·9–4·3)	0·9m (0·7–1·0)	6·9m (6·2–7·8)	0·7m (0·7–0·8)	1·1m (1·0–1·3)	6·2m (5·5–7·0)	0·4m (0·3–0·4)
	Averted deaths before 2050	2·3m (2·0–2·6)	1·1m (0·9–1·2)	0·007m (0·006–0·008)	0·2m (0·1–0·2)	0·007m (0·006–0·009)	0·9m (0·7–1·2)	0·1m (0·1–0·2)	2·0m (1·8–2·3)	0·2m (0·2–0·3)	0·3m (0·2–0·3)	1·9m (1·6–2·2)	0·1m (0·1–0·1)
	IRR in 2050 (%)	14·3% (13·0–16·7)	16·7% (15·4–21·6)	4·6% (4·2–5·2)	17·6% (14·5–22·3)	7·5% (6·2–9·8)	12·9% (11·0–15·8)	10·3% (8·7–12·6)	14·4% (13·0–17·0)	13·4% (12·4–14·9)	16·3% (15·1–18·1)	14·9% (13·3–17·9)	6·5% (5·6–7·8)
	MRR in 2050 (%)	15·9% (14·2–19·3)	17·5% (15·9–24·1)	5·8% (5·2–6·6)	19·2% (15·5–24·7)	7·7% (6·5–9·5)	13·4% (11·2–17·0)	15·0% (12·0–19·3)	16·1% (14·3–19·9)	14·1% (13·1–15·3)	16·8% (15·6–18·5)	16·3% (14·4–20·3)	8·9% (7·5–11·1)
Low and high coverage													
Basecase Low coverage, 80% efficacy, 10 years protection	Averted cases before 2050	6·0m (5·2–6·8)	2·6m (2·2–3·0)	0·02m (0·02–0·03)	0·7m (0·5–1·0)	0·01m (0·01–0·02)	1·9m (1·5–2·5)	0·7m (0·5–0·9)	5·5m (4·7–6·3)	0·5m (0·4–0·6)	0·8m (0·6–1·0)	4·8m (4·2–5·5)	0·4m (0·3–0·5)
	Averted tx before 2050	2·4m (2·2–2·6)	0·8m (0·7–0·8)	0·01m (0·01–0·02)	0·4m (0·3–0·5)	0·008m (0·007–0·009)	0·9m (0·7–1·0)	0·3m (0·3–0·4)	2·2m (2·0–2·4)	0·20m (0·18–0·23)	0·4m (0·3–0·4)	1·8m (1·7–2·1)	0·2m (0·1–0·2)
	Averted deaths before 2050	0·8m (0·7–0·9)	0·4m (0·4–0·5)	0·003m (0·002–0·003)	0·1m (0·0–0·1)	0·002m (0·001–0·002)	0·2m (0·2–0·3)	0·1m (0·0–0·1)	0·7m (0·6–0·8)	0·06m (0·05–0·07)	0·09m (0·08–0·12)	0·7m (0·6–0·8)	0·0m (0·0–0·1)

	IRR in 2050 (%)	7·9% (7·1–9·3)	9·8% (9·0–13·1)	2·4% (2·2–2·8)	10·8% (8·6–14·0)	2·6% (2·3–3·0)	6·2% (5·2–7·7)	6·5% (5·3–8·2)	8·1% (7·2–9·6)	6·3% (5·7–7·3)	8·7% (7·9–9·9)	8·2% (7·2–9·9)	4·2% (3·5–5·2)
	MRR in 2050 (%)	8·7% (7·8–10·7)	10·1% (9·0–14·1)	3·3% (2·9–3·9)	12·0% (9·4–16·2)	2·9% (2·5–3·4)	6·4% (5·2–8·6)	10·0% (7·6–13·8)	9·0% (8·0–11·2)	6·3% (5·7–7·2)	8·8% (8·0–10·0)	8·9% (7·7–11·2)	5·9% (4·8–7·5)
Basecase High coverage, 80% efficacy, 10 years protection	Averted cases before 2050	7·4m (6·5–8·6)	3·3m (2·8–3·7)	0·03m (0·03–0·04)	0·9m (0·7–1·2)	0·018m (0·015–0·022)	2·4m (1·8–3·1)	0·9m (0·7–1·1)	6·9m (5·9–7·9)	0·6m (0·5–0·7)	1·0m (0·8–1·2)	6·0m (5·2–6·9)	0·5m (0·4–0·6)
	Averted tx before 2050	3·0m (2·7–3·3)	1·0m (0·9–1·0)	0·017m (0·015–0·019)	0·5m (0·4–0·6)	0·010m (0·009–0·011)	1·1m (0·9–1·3)	0·4m (0·4–0·5)	2·7m (2·5–3·0)	0·3m (0·2–0·3)	0·5m (0·4–0·5)	2·3m (2·1–2·6)	0·2m (0·2–0·2)
	Averted deaths before 2050	1·0m (0·9–1·1)	0·5m (0·4–0·6)	0·003m (0·003–0·004)	0·08m (0·06–0·12)	0·0020m (0·0017–0·0024)	0·3m (0·2–0·4)	0·1m (0·0–0·1)	0·9m (0·8–1·1)	0·08m (0·06–0·09)	0·12m (0·10–0·14)	0·8m (0·7–1·0)	0·1m (0·0–0·1)
	IRR in 2050 (%)	9·7% (8·8–11·4)	12·1% (11·1–16·0)	3·0% (2·7–3·5)	13·3% (10·7–17·1)	3·2% (2·8–3·7)	7·7% (6·4–9·5)	8·0% (6·5–10·1)	9·9% (8·9–11·8)	7·8% (7·0–9·1)	10·8% (9·8–12·2)	10·1% (8·9–12·2)	5·2% (4·4–6·5)
	MRR in 2050 (%)	10·8% (9·6–13·2)	12·5% (11·2–17·3)	4·1% (3·6–4·8)	14·8% (11·6–19·9)	3·7% (3·2–4·3)	8·0% (6·5–10·6)	12·3% (9·4–16·9)	11·2% (9·9–13·8)	7·9% (7·2–8·9)	10·9% (9·9–12·3)	11·1% (9·6–13·8)	7·4% (6·0–9·3)
Accelerated Scale-up Low coverage, 80% efficacy, 10 years protection	Averted cases before 2050	14·6m (12·6–16·8)	5·6m (4·8–6·4)	0·06m (0·05–0·07)	1·5m (1·1–2·0)	0·06m (0·05–0·08)	5·9m (4·6–7·7)	1·4m (1·1–1·7)	13·1m (11·3–15·3)	1·4m (1·2–1·7)	2·0m (1·6–2·5)	11·9m (10·2–13·9)	0·7m (0·5–0·8)
	Averted tx before 2050	6·9m (6·2–7·7)	2·0m (1·8–2·2)	0·04m (0·03–0·04)	0·8m (0·7–1·1)	0·04m (0·03–0·05)	3·2m (2·6–3·9)	0·8m (0·6–0·9)	6·2m (5·5–7·0)	0·7m (0·6–0·7)	1·0m (0·9–1·2)	5·5m (4·9–6·3)	0·3m (0·3–0·4)
	Averted deaths before 2050	2·0m (1·8–2·3)	1·0m (0·8–1·1)	0·006m (0·005–0·008)	0·1m (0·1–0·2)	0·006m (0·005–0·008)	0·8m (0·6–1·0)	0·1m (0·1–0·2)	1·8m (1·6–2·1)	0·20m (0·17–0·22)	0·3m (0·2–0·3)	1·7m (1·4–1·9)	0·1m (0·1–0·1)
	IRR in 2050 (%)	12·9% (11·7–15·1)	15·0% (13·9–19·5)	4·1% (3·8–4·7)	15·8% (13·0–20·1)	6·7% (5·5–8·8)	11·6% (9·9–14·2)	9·2% (7·8–11·3)	13·0% (11·6–15·4)	12·0% (11·1–13·5)	14·6% (13·5–16·3)	13·4% (11·9–16·1)	5·8% (5·0–7·0)
	MRR in 2050 (%)	14·3% (12·8–17·4)	15·7% (14·2–21·8)	5·2% (4·7–5·9)	17·3% (13·9–22·3)	6·9% (5·8–8·5)	12·1% (10·1–15·4)	13·5% (10·8–17·4)	14·5% (12·8–18·0)	12·6% (11·7–13·8)	15·1% (14·0–16·7)	14·6% (12·9–18·3)	8·0% (6·7–9·9)
Accelerated Scale-up High coverage, 80% efficacy, 10 years protection	Averted cases before 2050	18·0m (15·5–20·7)	6·9m (5·9–7·9)	0·08m (0·07–0·09)	1·9m (1·4–2·4)	0·08m (0·06–0·10)	7·3m (5·7–9·4)	1·7m (1·3–2·1)	16·2m (13·9–18·9)	1·8m (1·5–2·1)	2·5m (2·0–3·1)	14·6m (12·5–17·1)	0·9m (0·7–1·0)
	Averted tx before 2050	8·5m (7·6–9·5)	2·5m (2·2–2·7)	0·05m (0·04–0·05)	1·0m (0·8–1·3)	0·05m (0·04–0·06)	3·9m (3·3–4·8)	0·9m (0·8–1·1)	7·7m (6·9–8·6)	0·8m (0·7–0·9)	1·3m (1·1–1·4)	6·8m (6·1–7·8)	0·4m (0·3–0·5)
	Averted deaths before 2050	2·5m (2·2–2·8)	1·2m (1·0–1·4)	0·008m (0·007–0·009)	0·2m (0·1–0·2)	0·008m (0·007–0·010)	1·0m (0·7–1·3)	0·1m (0·1–0·2)	2·2m (1·9–2·6)	0·2m (0·2–0·3)	0·3m (0·3–0·4)	2·1m (1·8–2·4)	0·1m (0·1–0·1)
	IRR in 2050 (%)	15·7% (14·3–18·3)	18·3% (17·0–23·5)	5·1% (4·7–5·7)	19·3% (15·9–24·3)	8·2% (6·8–10·7)	14·1% (12·1–17·3)	11·3% (9·6–13·8)	15·8% (14·2–18·6)	14·7% (13·6–16·3)	17·8% (16·5–19·8)	16·3% (14·6–19·5)	7·2% (6·1–8·6)

	MRR in 2050 (%)	17·4% (15·7–21·1)	19·2% (17·5–26·2)	6·4% (5·8–7·3)	21·0% (17·1–27·0)	8·4% (7·2–10·4)	14·7% (12·4–18·6)	16·5% (13·3–21·1)	17·7% (15·7–21·7)	15·5% (14·4–16·8)	18·5% (17·1–20·3)	17·9% (15·8–22·2)	9·8% (8·3–12·2)
Lifelong protection													
Basecase Medium coverage, 80% efficacy, lifelong protection	Averted cases before 2050	11·8m (10·2–13·7)	5·2m (4·4–6·0)	0·1m (0·0–0·1)	1·4m (1·1–1·8)	0·029m (0·025–0·034)	3·8m (2·9–4·9)	1·4m (1·1–1·8)	10·9m (9·4–12·6)	0·9m (0·8–1·1)	1·5m (1·2–1·9)	9·5m (8·2–11·0)	0·8m (0·6–1·0)
	Averted tx before 2050	4·6m (4·2–5·0)	1·5m (1·3–1·6)	0·029m (0·025–0·032)	0·7m (0·6–0·9)	0·02m (0·01–0·02)	1·7m (1·4–2·0)	0·7m (0·6–0·8)	4·2m (3·8–4·6)	0·4m (0·3–0·4)	0·7m (0·6–0·8)	3·6m (3·2–4·0)	0·3m (0·3–0·4)
	Averted deaths before 2050	1·5m (1·3–1·7)	0·8m (0·7–0·9)	0·01m (0·00–0·01)	0·1m (0·1–0·2)	0·003m (0·003–0·004)	0·5m (0·3–0·6)	0·1m (0·1–0·2)	1·4m (1·2–1·6)	0·11m (0·09–0·13)	0·2m (0·1–0·2)	1·2m (1·1–1·4)	0·1m (0·1–0·1)
	IRR in 2050 (%)	17·4% (15·9–20·1)	21·6% (20·0–27·5)	6·1% (5·5–7·0)	23·4% (19·2–29·6)	5·8% (5·2–6·6)	13·7% (11·7–16·7)	15·1% (12·5–18·8)	17·8% (16·2–20·9)	13·6% (12·3–15·6)	18·8% (17·2–21·2)	18·0% (16·1–21·4)	10·5% (8·8–12·9)
	MRR in 2050 (%)	18·1% (16·2–21·7)	20·9% (18·9–28·2)	7·5% (6·5–8·6)	24·6% (19·7–32·0)	6·4% (5·6–7·3)	13·5% (11·1–17·5)	20·8% (16·1–27·7)	18·7% (16·7–22·7)	12·8% (11·6–14·4)	17·9% (16·4–20·1)	18·5% (16·2–22·7)	13·4% (11·1–16·7)
Accelerated Scale-up Medium coverage, 80% efficacy, lifelong protection	Averted cases before 2050	32·2m (27·5–37·5)	12·0m (10·4–14·1)	0·1m (0·1–0·2)	3·2m (2·4–4·2)	0·1m (0·1–0·2)	13·5m (10·6–17·0)	3·1m (2·5–3·9)	29·1m (24·6–34·0)	3·2m (2·6–3·7)	4·4m (3·6–5·4)	26·2m (22·3–30·9)	1·6m (1·3–2·0)
	Averted tx before 2050	15·3m (13·7–17·1)	4·4m (4·0–4·7)	0·09m (0·08–0·10)	1·8m (1·4–2·2)	0·09m (0·07–0·10)	7·2m (6·0–8·7)	1·7m (1·4–2·0)	13·8m (12·3–15·6)	1·5m (1·3–1·6)	2·2m (1·9–2·5)	12·3m (10·9–14·0)	0·8m (0·7–0·9)
	Averted deaths before 2050	4·2m (3·7–4·8)	2·0m (1·7–2·2)	0·01m (0·01–0·02)	0·3m (0·2–0·4)	0·01m (0·01–0·02)	1·7m (1·3–2·2)	0·2m (0·2–0·3)	3·8m (3·3–4·3)	0·4m (0·4–0·5)	0·5m (0·5–0·6)	3·5m (3·0–4·0)	0·2m (0·1–0·3)
	IRR in 2050 (%)	31·8% (29·4–35·5)	36·2% (34·2–43·3)	11·8% (10·9–13·0)	37·1% (31·7–45·4)	17·1% (14·6–21·3)	29·6% (26·1–34·7)	23·7% (20·4–28·1)	32·1% (29·5–36·2)	29·5% (27·9–32·0)	35·5% (33·4–38·5)	33·1% (30·1–37·7)	15·9% (13·7–18·8)
	MRR in 2050 (%)	33·0% (30·2–38·3)	35·5% (33·0–45·5)	13·4% (12·2–14·9)	38·4% (32·2–47·3)	16·7% (14·6–19·8)	29·2% (25·3–35·1)	30·5% (25·3–37·4)	33·5% (30·3–39·3)	29·3% (27·7–31·4)	34·7% (32·7–37·4)	33·7% (30·4–40·1)	19·8% (16·9–24·0)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

10.2 Absolute differences in numbers averted between scenarios

In Table S10.3 we quantify the absolute difference in the number of cases, treatments, and deaths averted by each of the primary delivery scenarios presented in the main text for the adolescent/adult vaccine and the infant vaccine.

Table S10.3 Absolute differences in cases, treatments, and deaths averted by the primary vaccine delivery scenarios presented in the main text

			WHO Region						TB Burden Level		World Bank Income Group		
Vaccine Scenario	**Health Impact Measure**	**All modelled countries**	**AFR**	**AMR**	**EMR**	**EUR**	**SEAR**	**WPR**	**HBC**	**All other countries**	**LIC**	**LMIC**	**UMIC**
Adolescent/adult vaccine													
Difference between Accelerated Scale-up scenario and Basecase scenario	Averted cases before 2050	21·5m (4·0–38·8)	5·6m (0·0–11·4)	0·3m (0·1–0·5)	1·5m (-0·5–3·6)	0·3m (0·1–0·4)	11·5m (2·7–20·5)	2·2m (0·0–4·5)	18·8m (3·1–34·3)	2·8m (0·9–4·8)	2·5m (0·2–4·9)	17·4m (3·2–31·6)	1·7m (0·2–3·1)
	Averted tx before 2050	13·7m (7·1–20·4)	2·9m (1·7–4·2)	0·2m (0·1–0·3)	1·0m (0·1–2·0)	0·2m (0·1–0·3)	7·7m (3·3–12·1)	1·6m (0·5–2·6)	12·0m (5·9–18·0)	1·7m (1·0–2·4)	1·6m (0·7–2·4)	11·0m (5·4–16·7)	1·1m (0·6–1·7)
	Averted deaths before 2050	2·9m (1·9–3·9)	1·0m (0·5–1·5)	0·02m (0·01–0·03)	0·1m (0·0–0·3)	0·03m (0·02–0·03)	1·5m (0·7–2·4)	0·1m (0·1–0·2)	2·5m (1·5–3·4)	0·4m (0·2–0·5)	0·3m (0·2–0·5)	2·4m (1·5–3·3)	0·1m (-0·1–0·3)
Difference between Basecase scenario and Routine Only scenario	Averted cases before 2050	35·2m (27·1–44·0)	10·4m (7·8–13·7)	0·5m (0·4–0·6)	3·0m (1·9–4·1)	0·3m (0·3–0·4)	16·1m (11·6–20·4)	4·9m (3·8–6·2)	31·7m (24·3–39·7)	3·4m (2·6–4·3)	3·9m (2·8–5·2)	27·1m (20·3–34·1)	4·2m (3·4–5·0)
	Averted tx before 2050	20·8m (17·3–23·6)	5·1m (4·3–5·7)	0·3m (0·3–0·4)	1·9m (1·4–2·4)	0·2m (0·2–0·2)	10·0m (7·9–12·0)	3·2m (2·7–3·7)	18·8m (15·7–21·4)	2·0m (1·6–2·3)	2·3m (1·9–2·7)	15·7m (12·9–18·3)	2·7m (2·3–2·9)
	Averted deaths before 2050	3·9m (3·4–4·5)	1·6m (1·3–1·9)	0·03m (0·03–0·04)	0·2m (0·1–0·3)	0·03m (0·02–0·03)	1·9m (1·4–2·3)	0·2m (0·2–0·3)	3·6m (3·0–4·1)	0·4m (0·3–0·4)	0·4m (0·4–0·5)	3·2m (2·7–3·7)	0·3m (0·2–0·4)
Difference between Accelerated Scale-up scenario and Routine Only scenario	Averted cases before 2050	56·7m (45·6–68·4)	16·0m (12·8–20·2)	0·8m (0·7–0·9)	4·5m (3·1–6·0)	0·6m (0·5–0·7)	27·6m (21·4–33·8)	7·1m (5·7–8·7)	50·5m (40·5–60·9)	6·3m (5·0–7·7)	6·4m (4·9–8·1)	44·5m (35·3–54·0)	5·9m (4·9–6·8)
	Averted tx before 2050	34·5m (29·8–38·6)	8·0m (7·1–8·8)	0·6m (0·5–0·6)	2·9m (2·2–3·6)	0·4m (0·4–0·5)	17·7m (14·6–20·8)	4·8m (4·1–5·5)	30·8m (26·5–34·5)	3·7m (3·2–4·1)	3·9m (3·3–4·5)	26·7m (22·8–30·4)	3·8m (3·4–4·1)
	Averted deaths before 2050	6·8m (6·1–7·6)	2·6m (2·2–3·0)	0·1m (0·1–0·1)	0·4m (0·3–0·5)	0·1m (0·0–0·1)	3·4m (2·8–4·0)	0·3m (0·3–0·4)	6·1m (5·3–6·8)	0·8m (0·7–0·9)	0·8m (0·7–0·9)	5·6m (4·9–6·3)	0·5m (0·3–0·6)
Infant vaccine													

Difference between Accelerated Scale-up scenario and Basecase scenario	Averted cases before 2050	9·6m (6·3–13·0)	3·3m (2·0–4·7)	0·04m (0·03–0·06)	0·9m (0·2–1·6)	0·05m (0·04–0·08)	4·5m (2·4–6·9)	0·8m (0·2–1·3)	8·5m (5·5–11·8)	1·1m (0·7–1·4)	1·4m (0·7–2·1)	7·9m (5·2–10·8)	0·4m (0·1–0·6)
	Averted tx before 2050	5·0m (4·0–6·2)	1·4m (1·1–1·7)	0·03m (0·02–0·03)	0·5m (0·2–0·9)	0·03m (0·03–0·04)	2·6m (1·8–3·5)	0·5m (0·2–0·7)	4·5m (3·5–5·6)	0·5m (0·4–0·6)	0·7m (0·5–1·0)	4·1m (3·2–5·2)	0·2m (0·1–0·3)
	Averted deaths before 2050	1·4m (1·0–1·8)	0·6m (0·3–0·8)	0·004m (0·003–0·006)	0·1m (0·0–0·2)	0·005m (0·004–0·007)	0·6m (0·3–1·0)	0·1m (0·0–0·1)	1·2m (0·8–1·6)	0·2m (0·1–0·2)	0·2m (0·1–0·3)	1·1m (0·7–1·5)	0·05m (0·0–0·1)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

10.3 Comparing to the 2035 End TB incidence target

We calculated the incidence rate in 2035 for each *No-New-Vaccine* baseline and for each vaccine scenario to compare with the 2035 End TB incidence target of a 90% reduction in the tuberculosis incidence rate compared to the 2015 incidence rate. Results for all modelled countries, and for each of the select model groupings for outcome reporting are provided in Table S10.4, as the median estimate of the incidence rate per 100,000 population and 95% uncertainty range, with all vaccine scenarios assuming medium coverage and 10-years protection.

For all modelled countries, the estimated incidence rate in 2015 was approximately 164·2 per 100,000 population. A 90% reduction is equivalent to an incidence rate of 16·4 per 100,000 population. With the *Status Quo No-New-Vaccine* baseline, the closest vaccine scenario to reaching this target reduction is the *Accelerated Scale-up* scenario of an adolescent/adult vaccine with vaccine efficacy increased to 75%, which has an estimated incidence rate of 88·1 (70·9–104·7) per 100,000 population or meeting approximately 52% of the goal. With the *2025 End TB No-New-Vaccine* baseline, progress is increased, with the standard *Basecase* scenario of the adolescent/adult vaccine achieving an incidence rate of 42·5 (37·1–50·6) per 100,000 population, and the standard *Accelerated Scale-up* scenario achieving an incidence rate of 43·4 (37·7–51·6) per 100,000 population, or 82% of the target.

Table S10.4 Estimated incidence rate (per 100,000 population) for each vaccine scenario in 2035 to compare to meeting the 2035 End TB target

	All modelled countries	WHO Region						World Bank Income Group			TB Burden Level	
Scenario		AFR	AMR	EMR	EUR	SEAR	WPR	LIC	LMIC	UMIC	HBC	All other countries
Status Quo No-New-Vaccine baseline	138·8 (114·2–163·6)	196·8 (154·9–240·4)	26·2 (22·3–30·0)	94·8 (76·2–117·4)	31·4 (26·8–36·4)	213·2 (179·1–245·2)	85·3 (70·6–101·5)	132·3 (108·2–158·7)	199·6 (163·1–236·4)	50·6 (43·6–57·5)	169·9 (139·7–200·0)	55·9 (46·0–65·9)
Adolescent/adult vaccine: *Basecase*, 50% efficacy	113·5 (93·1–133·9)	155·4 (121·6–191·1)	20·6 (17·4–23·7)	70·9 (56·8–88·3)	26·0 (22·1–30·3)	183·9 (154·4–211·4)	65·2 (53·5–78·3)	110·6 (90·2–133·0)	165·0 (134·6–195·3)	38·1 (32·6–43·6)	138·0 (113·1–162·5)	48·3 (39·6–57·4)
Adolescent/adult vaccine: *Accelerated Scale-up*, 50% efficacy	103·8 (84·1–123·0)	145·4 (110·6–179·3)	21·2 (18·0–24·4)	69·3 (54·9–86·7)	25·0 (21·3–29·3)	157·2 (130·8–180·5)	67·2 (54·8–80·4)	96·9 (78·3–116·9)	147·6 (118·4–175·3)	41·0 (35·0–46·8)	126·9 (102·8–150·2)	42·3 (34·7–50·6)
Adolescent/adult vaccine: *Routine Only*, 50% efficacy	137·3 (112·9–162·0)	193·6 (151·8–236·6)	26·1 (22·2–29·8)	93·2 (74·8–115·4)	31·3 (26·7–36·3)	212·2 (178·3–243·8)	84·1 (69·6–100·4)	130·8 (107·0–156·8)	197·5 (161·3–233·9)	50·1 (43·2–56·9)	168·1 (138·0–197·9)	55·5 (45·7–65·5)
Adolescent/adult vaccine: *Basecase*, 75% efficacy	100·9 (82·7–119·1)	135·1 (105·4–166·1)	17·8 (15·0–20·5)	59·3 (47·4–74·1)	23·2 (19·7–27·2)	169·1 (141·8–194·1)	55·3 (45·1–66·8)	99·9 (81·3–120·5)	148·0 (120·7–174·7)	31·8 (26·9–36·4)	122·2 (100·0–143·6)	44·5 (36·4–53·1)

Adolescent/adult vaccine: *Accelerated Scale-up*, 75% efficacy	88·1 (70·9–104·7)	122·0 (91·2–150·7)	18·8 (15·9–21·7)	58·4 (45·7–72·9)	22·1 (18·7–25·8)	132·4 (110·2–153·1)	58·4 (47·4–70·0)	80·9 (65·1–98·1)	124·3 (99·0–148·4)	36·2 (30·8–41·3)	107·5 (86·4–127·8)	36·1 (29·6–43·4)
Infant vaccine: *Basecase*, 80% efficacy	138·0 (113·5–162·7)	194·8 (153·1–237·9)	26·1 (22·2–29·9)	93·8 (75·3–116·2)	31·3 (26·8–36·4)	212·8 (178·8–244·6)	84·6 (70·1–100·9)	131·5 (107·5–157·7)	198·5 (162·2–235·1)	50·3 (43·4–57·2)	169·0 (138·8–198·9)	55·7 (45·8–65·7)
Infant vaccine: *Accelerated Scale-up*, 80% efficacy	133·1 (109·1–157·0)	186·6 (145·6–228·0)	25·8 (22·0–29·6)	89·0 (71·5–110·6)	30·8 (26·3–35·8)	205·8 (172·8–236·1)	82·8 (68·6–98·9)	125·3 (102·3–150·1)	191·0 (155·9–226·0)	49·7 (42·9–56·5)	163·0 (133·4–192·0)	53·8 (44·2–63·7)
2025 End TB No-New-Vaccine baseline	51·5 (45·0–61·2)	70·2 (58·8–85·5)	12·3 (11·1–13·4)	36·4 (28·3–58·2)	17·4 (14·7–21·2)	73·0 (56·8-100·1)	37·1 (30·2–49·2)	46·9 (40·3–56·1)	69·0 (57·5–87·5)	26·4 (23·5–31·5)	62·0 (53·2–75·2)	23·3 (20·7–26·2)
Adolescent/adult vaccine: *Basecase*, 50% efficacy	42·5 (37·1–50·6)	56·6 (47·5–68·0)	9·8 (8·9–10·7)	28·0 (21·9–44·0)	14·3 (12·2–17·2)	63·1 (49·3–85·9)	29·3 (24·0–38·2)	39·7 (34·0–46·7)	57·7 (48·4–73·2)	20·3 (18·1–24·2)	50·6 (43·4–61·8)	20·4 (18·1–23·0)
Adolescent/adult vaccine: *Accelerated Scale-up*, 50% efficacy	43·4 (37·7–51·6)	58·5 (48·5–70·9)	10·6 (9·6–11·6)	30·5 (23·7–45·7)	15·0 (12·6–18·3)	61·7 (47·9–83·2)	31·8 (26·0–41·4)	39·4 (33·9–46·4)	58·0 (48·2–72·8)	22·7 (20·3–27·0)	52·2 (44·7–63·3)	19·9 (17·7–22·2)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

10.4 Averted cases of drug-resistant tuberculosis

Table S10.5 Estimated number of drug-resistant cases averted between vaccine introduction and 2050 for the primary vaccine scenarios for the adolescent and adult vaccine

	All modelled countries	WHO Region						World Bank Income Group			TB Burden Level	
Scenario		AFR	AMR	EMR	EUR	SEAR	WPR	LIC	LMIC	UMIC	HBC	All other countries
Base-case, 50% efficacy	1.4m (1.2–1.6)	0.4m (0.3–0.5)	0.02m (0.01–0.02)	0.1m (0.1–0.2)	0.1m (0.1–0.1)	0.5m (0.4–0.6)	0.2m (0.2–0.2)	0.1m (0.1–0.1)	1.0m (0.8–1.2)	0.3m (0.2–0.3)	1.2m (1.0–1.4)	0.2m (0.1–0.2)
Accelerated Scale-up, 50% efficacy	2.0m (1.7–2.3)	0.5m (0.5–0.6)	0.02m (0.02–0.03)	0.2m (0.2–0.3)	0.1m (0.1–0.2)	0.8m (0.7–1.0)	0.3m (0.3–0.3)	0.1m (0.1–0.2)	1.5m (1.3–1.7)	0.4m (0.3–0.4)	1.7m (1.5–2.0)	0.3m (0.3–0.3)
Routine-only, 50% efficacy	0.3m (0.2–0.3)	0.1m (0.09–0.1)	0.001m (0.001–0.002)	0.03m (0.03–0.05)	0.005m (0.004–0.006)	0.09m (0.07–0.1)	0.02m (0.02–0.03)	0.02m (0.02–0.03)	0.2m (0.2–0.2)	0.03m (0.02–0.03)	0.2m (0.2–0.3)	0.02m (0.02–0.02)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

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3.4 Comparison with Knight et al., 2014

The objective of Research Paper 1 was to generate evidence for global decision makers based on the estimated impact of vaccines with characteristics aligned with WHO PPCs in LMICs.[2] In 2014, Knight et al. published *Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries* to investigate the impact of hypothetical tuberculosis vaccines in 91 LMICs.[3] In order to place the results from Research Paper 1 in the wider context of previously available evidence from modelling studies on tuberculosis vaccine impact in LMICs, I have summarised the results from both studies below, discussed similarities and differences between approaches, and described the implications of the results for decision makers.

Comparison of key results

Knight et al. found a lower impact from a vaccine for infants compared to a vaccine for adolescents/adults.[3] By introducing a 60% efficacy vaccine with 10 years duration of protection, 0.7–2.7% of the cumulative cases between 2024–2050 in LMICs could be averted with an infant vaccine, compared to 42.4–52.8% of cumulative cases averted with an adolescent/adult vaccine delivered routinely to those age 10 and through repeat campaigns to those aged 11+.[3] The study also estimated that the cost per dose of an adolescent/adult vaccine could be higher than an infant vaccine and still be cost-effective.[3]

Clark et al. investigated the impact of an 80% efficacy infant vaccine to prevent disease and a 50% efficacy adolescent/adult vaccine to prevent disease under varying delivery strategies.[2] With neonatal delivery of the infant vaccine, 6.7 (5.8–7.7) million cases could be averted by 2050 with country-specific delivery between 2028–2047, compared to 16.3 (14.0–18.8) million cases averted if all countries introduced the vaccine in 2025.[2] The adolescent/adult vaccine delivered routinely to those age 10 and as a mass vaccination campaign to ages 11+ could avert 44.0 (37.2–51.6) million cases by 2050 if delivered in country-specific years over 2028–2047, compared to 65.5 (55.6–76.0) million cases if all countries introduced the vaccine in 2025.[2]

Comparison of model and vaccine characteristics

There were notable differences in the model and vaccine characteristics between Knight et al., 2014[3] and Clark et al., 2023[2] which are compared in Table 7 and summarised below.

Table 7 Model and vaccine characteristics in Knight et al. and Clark et al.

	Knight et al., 2014[3]	Clark et al., 2023[2]
Model Characteristics		
Natural history model structure	Five compartments: Susceptible, Latent, Infectious TB, Non-infectious TB, and Treated & Recovered	Eight compartments: Uninfected-Naive, Uninfected-Cleared, Infection-Fast, Infection-Slow, Subclinical disease, Clinical disease, On-treatment, Recovered
Age structure	Single ages	Single ages from 0–79, one age group from 80–89, and one age group from 90–99
Calibration method	Approximation Bayesian Computation - Markov chain Monte Carlo	History matching with emulation
Calibration targets	Calibrated to the population size in 2009 and 2050, and the tuberculosis incidence and mortality in 2009 for those with and without HIV	Nine (non-HIV) or thirteen (HIV) targets in 2019: • TB incidence rate (all ages/children/adults), • TB notification rate (all ages/children/adults), • TB mortality rate (all ages) • fraction of subclinical TB • Risk of TB for high- vs low-access-to-care • HIV prevalence • ART coverage • TB incidence rate in PLHIV • TB mortality rate in PLHIV
Risk groups	HIV	HIV, access-to-care (low and high)
Vaccine Characteristics		
Vaccine product	A hypothetical infant and adolescent/adult vaccine	An infant and adolescent/adult vaccine aligned with the characteristics from WHO PPCs
Vaccine efficacy	Both infant and adolescent/adult vaccines: 40%, 60%, 80%	Infant: 80% Adolescent/adult: 50%, 75%
Mechanism of effect	Prevention of disease	Prevention of disease
Host infection status required for efficacy	Both infant and adolescent/adult vaccines: Any-infection status	Infant: No-current-infection Adolescent/adult: Any-infection
Duration of protection	5 years, 10 years, lifelong	10 years, lifelong
Time horizon	2024–2050	2025–2050

Model Characteristics

Knight et al. represented tuberculosis natural history with five compartments and disaggregated disease into infectious and non-infectious tuberculosis. Uninfected individuals could become infected and progress to the latent compartment but could also progress directly to the infectious or non-infectious disease compartments. The model structure in Clark et al. included eight compartments, including active disease disaggregated into subclinical and clinical tuberculosis. The force of infection was adjusted to account for the proportion of extrapulmonary tuberculosis instead of explicitly modelling non-infectious tuberculosis. In contrast to Knight et al., once previously infection-naive individuals became infected, they progressed through the latency compartments before entering the active tuberculosis compartment. Individuals in the latency compartments could also self-clear their infection, where it was assumed that they would no longer be able to progress to active tuberculosis without reinfection, as opposed to Knight et al. where it was assumed that infection was lifelong. In Knight et al, individuals in the treated and recovered compartment could return to the latent, infectious, and non-infectious compartments through reinfection and/or relapse. Clark et al. assumed that reinfection or relapse from the resolved class would result in progression to the active disease compartment, but not the latency compartments. Differences in the model structures could have resulted in different representations of the epidemic for each country between Knight et al. and Clark et al., and therefore differences in estimated intervention impact.

Knight et al. assumed scale-up of non-vaccine interventions before vaccine introduction to estimate the most conservative vaccine impact, and therefore the calibrated burden of disease in 2050 is in line with a 2% per year decline. However, all the decline was assumed to happen before 2024 (when vaccines were introduced), and therefore no interactions between vaccine introduction and intervention scale-up were included. Clark et al. assumed that non-vaccine interventions (such as tuberculosis diagnostics and treatment) would continue at their current trends, and therefore simulated a higher level of burden to 2050. The higher burden projected in Clark et al. in the scenario where no new vaccine was introduced implied that more burden was available for vaccines to address, and therefore the estimated vaccine impact could have been overestimated, compared to Knight et al. where a portion of the burden was already reduced by other non-vaccine interventions.

Knight et al. used estimates from the United Nations population data and projections, 2010 revision to calibrate the model for each country to the population size in 2009 and 2050. Additional calibration targets included estimates of the tuberculosis incidence and mortality rates for those with and without HIV in 2009. In Clark et al., yearly demographic adjustments ensured the model population for each age and country matched the United Nations population data and projections, 2019 revision.[4] All countries were calibrated to nine (non-HIV countries) or thirteen (HIV countries) epidemiological targets in 2019, including age-specific incidence and case notification rate targets. With more calibration targets in Clark et al. and fitting the demographic data for each age and year, the epidemiological and population trends predicted in each country were likely more consistent with the data and represented the underlying population more accurately.

Vaccine Characteristics

Both studies investigated a prevention of disease vaccine that was effective in all populations, but Clark et al. modelled more conservative vaccine characteristic assumptions. For all scenarios and all countries, the vaccine in Knight et al. was introduced in 2024 with instantaneous scale-up to target coverage. The *Accelerated Scale-up* scenario from Clark et al. introduced the vaccine in all countries in 2025, but the primary *Basecase* scenario and the *Routine Only* scenario introduced the vaccine in more realistic country-specific introduction years between 2028–2047, with scale-up to target vaccine coverage occurring over 5 years. All countries would have reached their maximum achieved coverage by the end of 2024 in Knight et al., whereas some countries in the Basecase Clark et al. scenario would only be in year three of scale-up to target coverage when impact measurements were calculated in 2050. Therefore, the earlier and instantaneous introduction in Knight et al. would have contributed to the increased health impact by 2050 compared to the Clark et al. *Basecase* scenario.

Knight et al. modelled vaccine protection as *take*, where individuals who are vaccinated are assumed to have no risk of progressing to disease while they are protected, and therefore the vaccine efficacy represents the proportion of those vaccinated who are fully protected. In Clark et al., vaccine protection was modelled as *degree*, where all individuals who were vaccinated received some protection from the vaccine equal to the vaccine efficacy. Vaccine protection waning was modelled as *exact* in Knight et al., and modelled with exponential waning in Clark et

al., with protection equal to 10 years on average. Given that individuals who received a vaccine in Clark et al. still were at risk of progressing to disease, and were not protected for ten years exactly, the more conservative vaccine characteristic assumptions in Clark et al. would have resulted in a lower health impact.

Both authors modelled an infant vaccine delivered neonatally, and an adolescent/adult vaccine that was routinely delivered to those aged 10, and as a campaign for ages 11+. Knight et al. included repeat campaigns of the adolescent/adult vaccine every 10 years, but no repeat campaigns were modelled in Clark et al. The lack of repeat campaigns in Clark et al. would have resulted in a lower health impact by 2050.

Summary of comparison and implications for decision makers

Regardless of the differences between Knight et al. and Clark et al., both papers demonstrated that novel tuberculosis vaccines could have a positive health impact in LMICs. The conservative vaccine assumptions modelled in Clark et al., including later vaccine introduction and scale-up over five years, degree vaccine efficacy and exponential waning of protection, as well as no repeat campaigns for the adolescent/adult vaccine, contributed to the smaller predicted impact. However, given that the assumptions in Clark et al. were based on real world characteristics, it is possible that this modelling gives a more realistic example of the likely impact following introduction. Comparing between the two studies however, findings are largely consistent, and therefore provide clear evidence for decision makers when considering new vaccine introduction.

3.5 Subsequent LMIC modelling work I contributed to

Building off of the health impact of alternative delivery strategies for new tuberculosis vaccines, I contributed to three closely-related published economics papers describing the cost and cost-effectiveness,[5] health equity and financial protection,[6] and macroeconomic benefits[7] of introducing new tuberculosis vaccines in LMICs. These papers are not included here, but I list the key results to highlight additional findings of the economic impact of new tuberculosis vaccines in LMICs which would be of interest to global decision makers during decisions surrounding vaccine investment and development.

1. *Portnoy A, **Clark RA,** Quaife M, et al. The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study. PLOS Med 2023; 20: e1004155.*

In the first economics paper, we estimated the costs and cost-effectiveness of the vaccine scenarios described in Research Paper 1. When compared to our primary opportunity cost threshold, 1× gross domestic product (GDP) per capita threshold, from the health-system perspective, the *Basecase* vaccine scenario for the infant and adolescent/adult vaccines could be cost-effective in 45% and 61% of the LMICs respectively. In particular, for the 27 high tuberculosis burden countries that were modelled, the *Basecase* infant vaccine could be cost-effective in 89% of the countries, and the *Basecase* adolescent/adult vaccine could be cost-effective in all countries. The vaccine scenarios were more likely to be cost-effective with instantaneous introduction in 2025 (*Accelerated Scale-up*) and when accounting for patient non-medical and productivity costs from the societal perspective. Overall, we demonstrated that vaccines with characteristics aligned with WHO PPCs could be a cost-effective intervention in 105 LMICs, particularly in countries with a high burden of tuberculosis.

2. *Portnoy A, **Clark RA,** Weerasuriya CK, et al. The potential impact of novel tuberculosis vaccines on health equity and financial protection in low-income and middle-income countries. BMJ Glob Health 2023; 8: e012466.*

In the second economics paper, we used the access-to-care structure of the model described in Research Paper 1 to investigate the distribution of cases and household catastrophic costs (defined as tuberculosis associated costs accounting for greater than 20% of a households annual income) averted from vaccination by wealth quintile. With the *Basecase* scenarios for both vaccine products, we found that 56% of the cumulative tuberculosis cases averted by vaccination and 66% of occurrences where costs exceed 20% of the total household income (catastrophic costs) could be averted in the lowest two wealth quintiles. Instances of catastrophic costs averted were increased from 22.9 (21.4–24.5) million households with costs averted in the *Basecase* adolescent/adult scenario, to 33.4 (31.2–35.8) and 33.9 (31.7–36.3) million households with a higher vaccine efficacy and the *Accelerated Scale-up* scenario respectively. Overall, introducing a

vaccine with characteristics aligned with WHO PPCs has the potential to reduce income-based inequalities in LMICs.

3. *Portnoy A, Arcand J-L, **Clark RA,** et al. The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries: A modeling study. PLOS Med 2023; 20: e1004252.*

In the third economics paper, a separate macroeconomic model was used to simulate country-specific trends in GDP between 2020–2080 to investigate changes in GDP after vaccination compared to no-new-vaccine introduction. In this paper, we focussed on the *Basecase* infant and *Basecase* adolescent/adult vaccine scenarios from Research Paper 1. An increase in GDP was observed following vaccination in both scenarios, with an estimated US$0.2 (0.1–0.4) trillion increase for the *Basecase* infant vaccine and $1.6 (0.8–3.0) trillion for the *Basecase* adolescent/adult vaccine over all 105 LMICs. The increase in GDP was delayed following vaccine introduction, particularly for the infant vaccine, to allow for the ageing of the population that was vaccinated. As with previous findings from our LMIC modelling work, the largest impact was found in countries with a higher burden of tuberculosis, such as those in the WHO South-East Asian region and lower-middle-income countries, where we observed a higher absolute and relative increase in GDP.

3.6 Summary

In Chapter 3, I addressed thesis **Aim 1** through **Objectives 1** and **2**. For **Objective 1**, described in Section 3.3, I developed a new tuberculosis model structure which incorporates novel aspects of tuberculosis natural history, and a new vaccine model structure which allows for protection from multiple vaccines and is able to represent sophisticated and realistic vaccine delivery strategies. I used the newly developed structures to address **Objective 2**, where I independently calibrated the tuberculosis model to the 105 LMICs, simulated the introduction of vaccines aligned with WHO PPCs, and calculated and compared the health impact between vaccine delivery scenarios by WHO region, World Bank Income Group, WHO burden level.

I demonstrated that multi-country modelling of vaccines with characteristics aligned with WHO PPCs could have a substantial health impact on the burden of tuberculosis in 105 LMICs. The largest impact could result in the WHO South-East Asian and African regions compared to other WHO regions, and for lower-middle-income countries compared to low-income countries or upper-middle-income countries. Accelerated introduction in 2025 similar to the pace of COVID-19 vaccine delivery could result in the largest number of cases, treatments, and deaths averted by 2050 in all countries. However, even introduction in country-specific years determined based on the historical pace of vaccine introduction and reaching target coverage over 5 years (the *Basecase* scenario) could have a large impact by 2050.

Research Paper 1 highlighted the importance of demonstrating the global health gains from new tuberculosis vaccines to provide evidence for global investors and support vaccine manufacturing and development. Where I was limited with the amount of detail I was able to incorporate for each country, sophisticated country-level modelling would help to provide tailored information to inform decisions surrounding vaccine delivery for particular countries with a large burden of tuberculosis, such as India.

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CHAPTER 4 Country-level modelling: Health and economic impacts of novel tuberculosis vaccines in India

Chapter 4 contains Research Paper 2 in section 4.2 which addresses thesis **Aim 2** and thesis **Objective 3.** The supplementary material for Research Paper 2 is provided in section 4.3 and addresses thesis **Objective 1**.

4.1 Introduction

Chapter 3 demonstrated the large health impacts possible from introducing new tuberculosis vaccines in LMICs using multi-country models.[1] The largest absolute impact in terms of cumulative cases and deaths averted was estimated in WHO South-East Asian Region, but these results did not report country-specific information about the impact of vaccines which would be beneficial information to inform policy within country.

Globally, India has the largest number of tuberculosis cases and deaths per year.[2] Previous modelling papers have demonstrated a positive impact of tuberculosis vaccines in India but did not use model structures which incorporated recent advances in the knowledge of tuberculosis natural history or looked at comparing the impact from introducing vaccines aligned with M72/AS01$_E$ and BCG-revaccination characteristics.[3–7]

Detailed country-level modelling could help provide Indian decision-makers tailored information to inform vaccine delivery strategies and decisions for moving forward with M72/AS01$_E$ and BCG-revaccination. To address this, in Research Paper 2, I developed a detailed mathematical model of tuberculosis natural history in India and calibrated to nineteen India-specific tuberculosis calibration targets. I used this model to estimate the health, cost, and budget impacts in India of thirteen M72/AS01$_E$ scenarios, where the vaccine is primarily assumed to prevent disease in individuals with any infection status, and twelve BCG-revaccination scenarios, where the vaccine is primarily assumed to prevent infection in those that are uninfected, to provide evidence for country-level policy and planning. Research Paper 2 has been published at *BMC Medicine*. It is reproduced in section 4.2 with no modifications or adaptations from the published version.

4.2 Research paper – New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination

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SECTION A – Student Details

Student ID Number	1804462	**Title**	Ms
First Name(s)	Rebecca Anne		
Surname/Family Name	Clark		
Thesis Title	Mathematical modelling of the impact of adolescent/adult tuberculosis vaccines to inform global, national, and subnational policy and delivery		
Primary Supervisor	Richard 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?	BMC Medicine		
When was the work published?	4 August 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

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 developed the natural history and vaccine model structure. I acquired the relevant epidemiologic data from the literature to parameterise and calibrate the model. I contributed to establishing the vaccine delivery scenarios based on clinical trial data and consultations with experts, and determined what impact data would be required to answer the research question. I calibrated the model and generated the impact data from the calibrated model. I prepared the results and organised sharing results with collaborators for input. I wrote the first full draft of the manuscript, and shared with co-authors for feedback, which I incorporated into the paper. I submitted the manuscript for publication, wrote the response to reviewers, and incorporated editor revisions.

SECTION E

Student Signature		
Date		

Supervisor Signature		
Date		

New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination

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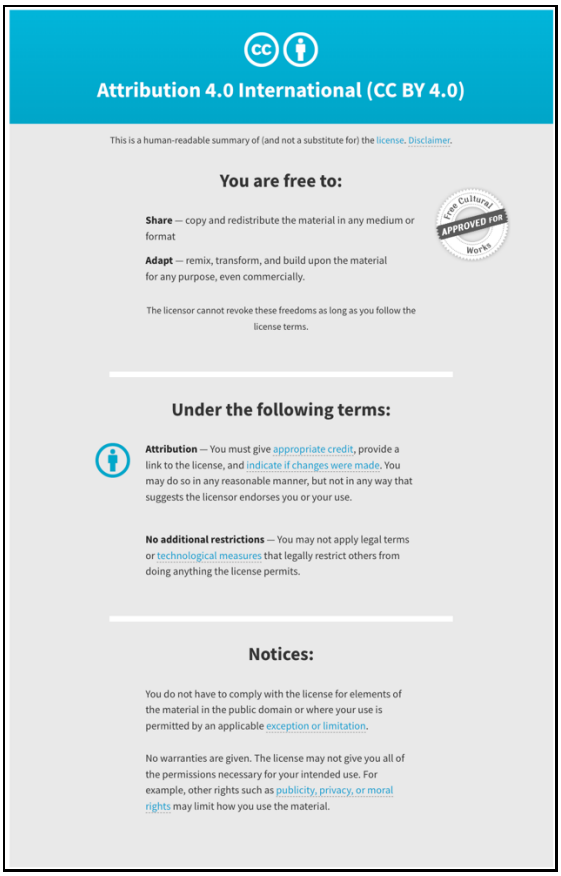

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RESEARCH ARTICLE

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New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination

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Abstract

Background India had an estimated 2.9 million tuberculosis cases and 506 thousand deaths in 2021. Novel vaccines effective in adolescents and adults could reduce this burden. M72/AS01$_E$ and BCG-revaccination have recently completed phase IIb trials and estimates of their population-level impact are needed. We estimated the potential health and economic impact of M72/AS01$_E$ and BCG-revaccination in India and investigated the impact of variation in vaccine characteristics and delivery strategies.

Methods We developed an age-stratified compartmental tuberculosis transmission model for India calibrated to country-specific epidemiology. We projected baseline epidemiology to 2050 assuming no-new-vaccine introduction, and M72/AS01$_E$ and BCG-revaccination scenarios over 2025–2050 exploring uncertainty in product characteristics (vaccine efficacy, mechanism of effect, infection status required for vaccine efficacy, duration of protection) and implementation (achieved vaccine coverage and ages targeted). We estimated reductions in tuberculosis cases and deaths by each scenario compared to the no-new-vaccine baseline, as well as costs and cost-effectiveness from health-system and societal perspectives.

Results M72/AS01$_E$ scenarios were predicted to avert 40% more tuberculosis cases and deaths by 2050 compared to BCG-revaccination scenarios. Cost-effectiveness ratios for M72/AS01$_E$ vaccines were around seven times higher than BCG-revaccination, but nearly all scenarios were cost-effective. The estimated average incremental cost was US$190 million for M72/AS01$_E$ and US$23 million for BCG-revaccination per year. Sources of uncertainty included whether M72/AS01$_E$ was efficacious in uninfected individuals at vaccination, and if BCG-revaccination could prevent disease.

Conclusions M72/AS01$_E$ and BCG-revaccination could be impactful and cost-effective in India. However, there is great uncertainty in impact, especially given the unknowns surrounding the mechanism of effect and infection status required for vaccine efficacy. Greater investment in vaccine development and delivery is needed to resolve these unknowns in vaccine product characteristics.

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Keywords Tuberculosis, Vaccines, Mathematical modelling, Health impact, Budget impact, Cost-effectiveness

Background

India has the largest global burden of tuberculosis. In 2021, there were an estimated 2.9 million cases and 506 thousand deaths—representing approximately 30% of the total globally [1]. The COVID-19 pandemic has negatively impacted tuberculosis prevention and care in India, with increases in the number of deaths per year seen for the first time since 2007 [1, 2]. Delays in diagnosis and treatment due to surveillance systems impacted by the pandemic (over 30% fewer notifications reported in 2021 than 2019) may lead to increases in the disease burden [1, 2].

Tuberculosis is a key focus for the Indian government. The National Strategic Plan to End Tuberculosis in India 2020–2025, developed by the National Tuberculosis Elimination Programme (NTEP), outlines ambitious goals for reducing *Mycobacterium tuberculosis* (*Mtb*) transmission, preventing tuberculosis disease, and addressing social determinants of health [3]. Despite the COVID-19 pandemic, the NTEP has made progress toward these goals, including expanding molecular diagnostics, implementing tuberculosis-COVID bidirectional screening, and expanding policy on preventive therapy to include all household contacts of people diagnosed with pulmonary tuberculosis [4].

The National Strategic Plan also calls for further development in tuberculosis vaccines, which has been a high priority for global organisations such as the World Health Organization (WHO). A recently completed WHO-commissioned study assessing the full value of tuberculosis vaccines made a strong case from the health and economic perspectives for continued investment [5–9], and previous work has demonstrated that novel vaccines or vaccination strategies will be needed to eliminate tuberculosis [10, 11].

Currently, sixteen candidates are in various phases throughout the vaccine pipeline, being trialled in a variety of ages and spanning prevention of disease, infection, and recurrence endpoints [12]. A phase IIb trial of M72/AS01$_E$ in adolescents and adults infected with *Mtb* demonstrated a prevention of disease efficacy of 49.7% (95% confidence interval: 2.1–74.2) after 3 years of follow-up [13]. However, M72/AS01$_E$ would need a supportive phase III trial for licensure, which is planned but likely to require years before results are available to inform policy.

Revaccination of uninfected adolescents with the Bacillus Calmette–Guérin (BCG) vaccine was assessed as a third parallel arm in a separate phase IIb trial and demonstrated an efficacy of 45.4% (6.4–68.1) against sustained infection [14], and an additional phase IIb confirmation trial is underway to verify this finding, with results expected mid-2024 [15]. The original Chingleput BCG vaccination trial reported efficacy of 27% (−8 to 50) against disease in children and no efficacy in adults [16]. A re-analysis of trial data restricted to participants with prior BCG vaccination and no tuberculosis disease at the time of vaccination showed a protective efficacy of 36% (11–54) against disease [17]. As BCG is already licensed, introducing BCG-revaccination may only require a policy change, which could happen quickly.

India is arguably the most important country for global tuberculosis elimination, and policy-makers require country-specific evidence of the anticipated health, cost, and budget impacts of specific vaccine candidates. As vaccines enter phase III trials, it is important to predict how variation in vaccine profile and implementation will affect the impact to maximise benefits and reduce delays between licensure and delivery. We estimated the potential health and economic impact of M72/AS01$_E$ and BCG-revaccination in India and investigated the impact of variation in vaccine characteristics and delivery strategies.

Methods

Data

We obtained demographic data for India from the United Nations Population Division with estimates for single ages and years from 1900 to 2100 [18]. Tuberculosis disease and infection prevalence estimates were derived from the National TB Prevalence Survey in India 2019–2021 [19]. Incidence, notifications, and mortality estimates were obtained from WHO [2].

Structure

We adapted previous models and developed a compartmental dynamic model of tuberculosis in India [5, 11, 20]. Our model was stratified by tuberculosis natural history and treatment, differences in access-to-care, vaccination, and age. We represented tuberculosis natural history by allowing for *Mtb* infection along a spectrum from uninfected to active clinical disease. We assumed a progressive loss of ability to reactivate following infection, with a monotonic decline in reactivation rates for subsequent latency compartments. Active disease was represented by both subclinical and clinical tuberculosis compartments to align with prevalence survey data [19]. Anti-tuberculosis treatment was assumed to begin in 1960 and increase following a sigmoid curve to 2020. Due to the

large contribution of private sector treatment in India, we incorporated differences in treatment mortality and completion probabilities between the public and private sectors. Full model structure and parameters are in Additional file 1 Sects. 1, 2 [5, 18, 21–37].

Calibration

The model was fit to 19 tuberculosis-related calibration targets: the incidence rate (all ages, children, and adults in 2000, 2020, and 2025), mortality rate (all ages in 2000, 2020, and 2025), notification rate (all ages, children, and adults in 2000 and 2020), disease prevalence (all ages, children, and adults in 2015 and 2021), infection prevalence (all ages in 2021), the proportion of incident cases with treatment history in 2020, the fraction of subclinical tuberculosis among active tuberculosis in 2020, and the prevalence ratio of active tuberculosis between access-to-care compartments in 2020 all assuming a uniform distribution between lower and upper bounds. We calibrated using the *hmer* R package [38] to perform history matching with emulation followed by ABC-MCMC until we obtained 1000 parameter sets fitting all targets (further information in Additional file 1 Sect. 3) [4, 38–52].

Scenarios

No-new-vaccine baselines

Assuming the quality and coverage of services remain constant post-2020, we used the calibrated model to project baseline epidemiology to 2050 (the *Status Quo* no-new-vaccine baseline). We assumed that neonatal BCG vaccination would not be discontinued during the period of our analysis and was not explicitly modelled as its effect is implicitly included in country burden estimates.

As an alternative future scenario, we calibrated a *Strengthened Current Interventions* no-new-vaccine baseline. This baseline assumed scale-up of non-vaccine tuberculosis interventions between 2021 and 2035 to meet the target of a 50% reduction in tuberculosis incidence in 2035 compared to the 2015 estimates. This scale-up was included in the model by introducing multipliers on the rate of progression to disease and in the force of infection equation.

Vaccine scenarios

Using the calibrated *Status Quo*no-new-vaccine model, we simulated Basecase scenarios over 2025–2050 for each product with characteristics informed a priori by clinical trial data and expert opinion [13, 14]. The Basecase M72/AS01$_E$ scenario assumed a 50% efficacy prevention of disease vaccine with 10-year protection, efficacious with any infection status aside from active disease at vaccination. We assumed the vaccine would be introduced in 2030 routinely to those aged 15 (reaching 80% coverage) and as a campaign for ages 16–34 (reaching 70% coverage), with a repeat campaign in 2040. Based on expert advice, the vaccine price was $2.50 per dose, assuming two doses per course.

The Basecase BCG-revaccination scenario assumed a 45% efficacy vaccine to prevent infection with 10-year protection, and efficacious without infection at time of vaccination. We assumed the vaccine would be introduced in 2025 routinely to those aged 10 (reaching 80% coverage) and as a campaign for ages 11–18 (reaching 80% coverage) with repeat campaigns in 2035 and 2045. Based on the average estimated BCG price from UNICEF [53], the vaccine price was set at US$0.17 per dose, assuming one dose per course.

Vaccine introduction costs for both vaccine products were assumed to be US$2.40 (95% uncertainty interval = 1.20–4.80) per individual in the targeted age group based on vaccine introduction support policy from Gavi, the Vaccine Alliance [54]. A further US$0.11 (0.06–0.22) supply costs and US$2.50 (1.00–5.00) delivery costs per dose were included [55], as well as US$0.94 (0.13–1.52) in patient and caregiver productivity losses per dose, to account for the time taken to receive vaccination [56, 57]. We assumed a 5% wastage rate.

Through consultation with vaccine and country-specific experts, we established specific M72/AS01$_E$ and BCG-revaccination *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios*. *Policy Scenarios* represented features of vaccination strategy under the control of decision-makers, which compared different age groups to target for vaccination. *Vaccine Characteristic and Coverage Scenarios* represented current uncertainties around vaccine performance and uptake, in which we varied unknowns in vaccine profile (such as efficacy, duration of protection, mechanism of effect) and achieved coverage, univariately from each Basecase scenario. We compared *Policy Scenarios* to identify the optimal implementation approach, and *Vaccine Characteristic and Coverage Scenarios* to quantify the impact of different sources of uncertainty (Table 1). Further details are provided in Additional file 1 Sect. 4 [13, 14, 58].

Outcomes

We estimated the cumulative number of tuberculosis cases and deaths averted between vaccine introduction and 2050 for each scenario compared to the predicted numbers in both no-new-vaccine baselines.

For each vaccine product, we conducted cost-effectiveness analyses for the *Policy Scenarios* indicated in Table 1, discounting both costs and health outcomes to 2025 (when vaccination began) at 3% per year as per guidelines [59]. We calculated the difference in total disability-adjusted life years (DALYs) from vaccine

Table 1 Assumed M72/AS01$_E$ and BCG-revaccination scenarios

	M72/AS01$_E$		BCG-revaccination	
Characteristic	**Basecase**	**Varied in univariate**	**Basecase**	**Varied in univariate**
Policy scenarios				
Age targeting	Routine age 15, campaign for ages 16–34	Older ages (campaign for ages 18–55) Elderly ages (routine age 60, campaign for ages 61 +)	Routine age 10, campaign for ages 11–18	Older ages (routine age 15, campaign for ages 16–34) Elderly ages (routine age 60, campaign for ages 61 +)
Vaccine characteristic and coverage scenarios				
Vaccine efficacy	50%	60% 70%	45%	70%
Duration of protection	10 years	5 years 15 years 20 years	10 years	5 years 15 years 20 years
Host infection status	AI	CI	NCI	AI
Mechanism of effect	Prevention of disease	Prevention of infection and disease	Prevention of infection	Prevention of infection and disease
Introduction year (years of any repeat campaigns)	2030 (2040)	2036 (2046)	2025 (2035, 2045)	2031 (2041)
Achieved vaccine coverage	Routine = 80%, campaign = 70%	Routine = 70%, campaign = 50% Routine = 90%, campaign = 90%	Routine and campaign = 80%	Routine and campaign = 70% Routine and campaign = 90%

Abbreviations: *AI* Any infection; *CI* Current infection; *NCI* No current infection

See Additional file 1 Sect. 4 for full details and references

introduction to 2050, using the disability weight for tuberculosis disease from the Global Burden of Disease 2019 study [60], and country- and age-specific life expectancy estimates from the United Nations Development Programme assuming no post-tuberculosis morbidity or mortality [61]. We calculated incremental cost-effectiveness ratios (ICERs) as the ratio of mean incremental costs to mean incremental benefits in DALYs averted, and 95% uncertainty intervals from the health-system perspective for each efficient strategy for the analytic period 2025–2050. Higher cost-effectiveness ratios indicate greater spending is needed to achieve health improvements, such that the intervention is less likely to be cost-effective. We measured cost-effectiveness by 2050 against three India-specific cost thresholds: 1 × gross domestic product (GDP) per capita (US$1,927.71) [57], and country-level opportunity cost thresholds defined by Ochalek et al. (country-level upper [US$363] and lower [US$264] bounds) [62].

To investigate how the consequences of vaccine introduction (versus no vaccination) changed based on the vaccine product characteristics, we examined the difference in ICERs for *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline assuming the vaccine was introduced using the delivery strategy from the most efficient *Policy Scenario* at the country-level lower bound.

We estimated the annual incremental costs of diagnosis, treatment, and vaccination for each scenario, as compared to the no-new-vaccine baseline in 2020 US dollars from health-system and societal perspectives. Further details are provided in Additional file 1 Sect. 5 [53–57, 59–69].

Results

The *Status Quo* baseline model fits all 19 calibration targets with at least 1000 parameter sets. Epidemiological projections from 2020 to 2050 are in Additional file 1 Sect. 7. The *Status Quo* baseline predicted 72.2 (63.3–79.7) million incident tuberculosis cases and 13.8 (12.9–15.2) million tuberculosis deaths between 2025 and 2050. Assuming current non-vaccine tuberculosis interventions would be strengthened such that the incidence rate in 2035 was 50% of the incidence rate in 2015, the *Strengthened Current Interventions* baseline predicted 36.0 (28.9–66.4) million incident cases and 7.6 (6.1–13.2) million deaths between 2025 and 2050.

With the *Status Quo* no-new-vaccine baseline, we found a 50% efficacy M72/AS01$_E$ prevention of disease vaccine, efficacious with any infection status, introduced in 2030 routinely to 15-year-olds and as a campaign for ages 16–34 (the Basecase M72/AS01$_E$ scenario), could avert approximately 12.7 (11.0–14.6) million cases and 2.0 (1.8–2.4) million deaths between 2030 and 2050 (Fig. 1). With a 70% efficacy vaccine, the number of averted cases and deaths by 2050 could be increased by

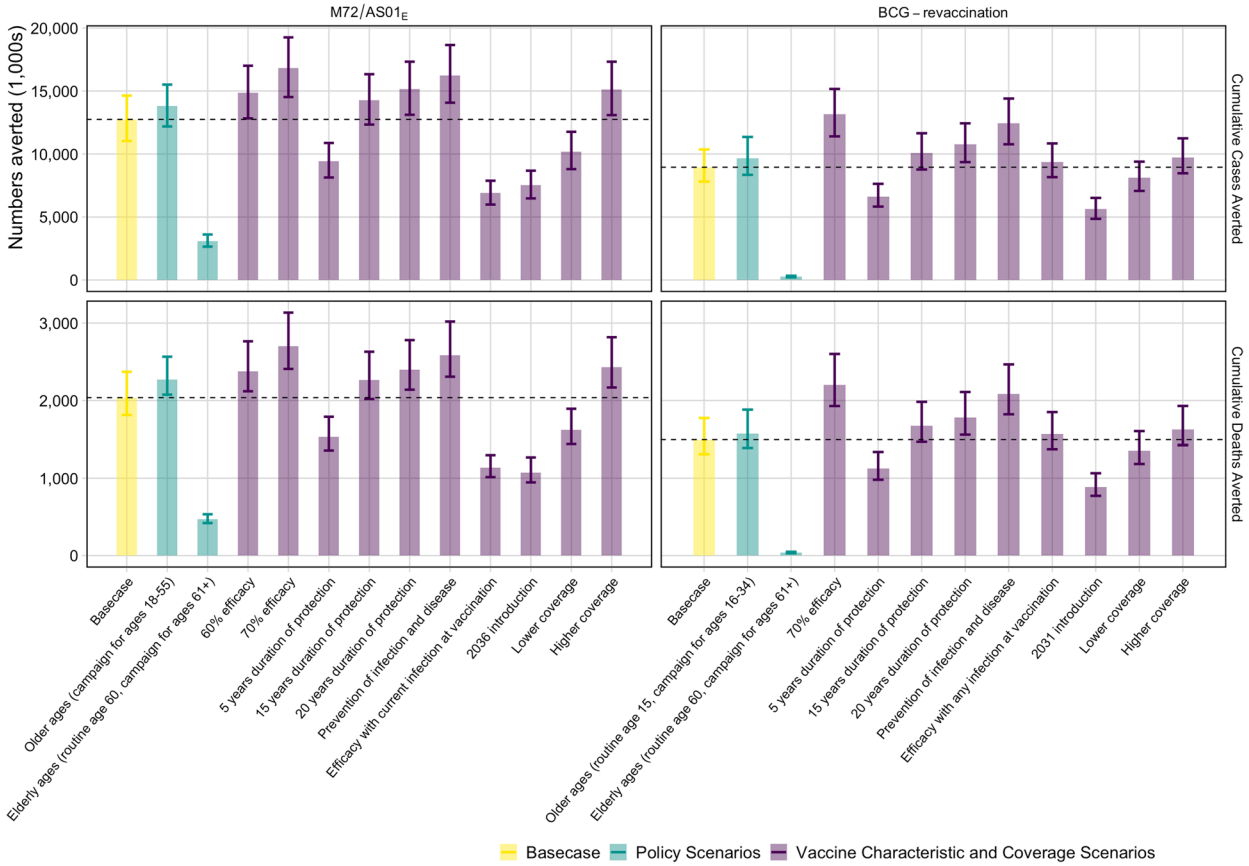

Fig. 1 Cumulative cases and deaths averted (in 1000 s) by 2050 from M72/AS01$_E$ and BCG-revaccination scenarios. The top of the bar is the median estimate of the number averted for each scenario compared to the estimated number predicted by 2050 with the *Status Quo* no-new-vaccine baseline with 95% uncertainty range. The horizontal line is the median value of the Basecase for each vaccine. The cases and deaths averted by each scenario are compared to 72.2 (63.3–79.7) million incident tuberculosis cases and 13.8 (12.9–15.2) million tuberculosis deaths predicted by the *Status Quo* baseline between 2025 and 2050

32–35% but delaying introduction of a vaccine until 2036 could lead to 5.2 million more cases and 968 thousand more deaths compared to the Basecase M72/AS01$_E$ scenario before 2050 (Fig. 1). If the vaccine was only efficacious with current infection at vaccination, 5.8 million fewer cases and 900 thousand fewer deaths could be averted compared to the Basecase M72/AS01$_E$ scenario.

A 45% efficacy prevention of infection BCG vaccine, efficacious in those with no current infection, introduced in 2025 as routine vaccination of 10-year-olds and a campaign for ages 11–18 (the Basecase BCG-revaccination scenario) could avert 9.0 (7.8–10.4) million cases and 1.5 (1.3–1.8) million deaths (Fig. 1). If the vaccine prevented infection and disease, 3.4 million more cases and 600 thousand more deaths could be averted by 2050 compared to the Basecase BCG-revaccination scenario. Fewer numbers could be averted compared to the Basecase BCG-revaccination scenario with reduced duration of protection, later introduction, lower coverage, or only delivering the vaccine to ages 60 years and older (Fig. 1).

Comparing the two products, even with a later introduction year for M72/AS01$_E$ scenarios, we found a higher health impact from M72/AS01$_E$ vaccines compared to BCG-revaccination. The Basecase M72/AS01$_E$ scenario was predicted to avert around 40% more tuberculosis cases and deaths before 2050 than the Basecase BCG-revaccination scenario.

With the *Strengthened Current Interventions* baseline, the Basecase M72/AS01$_E$ scenario could avert 3.0 (1.1–11.3) million tuberculosis cases and 0.51 (0.19–1.9) million tuberculosis deaths between 2025 and 2050, averting 8.3% of the median total cases and 6.7% of the median total deaths predicted to occur during the same period. The Basecase BCG-revaccination scenario could avert 1.9 (0.42–8.0) million cases and 0.34 (0.08–1.4) million deaths between 2025 and 2050, or 5.3% of the median total tuberculosis cases and 4.5% of the median total tuberculosis deaths predicted to occur during the same period. Health impact values for all scenarios of both vaccines are in Additional file 1 Sect. 8.

Table 2 Cost-effectiveness analysis for M72/AS01$_E$ and BCG-revaccination *Policy Scenarios*

Scenario	Total costs (USD, 1000 s)	Total DALYs (1000 s)	Total DALYs averted (1000 s)	Incremental cost (USD, 1000 s)	Incremental DALYs averted (1000 s)	Cost (USD) per DALY averted
M72/AS01$_E$ policy scenarios						
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Elderly ages (routine age 60, campaign for ages 61 +)	17,523,764	3,986,463	5257	–	–	*Weakly dominated*
Basecase (routine age 15, campaign for ages 16–34)	19,596,068	3,954,863	36,857	5,333,593	36,857	$145
Older ages (campaign for ages 18–55)	21,456,380	3,953,202	38,518	1,860,312	1661	$1120
BCG-revaccination policy scenarios						
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Basecase (routine age 10, campaign for ages 11–18)	14,918,037	3,962,629	29,091	655,526	29,091	$23
Older ages (routine age 15, campaign for ages 16–34)	15,819,567	3,961,671	30,049	901,530	958	$941
Elderly ages (routine age 60, campaign for ages 61 +)	15,922,705	3,991,270	450	–	–	*Strongly dominated*

Abbreviations: *DALYs* Disability-adjusted life years; *USD* United States dollars

Cost-effectiveness analysis is shown in Table 2 and Fig. 2 for the *Policy Scenarios* for each vaccine product. For M72/AS01$_E$, delivering the vaccine routinely to those age 60 and as a campaign for ages 61 + (Elderly Ages M72/AS01$_E$ scenario) was not efficient and removed from consideration. Scenarios delivering the vaccine routinely to age 15 and as a campaign for ages 16–34 (Basecase M72/AS01$_E$ scenario) and delivering the vaccine as a campaign for ages 18–55 (Older Ages M72/AS01$_E$ scenario) were considered efficient and displayed on the efficiency frontier in Fig. 2. The Basecase M72/AS01$_E$ scenario was optimal at both country-level thresholds (ICER = US$145 per DALY averted), and the Older Ages M72/AS01$_E$ scenario was optimal at 1 × GDP threshold (ICER = US$1,120 per DALY averted). The incremental cost of the Basecase M72/AS01$_E$ scenario was US$5.3 billion, with vaccination averting 36.9 million of the 4.0 billion DALYs predicted by the no-new-vaccine baseline between 2025 and 2050.

For BCG-revaccination, delivering the vaccine routinely to those age 60 and as a campaign for ages 61 + (Elderly Ages BCG-revaccination scenario) was dominated by other strategies and removed from

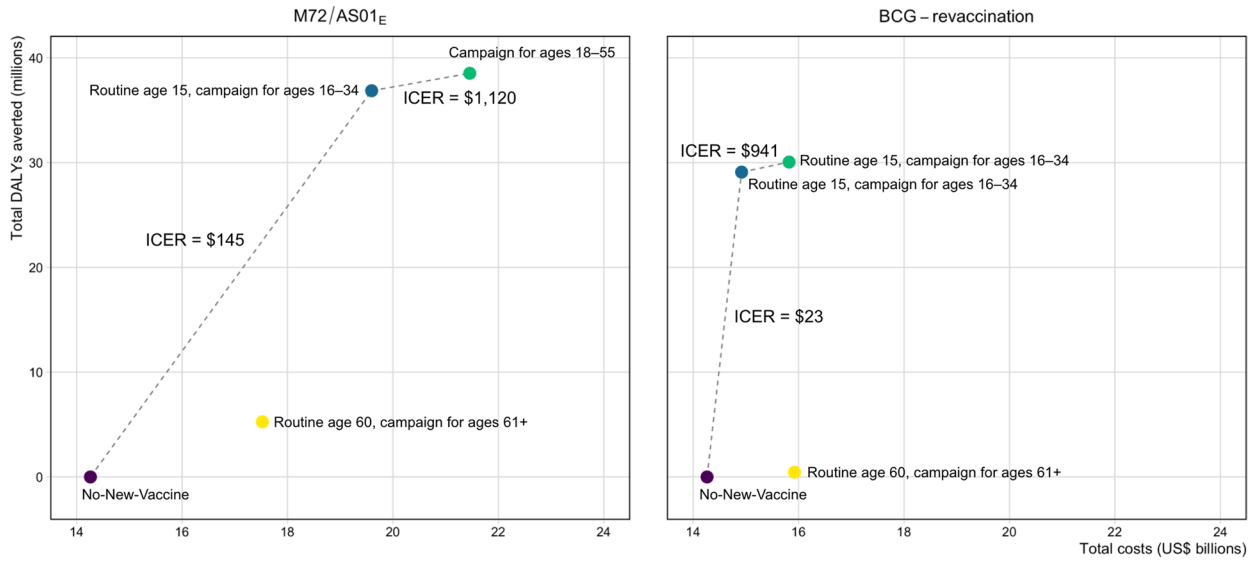

Fig. 2 Efficiency frontiers (discounted total costs [US$ billions] per disability-adjusted life year (DALY) averted) for *Policy Scenarios* for each vaccine product

consideration. Scenarios delivering the vaccine routinely to age 10 and as a campaign for ages 11–18 (Basecase BCG-revaccination scenario) and delivering the vaccine routinely to those aged 15 and as a campaign for ages 16–34 (Older Ages BCG-revaccination scenario) were considered efficient and displayed on the efficiency frontier in Fig. 2. The Basecase BCG-revaccination scenario (ICER = US$23 per DALY averted) was optimal at both country-level thresholds and the Older Ages BCG-revaccination scenario (ICER = US$941 per DALY averted) was optimal at 1xGDP threshold. The incremental cost of the Basecase BCG-revaccination scenario was US$656 million, and this strategy averted 29.1 million of the 4.0 billion DALYs predicted by the no-new-vaccine baseline between 2025–2050.

Figure 3 displays the ICERs for each *Vaccine Characteristic and Coverage Scenario* compared to the no-new-vaccine baseline for each vaccine product. For every M72/AS01$_E$ scenario shown in the figure, we assumed that the vaccine would be introduced routinely to those aged 15 and as a campaign to ages 16–34 (the most efficient strategy at the country-level lower bound from the cost-effectiveness analysis). Even with changes in the vaccine product characteristics, introducing an M72/AS01$_E$ vaccine would be cost-effective compared to not implementing a vaccine (Fig. 3). For every BCG-revaccination scenario, we assumed that the vaccine would be introduced routinely to those aged 10 and as a campaign to ages 11–18 (the most efficient strategy at the country-level lower bound from the cost-effectiveness analysis). Similarly, regardless of the resulting product characteristics, introducing BCG-revaccination to this age group would be cost-effective compared to not implementing a vaccine (Fig. 3).

From the health-system perspective, the annual average cost of vaccination in the Basecase M72/AS01$_E$ scenario was approximately US$251 (170–368) million between 2025 and 2050. The annual average cost-savings in treatment and diagnostics were US$60 (49–74) million over 2025–2050. The annual average cost of vaccination in the Basecase BCG-revaccination scenario was US$67 (29–122) million over 2025–2050. The annual average cost-savings in treatment and diagnostics were US$43 (35–55) million over 2025–2050. The average annual cost of vaccination in the Basecase M72/AS01$_E$ scenario was almost four times greater than the average annual cost of vaccination with the Basecase BCG-revaccination scenario. Accounting for cost-savings, the average annual incremental programme cost in the Basecase M72/AS01$_E$ scenario (US$190 million) was over eight times greater than the average annual incremental programme cost with the Basecase BCG-revaccination scenario (US$23 million).

Figure 4 demonstrates the distribution of costs and cost-savings per year from vaccine introduction to 2050

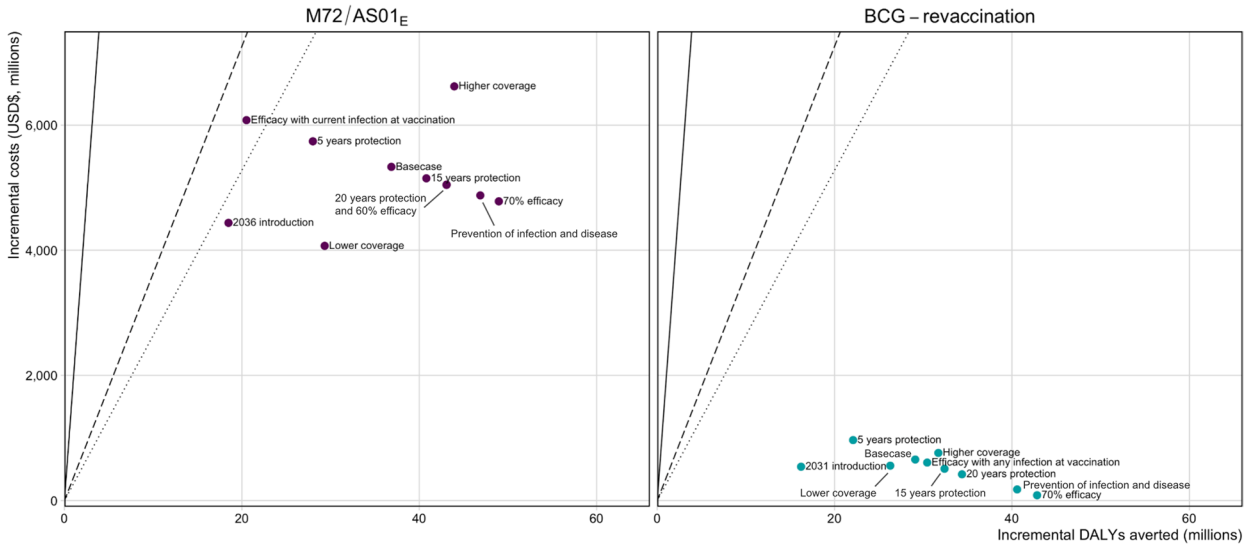

Fig. 3 Comparison of ICERs for *Vaccine Characteristic and Coverage Scenarios* compared to the *Status Quo* no-new-vaccine baseline for each vaccine product. The Basecase M72/AS01$_E$ scenario assumes a 50% efficacy POD vaccine efficacious with any infection status at the time of vaccination, with 10 years' duration of protection reaching 80% coverage for 15-year-olds and 70% coverage for those aged 16–34. Each M72/AS01$_E$ scenario is delivered routinely to those aged 15 and as a campaign for those aged 16–34. The Basecase BCG-revaccination scenario assumes a 45% efficacy POI vaccine efficacious with no current infection at the time of vaccination, with 10 years duration of protection and reaching 80% coverage. Each BCG-revaccination scenario is delivered routinely to those aged 10 and as a campaign for those aged 11–18. The scenarios on the figure are labelled with the difference in product characteristics for that scenario compared to the Basecase. The 20 years' protection and 60% efficacy scenarios for M72/AS01$_E$ overlap and appear as one point on the figure

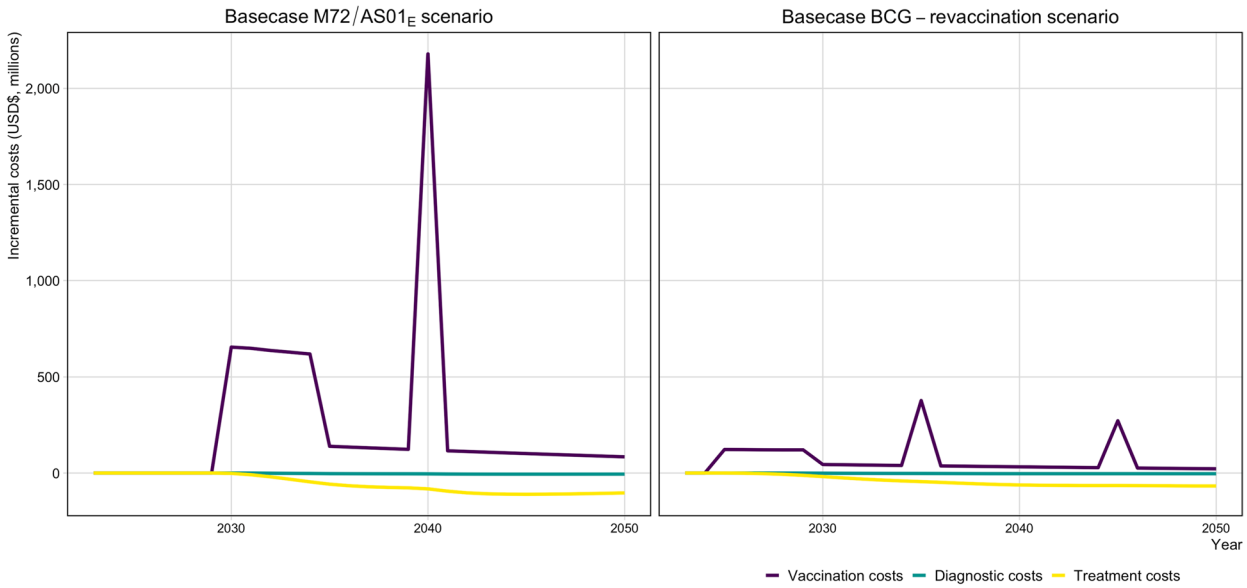

Fig. 4 Incremental costs by year until 2050 for the Basecase M72/AS01$_E$ and BCG-revaccination scenarios compared to the *Status Quo* no-new-vaccine baseline. USD$, United States dollars

for the Basecase scenarios for both vaccine products. During the initial 5-year scale-up to maximum achieved coverage, the average vaccination cost for the Basecase M72/AS01$_E$ scenario was US$638 million per year, compared to US$121 million per year for the Basecase BCG-revaccination scenario. The cost during the repeat campaign in 2040 for the Basecase M72/AS01$_E$ vaccine was US$2.2 billion, compared to US$377 million and US$272 million, respectively, for the two repeat campaigns in 2035 and 2045 for the Basecase BCG-revaccination scenario. Full economic results are in Additional file 1 Sect. 9.

Discussion

We found that M72/AS01$_E$ scenarios could avert approximately 12.7 (11.0–14.6) million cases and 2.0 (1.8–2.4) million deaths, and BCG-revaccination scenarios could avert approximately 9.0 (7.8–10.4) million cases and 1.5 (1.3–1.8) million deaths of the 72.2 (63.3–79.7) million cases and 13.8 (6.1–13.2) million deaths predicted by the *Status Quo* baseline between 2025 and 2050. Cost-effectiveness ratios for the Basecase M72/AS01$_E$ scenario were around seven times higher than that for the Basecase BCG-revaccination scenario, but regardless of the realised product characteristics, nearly all *Vaccine Characteristic and Coverage Scenarios* were cost-effective at the most conservative country-level threshold compared to the no-new-vaccine baseline. The average annual cost of M72/AS01$_E$ vaccination was four times greater than BCG-revaccination. Introducing the vaccine could lead to an annual incremental programme cost of US$190 million for M72/AS01$_E$ and US$23 million for BCG-revaccination, accounting for vaccination costs as well as savings in diagnostic and treatment costs.

Our modelling demonstrated a 40% greater health impact from M72/AS01$_E$ compared to BCG-revaccination. The difference in impact was due to assumptions made on vaccine characteristics and delivery. Based on clinical trial data and expert opinion, we assumed the Basecase M72/AS01$_E$vaccine would prevent disease and be efficacious in everyone without active disease at vaccination. In contrast, based on trial data [14, 70], we assumed the Basecase BCG-revaccination scenario would be efficacious only in people without infection at the time of vaccination, and would prevent infection. Therefore, M72/AS01$_E$would be effective in a larger proportion of the population compared to BCG-revaccination and have a more rapid impact on tuberculosis incidence. The effect of BCG-revaccination on disease will be delayed by the time between vaccination and infection in addition to the time from infection to disease. This is consistent with previous work showing more rapid impact on disease of a vaccine that prevents disease directly in those currently infected [11].

As demonstrated in the National Tuberculosis Prevalence Survey, the highest tuberculosis prevalence estimates are found in older adolescents and adults [19]. The Basecase scenario for M72/AS01$_E$ delivered the vaccine routinely to those aged 15 and as a campaign for ages 16–34, as opposed to the Basecase BCG-revaccination scenario which was targeted routinely to those aged 10

and a campaign for ages 11–18. As the M72/AS01$_E$ vaccine was targeted to an age group with a higher burden, we saw an increased impact on the burden.

We explored variation in decisions regarding delivery and the realised vaccine by evaluating *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios* where we varied characteristics univariately from the Basecase for each vaccine product, and found all uncertainties had the anticipated direction of effect. Both M72/AS01$_E$ and BCG-revaccination were highly influenced by vaccine efficacy and duration of protection, with higher efficacies and longer durations of protection increasing health impact and cost-effectiveness. Key sources of uncertainty were whether M72/AS01$_E$ was efficacious without infection at vaccination, and if BCG-revaccination was also able to prevent disease in adults, both of which are key areas of research. Given the uncertainty surrounding prevention of disease efficacy from BCG-revaccination, any roll out of BCG to adolescents and adults should be rigorously evaluated with a prevention of disease outcome.

M72/AS01$_E$ scenarios were predicted to have higher vaccination costs per year compared to BCG-revaccination. The assumed M72/AS01$_E$ vaccine price per course of US$5.00 (two doses for US$2.50 each) was almost 30 times the US$0.17 price per course of BCG-revaccination, in addition to duplicated delivery and supply costs necessary to deliver two doses of M72/AS01$_E$ compared to one dose of BCG. These cost differences directly contribute to higher cost-effectiveness ratios and larger annual cost for M72/AS01$_E$. Our analyses demonstrated that both vaccines could be cost-effective, aligning with previous cost-effectiveness analyses of tuberculosis vaccines [6, 32]. While vaccination could have a substantial budget impact, costs could be partially offset with diagnostic and treatment savings.

Comparing the ICERs for *Vaccine Characteristic and Coverage Scenarios*, we see that even if the product characteristics change from the Basecase scenario for each vaccine product, the decision remains the same. Introducing M72/AS01$_E$ or BCG-revaccination would be a cost-effective intervention.

This work has limitations. We modelled the impact of specific M72/AS01$_E$ and BCG-revaccination scenarios with characteristics based on clinical trial data and consultation with vaccine and country-specific experts, but it will be many years before the actual characteristics are known. To capture some uncertainty, we univariately varied efficacy, duration of protection, whether the vaccine prevents only infection or disease or both, and who the vaccine would be efficacious in. The majority of scenarios continued to demonstrate large potential health impact and cost-effectiveness. We were not investigating the separate question of determining the range of plausible conditions that M72/AS01$_E$ would no longer be cost-effective or scenarios where BCG-revaccination would have a greater impact, which is an important area for future work to address.

The Basecase M72/AS01$_E$ scenario assumed efficacy with any infection status at vaccination, implying that the vaccine would work in both those who were infected with *Mtb* and those who were uninfected. While the Phase IIb trial of M72/AS01$_E$ only enrolled adults with a positive interferon-gamma release assay (IGRA) value, previous trials have indicated that an immune response is invoked in adolescents both with and without infection, and the phase III trial will enrol IGRA positive and negative individuals aged 15–44 years. Therefore, the expected initial indicated population is everyone within these ages, and thus we aligned our primary assumption for host infection status with this. We evaluated a scenario assuming only current infection at vaccination and determined that efficacy in those who are uninfected at the time of vaccination is important to maximise health impact and cost-effectiveness. Investigating whether M72/AS01$_E$ works in populations with any infection status is a key aspect for future research.

We modelled a small subset of age-targeted delivery scenarios, which may differ from the strategies India will choose. We evaluated alternatives informed by expert opinion and results from interviews with key decision-makers in India [58], but did not investigate targeting specific groups, such as healthcare workers, people completing tuberculosis treatment, or household contacts of people with tuberculosis, who could be at high risk of developing tuberculosis disease and may be prioritised for vaccination. This strategy has previously been suggested to have a high population-level impact per individual vaccinated [71–73 and greater than 45% for BCG-revaccination (aligning with the estimates of protection from the Phase IIb trials). However, the true vaccine efficacy is currently unknown, and if our assumptions were too optimistic, we may have overestimated the health and economic impacts.

The burden of tuberculosis varies widely across India. From the recent National Tuberculosis Prevalence Survey, the prevalence per 100,000 population of pulmonary tuberculosis among adults ranged from 115 (47–184) in Kerala to 534 (365–704) in Delhi [19]. Optimal delivery strategies may vary by state, given the vast differences in age composition, population size, and tuberculosis burden. Modelling specific regions to investigate the generalisability of national predictions is an important area of future research.

We ran cost-effectiveness analysis for each product on the age-targeting *Policy Scenarios*. We selected the

Basecase vaccine profile characteristics for each vaccine product as it incorporates the primary assumptions from experts in the field on the likely vaccine product characteristics, but we did not run cost-effective analysis for the age-targeting strategies with other vaccine characteristics.

Our work is a modelling exercise, and limitations associated with mathematical models apply. We developed our tuberculosis natural history structure incorporating recent advances in knowledge regarding the clinical course of disease, such as subclinical tuberculosis and a latency structure with a progressive loss in the ability to reactivate. If our assumptions around these novel aspects, particularly around interactions with vaccines, are incorrect, we may have over- or underestimated the impact. While we used the best available data to inform calibration targets and natural history parameters, we were limited by what was available. We ensured that the modelled trends aligned with the most recent estimates of tuberculosis burden, as vaccines are not anticipated to be introduced until at least 2025. However, with only one estimate of whole-country disease prevalence and one estimate of whole-county infection prevalence in India, we were restricted with what we could infer about these measures over time, which highlights the need for more regularly collected data on disease prevalence and infection. We made decisions on natural history parameter ranges based on the most recent literature available, but this still resulted in wide prior ranges for some parameters. Further data collection into these areas would improve model estimates.

We projected the no-new-vaccine baseline as *Status Quo*, where we assume that the rate and quality of services remained constant from 2020 onwards, and the resulting trends in burden from 2020–2050 follows a slight decline. Given the commitment of the Indian government to improvements in tuberculosis care, prevention, and ending the tuberculosis epidemic, our model could be overestimating the burden of tuberculosis. Therefore, our health and economic impacts may be overestimated. We ran a sensitivity analysis for the Basecase scenario for each vaccine product using the *Strengthened Current Interventions* no-new-vaccine baseline. We found that vaccines would still have a positive health impact and would be cost-effective even if the incidence rate was declining faster than assumed in our primary scenario. We demonstrated that vaccines could also be an impactful and cost-effective investment for the Indian government if future tuberculosis burden is much lower.

The results from this study could be used to inform policy-makers considering novel tuberculosis vaccine introduction. We have demonstrated that both BCG-revaccination and M72/AS01$_E$ could have a positive health impact and would be cost-effective if delivered, given our current assumptions. We evaluated uncertainty surrounding vaccine characteristics and found that even if characteristics were changed, we would still see positive health impact and cost-effectiveness.

The decision for how to take these results forward to country-level introduction lies with the policy-maker, and how they are able to allocate their available budget. While we made some comparisons between products, the results of our study assume a reality where only one vaccine product is introduced. However, it is likely that both vaccine products could be introduced into the population, and the resulting health benefit could be increased. BCG is already licensed and recommended by the WHO for infants, and therefore BCG-revaccination of older adolescents and adults could be introduced earlier than M72/AS01$_E$ through a policy change. Resources may need to be spent on epidemiological studies investigating population characteristics, such as the infection prevalence, to determine where a vaccine effective in those who are uninfected will have the most impact. M72/AS01$_E$ is still a vaccine candidate and forward progression depends on results from the phase III trial which has yet to start. More uncertainty surrounding costs and product characteristics exists, but overall M72/AS01$_E$ predicted an increased health impact compared to BCG-revaccination.

Conclusions

We propose it is inadvisable to focus solely on one or two vaccine candidates to address the tuberculosis burden. While promising results have been seen from recent trials, it will be years before we can verify these characteristics, and therefore, we need a wide selection of options for the greatest likelihood of mitigating tuberculosis burden. We need to continue investment in all candidates currently in the pipeline, and support the development of new candidates, to increase the probability of success.

Our modelling suggests that M72/AS01$_E$ and BCG-revaccination may substantially reduce the tuberculosis burden in India over future decades and would be cost-effective regardless of the assumed product characteristics. We informed vaccine characteristics using clinical trial data but found variability in the vaccine profile as a crucial source of uncertainty. We cannot solely rely on M72/AS01$_E$ and BCG-revaccination in case the realised characteristics differ considerably from expectations. Investment in multiple vaccine developments and delivery should be increased to raise the probability of success.

Abbreviations

BCG	Bacillus Calmette–Guérin
DALY	Disability-adjusted life years
ICER	Incremental cost-effectiveness ratio
Mtb	Mycobacterium tuberculosis
NTEP	National Tuberculosis Elimination Programme
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-02992-7.

Additional file 1. The model structure, parameterisation, calibration, and simulation is described in detail, and additional epidemiological and economic results are provided. **Figure S1.1**--Tuberculosis natural history model structure. **Figure S3.1**--The estimated impact of the COVID-19 pandemic on tuberculosis incidence and mortality. **Figure S3.2**--Contribution of the private sector to reported case notifications. **Figure S4.1**--Vaccine structure for a NCI vaccine. **Figure S4.2**--Vaccine structure for a CI vaccine. **Figure S4.3**--Vaccine structure for an AI vaccine (protection does not build). **Figure S4.4**--Vaccine structure for an AI vaccine (protection builds). **Figure S7.1**--Tuberculosis incidence, disease prevalence, case notification and mortality rate trends. **Figure S7.2**--Tuberculosis infection prevalence, proportion retreated, access-to-care ratio and ratio of subclinical tuberculosis to total tuberculosis trends. **Figure S7.3**--Tuberculosis incidence and mortality rate trends. **Figure S7.4**--Tuberculosis disease and infection prevalence trends. **Figure S7.5**--Tuberculosis case notification and proportion retreated trends. **Figure S7.6**--Access-to-care ratio and the ratio of subclinical tuberculosis to all active tuberculosis trends. **Figure S7.7**--Posterior distributions for the 19 parameters varied during calibration. **Figure S7.8**--Tuberculosis incidence rate for the *Strengthened Current Interventions* baseline. **Figure S8.1**--Incidence and mortality rate reductions in 2050 for M72/AS01$_E$ scenarios. **Figure S8.2**--Cumulative tuberculosis cases, treatments, and deaths averted for M72/AS01$_E$ scenarios. **Figure S8.3**--Incidence and mortality rate reductions in 2050 for the BCG-revaccination scenarios. **Figure S8.4**--Cumulative tuberculosis cases, treatments, and deaths averted for BCG-revaccination scenarios. **Figure S9.1**--Efficiency frontiers for M72/AS01$_E$ *Policy Scenarios*. **Figure S9.2**--Comparison of ICERs for M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios*. **Figure S9.3**--Basecase M72/AS01$_E$ scenario incremental discounted costs by year. **Figure S9.4**--Efficiency frontiers for BCG-revaccination *Policy Scenarios*. **Figure S9.5**--Comparison of ICERs for BCG-revaccination *Vaccine Characteristic and Coverage Scenarios*. **Figure S9.6**--Basecase BCG-revaccination scenario incremental discounted costs by year. **Figure S9.7**--Cost-effectiveness planes for the M72/AS01$_E$ and BCG-revaccination Basecase scenarios with the *Strengthened Current interventions* baseline. **Table S2.1**--India national model parameter values and sources. **Table S2.2**--How age varying parameters are operationalized. **Table S2.3**--Calculating treatment outcome parameter values for adults and children. **Table S2.4**--Calculation of treatment outcomes for India by year. **Table S3.1**--India national model calibration targets. **Table S3.2**--Incidence and mortality rate targets for all ages for 2025. **Table S3.3**--Number of incident tuberculosis cases by year in India. **Table S3.4--**The fraction of tuberculosis treatment notifications in India from the private sector and overall. **Table S3.5**--The WHO reported and adjusted tuberculosis case notification targets for India. **Table S4.1**--M72/AS01$_E$ and BCG-revaccination scenarios evaluated in the analysis. **Table S4.2**--Increase in protection for the number of vaccine courses. **Table S5.1**--Tuberculosis testing, diagnostic, and vaccination related cost inputs. **Table S8.1**--Health impact results for M72/AS01$_E$ scenarios. **Table S8.2**--Health impact results for BCG-revaccination scenarios. **Table S9.1**--Cost-effectiveness analysis for M72/AS01E *Policy Scenarios*. **Table S9.2**--Incremental DALYs averted, incremental costs averted, and ICERs from health-system and societal perspectives for M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios*. **Table S9.3**--Total costs for the M72/AS01$_E$ scenarios from the health-system perspective. **Table S9.4**--Total costs for the M72/AS01$_E$ scenarios from the societal perspective. **Table S9.5**--Cost-effectiveness analysis for BCG-revaccination *Policy Scenarios*. **Table S9.6**--Incremental DALYs averted, incremental costs averted, and ICERs from health-system and societal perspectives for BCG-revaccination *Vaccine Characteristic and Coverage Scenarios*. **Table S9.7**--Total costs for the BCG-revaccination scenarios from the health-system perspective. **Table S9.8**--Total costs for the BCG-revaccination scenarios from the societal perspective.

Additional file 2. The CHEERS checklist for the study.

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Authors' contributions
Conception: RCH, RGW, NAM, CKW. Data acquisition and preparation: RAC, AP, CM, MQ, CKW. Data analysis: RAC, RGW, CM, CKW, RB. Interpretation of results: RAC, RGW, CKW, AP, NAM, CM. Manuscript drafting and revisions: RAC, RGW, AP, NAM, CKW, MQ, DT, KR, CM, RB, SKM, RCH, DS. All authors had the opportunity to access and verify the data and were responsible for the decision to submit the manuscript for publication. All authors read and approved the final manuscript.

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Availability of data and materials
Epidemiologic data used are available from the *World Health Organization Global TB Report CSV files to download* (https://www.who.int/teams/global-tuberculosis-programme/data) and summarised in Additional file 1. Population estimates and projections are available from the *United Nations Department of Economic and Social Affairs World Population Prospects 2019* (https://population.un.org/wpp/Download/Standard/Population/). Analytic code will be made available at https://doi.org/10.5281/zenodo.6421372 immediately following publication indefinitely for anyone who wishes to access the data for any purpose.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
RCH reports employment by Sanofi Pasteur, unrelated to tuberculosis and outside the submitted work. NAM received consulting fees from The Global Fund to Fight AIDS, Tuberculosis and Malaria, and the WHO, and reports funding to their institution from the US Centers for Disease Control and Prevention, the Bill & Melinda Gates Foundation, NIH, and US Council of State and Territorial Epidemiologists. RGW is also funded for other work by the Wellcome Trust (218261/Z/19/Z), NIH (1R01AI147321-01), EDCTP (RIA208D-2505B), UK MRC (CCF 17–7779 via SET Bloomsbury), ESRC (ES/P008011/1), BMGF (OPP1084276, OPP1135288 & INV-001754), and the WHO. All other authors declare no conflicts of interest.

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Publisher's Note

4.3 Supplementary Material – New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination

The Supplementary Material for Research Paper 2 was published at *BMC Medicine*. It is reproduced here with no modifications or adaptations from the published version.

Supplementary material for *New tuberculosis vaccines in India: Modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination*

Rebecca A. Clark et. al

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SUPPLEMENTARY METHODS

1. Model structure and equations

We created an age-stratified compartmental differential equation model of tuberculosis in India, including dimensions for age, tuberculosis natural history, vaccination, and access-to-care. The age and access-to-care structures are identical to those included in Clark et al.[5] Minor modifications from the Clark et al. natural history structure are described below. The vaccination structure is in section 4.3.

1.1 Natural history model structure

A natural history structure with eight compartments in Figure S1.1 was created by adapting features of previous models and has been described previously.[5] The latency structure in this model demonstrates a progressive loss of ability to reactivate, with the reactivation rate in the Latent-Fast compartment greater than in Latent-Slow and greater still than in Latent-Zero, where we assume the rate of reactivation is 0. We do not explicitly have a self-clearance compartment. We assume that those in Latent-Fast can only fast progress to subclinical disease or continue to remain latent and transition to Latent-Slow. There is no direct transition between Latent-Fast and Latent-Zero.

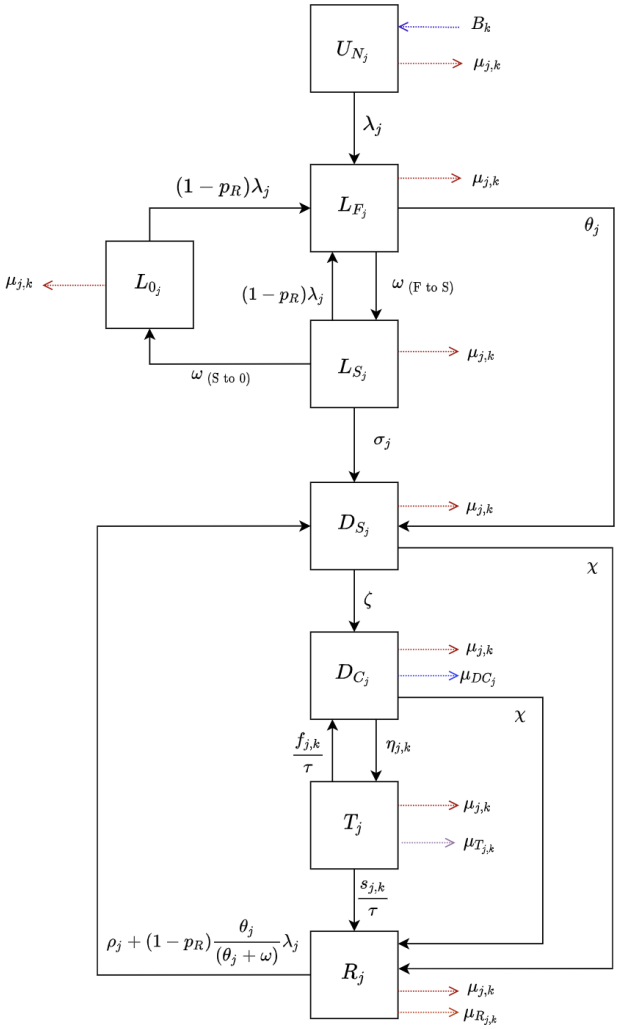


Figure S1.1 Tuberculosis natural history model structure

Abbreviations: U_N = Uninfected-Naive; L_F = Latent-Fast; L_S = Latent-Slow; L_0 = Latent-Zero, D_S = Subclinical Disease; D_C = Clinical Disease; T = On-Treatment; R = Recovered. Subscript j represents parameters that vary by age, and subscript k represents parameters that vary over time.

1.2 Natural history model equations

$Age\ j = 0$
$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$

$Age\ j \neq 0$
$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_j}$

$$\frac{dL_{F_j}}{dt} = \lambda_j U_{N_j} + (1-p_R)\lambda_j L_{0_j} + [(1-p_R)\lambda_j]L_{S_j} - (\omega_{FS} + \theta_j + \mu_{j,k})L_{F_j}$$

$$\frac{dL_{S_j}}{dt} = \omega_{FS} L_{F_j} - (\omega_{S0} + \sigma_j + (1-p_R)\lambda_j + \mu_{j,k})L_{S_j}$$

$$\frac{dL_{0_j}}{dt} = \omega_{S0} L_{S_j} - [(1-p_R)\lambda_j + \mu_{j,k}]L_{0_j}$$

$$\frac{dD_{S_j}}{dt} = \theta_j L_{F_j} + \sigma_j L_{S_j} + [\rho_j + (1-p_R)\frac{\theta_j}{\theta_j+\omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_j} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + \mu_{DC_j} + \mu_{j,k})D_{C_j}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k}+f_{j,k}}{\tau} + \mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [\rho_j + (1-p_R)\frac{\theta_j}{\theta_j+\omega}\lambda_j + \mu_{R_j} + \mu_{j,k}]R_j$$

2. Natural history

2.1 Natural history parameter values and data sources

Parameters used in the natural history model structure are provided in Table S2.1 below, along with their definitions, sources, and information on whether the parameter is fixed or varied (as well as whether they are varied by age or time) during calibration. Further details about how the age varying parameters are implemented are provided in section 2.2, and further details on parameters related to treatment are provided in section 2.3. The parameter ranges provided for the tuberculosis natural history parameters are priors fitted during calibration in a Bayesian analysis. We assume that all values within the prior range are equally likely. The prior ranges were pre-specified based on literature review and were reviewed as new data became available.

Table S2.1 India national model parameter values and sources

Description	Units	Symbol	Prior	Fixed or Varying During Calibration	Age Varying	Time Varying	Source
Births and deaths (excluding on-treatment mortality)							
Birth rate	Per year	B_k	United Nations World Population Prospects population estimates and projections	Fixed	No	Yes	[18]
Background mortality rate	Per year	$\mu_{j,k}$	Calculated in the model from United Nations population estimates and projections	Fixed	Yes, age specific mortality rates from demographic dataset	Yes	[18]
Mortality rate for clinical tuberculosis disease	Per person per year	μ_{DC_j}	(0–0.178)	Varying	Yes, value for children is greater than value for adults	No	[21]
Mortality rate post-tuberculosis disease	Per person per year	μ_{R_j}	$0.22\mu_{j,k}$	Fixed relationship	Yes because $\mu_{j,k}$ varies	Yes because $\mu_{j,k}$ varies	[22]
Natural History							
Force of infection	Per year	λ_j	Fitted	Fixed Equation	Yes, age specific contact rates[23]	No	*Calculated*
Probability of transmission per infectious contact	-	p_T	(0–0.0068)	Varying	No	No	*Assumed*

Fraction of total tuberculosis that is extrapulmonary	-	ep	0.222	Fixed	No	No	[24,25]
Infectiousness of subclinical relative to clinical tuberculosis	-	r	0.83	Fixed	No	No	[26]
Rate of fast progression to disease, by age	Per person per year	θ_j	(0.0696–0.111)	Varying	Yes; Retain if value for children is **less** than value for adults.	No	[27]
Rate from L_F to L_S	Per person per year	ω_{FS}	0.5	Fixed	No	No	*Defined*
Rate of reactivation from L_S, by age	Per person per year	σ	(0.000135–0.00113)	Varying	Yes; Retain if value for children is **less** than value for adults.	No	[27]
Rate from L_S to L_0	Per person per year	ω_{S0}	(0.0254–0.0467)	Varying	No	No	[27]
Rate of progression from D_S to D_C	Per person per year	ζ	(0–12)	Varying	No	No	*Assumed*
Rate of natural cure from D_C and D_S	Per person per year	χ	(0.10–0.25)	Varying	No	No	[28,29]
Rate of relapse from R, by age	Per person per year	ρ_j	(0.0001–0.07)	Varying	Yes; Retain if value for children is **less** than value for adults.	No	[30–32]
Protection Parameters							
Protection from reinfection L_S, L_F, L_0, R	-	p_R	(0.60–0.85)	Varying	No	No	[28,29,33–35]
Access-to-care parameter	-	p_E	(0–1)	Varying	No	No	*Assumed*

2.2 Operationalising age varying parameters

We assume that aspects of tuberculosis natural history and mortality vary by age. This is implemented by stratifying certain natural history parameters by age and applying age-specific prior ranges and relative constraints during calibration.[36] The following table describes the method used to operationalise the age varying differences in parameters between adults, defined as all ages greater than and equal to 15, and children, defined as all ages less than 15. For the rate per year of reactivation, relapse, and fast progression to tuberculosis disease, we assume that the rate for children is less than that for adults. For mortality rates, we assume the opposite: the rate for children is higher than that for adults.

Table S2.2 How age varying parameters are operationalized

Parameter	Range	Age Varying Description	Age Scaling Parameter	Adults (θ_{A15})	Children (θ_{A0})
θ_j Rate per year of fast progression	$(0.0696–0.111)$	Retain if value for children is **less** than value for adults	Sample j_1 from $(0–1)$	Sample θ_{A15} from $(0.0696–0.111)$	$\max(0.0696, \theta_{A15} \times j_1)$
σ_j Rate per year of reactivation	$(0.000135–0.00113)$	Retain if value for children is **less** than value for adults	Sample j_2 from $(0–1)$	Sample σ_{A15} from $(0.000135–0.00113)$	$\max(0.000135, \sigma_{A15} \times j_2)$
ρ_j Rate per year of relapse	$(0.01–0.07)$	Retain if value for children is **less** than value for adults	Sample j_3 from $(0–1)$	Sample ρ_{A15} from $(0.01–0.07)$	$\max(0.01, \rho_{A15} \times j_3)$
μ_{DC_j} Clinical TB mortality rate per year	$(0–0.178)$	Retain if value for children is **greater** than value for adults	Sample S_{Age} from $(0–1)$	$\mu_{DC_{A0}} \times S_{Age}$	Sample $\mu_{DC_{A0}}$ from $(0–0.178)$
$\mu_{T_j} = \frac{\kappa_j}{\tau}$ On-treatment mortality rate per year	$(0–0.270)$	Retain if value for children is **greater** than value for adults	Sample S_{Age} from $(0–1)$	$\frac{\kappa_{A0}}{\tau} \times S_{Age}$	Sample κ_{A0} from $(0–0.135)$

2.3 Treatment initiation and outcomes

Steps for calculating treatment initiation, treatment completion, non-completion, and mortality rates are described in the Supplementary Material for Clark et. al.[5] We assume the SFR is the ratio between treatment completions to the sum of treatment completions and non-completions. In India, $\mathrm{SFR} = 0.96$. The data used to calculate the on-treatment outcomes was obtained from the WHO. However, as the private sector accounts for a substantial portion of treatments in India, and not all of the treatments conducted in the private sector are reported, we make adjustments to the on-treatment completion and non-completion fractions from Table S2.3 as described below and in Table S2.4.

Table S2.3 Calculating treatment outcome parameter values for adults and children

Parameter	Adults	Children
κ_j On-treatment mortality fraction	$\kappa_{A0} \times S_{Age}$	Sample κ_{A0} from $(0\ 0.135)$
s_j On-treatment completion fraction	$(1-\kappa_{A15})\mathrm{SFR}$	$(1-\kappa_{A0})\mathrm{SFR}$
f_j On-treatment non-completion fraction	$(1-\kappa_{A15})(1-\mathrm{SFR})$	$(1-\kappa_{A0})(1-\mathrm{SFR})$

We assume that the total number of treatments is composed of the treatments that are reported and the treatments that are not reported. We assume that the on-treatment mortality fraction is the same in the public and private sector, but want to adjust the treatment completion and non-completion rates to account for differences between those reported and those not reported as in Table S2.4.

Table S2.4 Calculation of treatment outcomes for India by year

Description	Symbol	Year (k)								
		≤2012	2013	2014	2015	2016	2017	2018	2019	≥2020
Fraction of total treatments reported	$f_{T,k}$	0.60	0.63	0.68	0.67	0.73	0.77	0.80	0.83	0.87
On-treatment mortality rate	$\frac{\kappa_j}{\tau}$	$\frac{\kappa_j}{\tau}$ Sample κ_{A0} from $(0, 0.135)$, then $\kappa_{A15} = \kappa_{A0} \times S_{Age}$								
On-treatment completion rate	$\frac{s_j}{\tau}$	$\frac{f_{T,k}0.96(1-\kappa_j)+(1-f_{T,k})0.40}{\tau}$								
On-treatment non-completion rate	$\frac{f_j}{\tau}$	$\frac{f_{T,k}0.04(1-\kappa_j)+(1-f_{T,k})(0.60-\kappa_j)}{\tau}$								

We assume that 60% of the total treatment occurs in the public sector and the remaining 40% occurs in the private sector. We assume that all treatments not reported are from the private sector, that the treatment completion rate in the private sector is 40%, and that there is no reporting bias (in that they were equally likely to not report treatment completions or non-completions or deaths). Before 2012, only the treatment conducted in the public sector was reported, but since then, treatment in the private sector has begun to be reported.[37]

3. Model simulation and calibration

3.1 Model simulation

We specified a system of ordinary differential equations defining the derivatives with respect to time of a set of state variables, to simulate the country-specific tuberculosis epidemic between 1900 and 2050. We initialised the simulation by distributing the population between the eight tuberculosis natural history states using a fitted parameter representing the proportion of the population uninfected at the start of the simulation. For each year of the simulation (1900–2050), our models are designed to exactly match the age and country-specific UN population estimates and projections. Forty percent of the population was assigned to the low access-to-care stratum and the remaining sixty percent of the population was assigned to the high access-to-care stratum.

3.2 Model calibration

For this India modelling analysis, we followed the same modelling approach as in Clark et al.[5]

Broadly, this was as follows:

1. Construct a mechanistic model
2. Calibrate the model by identifying areas of the input parameter space where the output of the mechanistic model was consistent with the historical epidemiologic data
3. Use the calibrated model to simulate and predict future tuberculosis epidemiology and model new vaccines

In the context of this analysis, step 1 was achieved by creating the compartment differential equation model as specified in Section 1. For step 2, we independently calibrated a model by identifying areas of the parameter space that made the output of the model match the corresponding calibration targets (Table S3.1 below). Further details on the sources for the calibration targets and any additional modifications are in the subsequent sections.

The model was fitted to the calibration targets using history matching with emulation, a method that allows us to explore high-dimensional parameter spaces efficiently and robustly.[39–42] History matching progresses as a series of iterations, called waves, where implausible areas of the parameter space, i.e., areas that are unable to give a match between the model output (e.g., the predicted incidence rate by the model) and the empirical data (e.g., the incidence rate calibration target from the WHO data), are found and discarded. In order to identify implausible parameter sets, emulators, which are statistical approximations of model outputs that are built using a modest number of model runs, are used. Emulators provide an estimate of the value of the model at any parameter set of interest, with the advantage that they are orders of magnitude faster than the model.

History matching with emulation, implemented through the *hmer* package in R,[38,43] considerably reduced the size of the parameter space to investigate. Rejection sampling was then performed on the reduced space to identify at least 1000 parameter sets that matched all targets.

If we were unable to find at least 1000 fully fitted parameter sets using history matching with emulation, we subsequently used an Approximate Bayesian Computation using Markov Chain Monte Carlo method (ABC-MCMC). ABC-MCMC was conducted using the *easyABC* package in R, modified by the Sebastian Funk, Gwenan Knight, and the Tuberculosis Modelling group at LSHTM for adaptive sampling and to accept seeded parameter values.[44,45] We used parameter sets with the maximum number of targets fitted using history matching with emulation as starting seeds for multiple MCMC chains per country, with the ABC-MCMC algorithm continuously adapting using the last 1000 points, a burn in of 1000 samples, and the noise factor set to 0.0001.

Once we had obtained 1000 parameter sets that produced output consistent with the calibration targets, we used those parameter sets with the mechanistic model to simulate the future (step 3) for each country as the *Status Quo* no-new-vaccine baseline, where we assumed that current trends and quality of non-vaccine tuberculosis services continued into the future at the same rate.

As an alternative future, we calibrated a *Strengthened Current Interventions* no-new-vaccine baseline. This baseline assumed a scale up in other non-vaccine tuberculosis interventions between 2021 and 2035 in order to meet the target of a 50% reduction in tuberculosis incidence in 2035 compared to the 2015 estimates (an incidence rate of 108.5 (64–164 per 100,000 population). This scale-up was introduced in the model by introducing parameters (sampled between 0 and 1) which act as multipliers on the rate of progression to disease and in the force of infection equation.

The process of generating fits for the *Strengthened Current Interventions* no-new-vaccine baseline while capturing uncertainty was as follows:

1. Obtain 1000 full fits from the *Status Quo* baseline.
2. Subset the 1000 *Status Quo* full fits to 100 by:
    a. Ranking the 1000 *Status Quo* fits from smallest to largest tuberculosis incidence rate in 2020
    b. Retaining every 10th parameter set
3. Use emulation on each of the 100 parameter sets.
4. Obtain 100 "groups" of fully fitting parameter sets (one group for each original parameter).
5. Subset each group of fully fitting parameter sets to 10 by:
    a. Ranking the parameter sets in each group from smallest to largest tuberculosis incidence rate in 2035.
    b. Retaining every nth parameter set to obtain 10 across the range.
6. Obtain 1000 full fits for the *Strengthened Current Interventions* baseline by combining the 10 parameter sets from each of the 100 emulation sets.

Table S3.1 India national model calibration targets

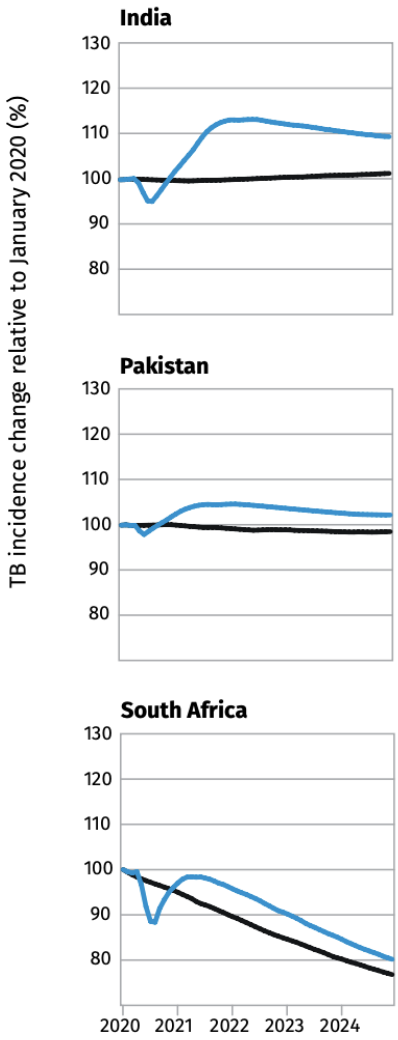
Calibration Targets	Year	Age (years)	Estimate	Lower	Upper
Tuberculosis incidence rate (per 100,000 population/year)	2000[24]	All	289	149	473
	2020[46]	All	188	129	257
		0-14	91	56	126
		≥15	224	138	310
	2025[47]	All	212	145	293
Tuberculosis mortality rate (per 100,000 population/year)	2000[24]	All	67	57	79
	2020[24]	All	37	34	40
	2025[47]	All	36	33	39
Tuberculosis case notification rate (per 100,000 population/year)	2000[18,25]	All	177	142	212
	2020[18,25]	All	136	109	163
		0-14	33	26	40
		≥15	173	138	208
Active tuberculosis prevalence (per 100,000 population)	2015[48,49]	All	315	210	529
	2021[4]	All	312	218	406
	2021[4]	≥15	394	276	512
Tuberculosis infection prevalence proportion	2021[4]	All	0.314	0.114	0.514
Access-to-care tuberculosis prevalence ratio	2020[50]	All	0.427	0.327	0.527
Subclinical tuberculosis prevalence ratio	2020[51]	All	0.504	0.361	0.797
Proportion of incident tuberculosis cases having previously been treated	2020[25]	All	0.191	0.139	0.241

3.3 Incorporating the COVID-19 pandemic

It will be a number of years before the full implications of disruptions to tuberculosis prevention and care during the COVID-19 pandemic are realised. The WHO provided estimates for the impact on the tuberculosis incidence and mortality rates between 2020–2025 relative to January 2020, shown in Figure S3.2.[47]

In order to ensure that the model is appropriately representing the future trends in incidence and mortality, we calibrated to the projected incidence and mortality for 2025, which is estimated as a 10% increase in both mortality and incidence in 2025 compared to January 2020. To implement this, we calculated a 10% increase to the incidence and mortality rates estimated by the WHO in 2019, shown in Table S3.2, and calibrated to both for 2025.

A–Impact on tuberculosis incidence rate



B–Impact on tuberculosis mortality rate

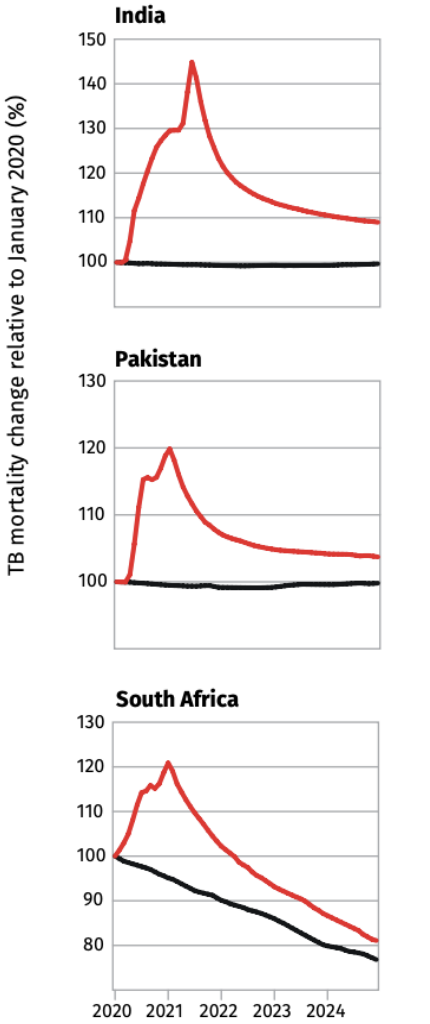


Figure S3.1 **The estimated impact of the COVID-19 pandemic on the (A) tuberculosis incidence and (B) mortality rates from the WHO Global Tuberculosis Report 2021[47]**

Table S3.2 **Incidence and mortality rate targets for all ages for 2025**

Year	Incidence rate (per 100,000)	Mortality rate (per 100,000)
2019	193 (126–260)	33 (30–35)
2025 (10% increase from 2019)	212 (145–293)	36 (33–39)

3.4 Modifications to calibration targets

3.4.1 Tuberculosis prevalence targets

i. Adjusting the 2015 target bounds

We obtained an estimate for the tuberculosis prevalence in 2015 from *Estimating tuberculosis incidence from primary survey data: a mathematical modelling approach* by Pandey et al., 2017.[48] In it, they estimate the prevalence of smear-positive cases across all ages in India, as well as the proportion of cases that are smear-positive. The mean and 95% confidence intervals for the estimates of these are 159.38 (122.9–196.59) and 0.63 (0.43–0.93) respectively.[49] Cited sources within the paper suggest that these quantities have been modelled as lognormal (smear-positive prevalence) and beta (smear-positive proportion) distributed.[48] The total prevalence, therefore, can be determined as

$$\text{Pulmonary tuberculosis prevalence} = \frac{\text{Smear-positive prevalence}}{\text{Smear-positive proportion}}$$

If we assume that the mean estimate for the proportion of cases that are smear-positive is accurate, then we simply quotient the smear-positive bounds by this value (0.63). This gives

$$\text{Pulmonary tuberculosis prevalence} = 253.0\ (195.1\text{–}312.0)$$

Since we have confidence intervals and a knowledge of the underlying distributions, we can attempt to determine the hyperparameters of the distributions. Once we have these, we can sample repeatedly from the quotient of the two distributions to get an estimate for its confidence interval. We sample from the numerator's distribution, sample from the denominator's distribution, and quotient them to represent a sample from the (unknown) prevalence distribution. Given enough samples, we can obtain a reasonable estimate of the confidence interval. Since the lognormal distribution has a closed-form, we can simply solve for the hyperparameters.

$$\text{Smear-positive prevalence} \sim \text{lognorm}(\mu = 5.046,\ \sigma^2 = 0.01436)$$

The beta-distribution is less straightforward, but we can use maximum likelihood estimation to find feasible parameter values. Doing so gives

$$\text{Smear-positive proportion} \sim \text{beta}(\alpha = 10, \beta = 6)$$

Then we perform Monte-Carlo sampling to generate a representative sample from our quotient distribution, from which we obtain a 95% confidence interval.

$$\text{Pulmonary tuberculosis prevalence} = 253.0\ (169.3\text{–}424.7)$$

ii. Adjusting for extrapulmonary tuberculosis

In our model we are representing everyone with tuberculosis, which includes both pulmonary (PTB) and extrapulmonary tuberculosis (EPTB). EPTB is not infectious but is included in the WHO estimates of yearly incidence and mortality rates. The 2021 prevalence estimates from the National Tuberculosis Prevalence Survey did not adjust for EPTB in the estimate provided for adults, and neither did the 2015 study which estimated the tuberculosis prevalence from subnational surveys. Therefore, we want to adjust the PTB prevalence estimates and range by the amount of EPTB in order to estimate the total TB prevalence. To estimate the proportion of EPTB, we used the average of the proportion of incident extrapulmonary tuberculosis cases from 2013–2020 (Table S3.3).[25]

Table S3.3 Number of incident tuberculosis cases by year in India

Year	New EPTB cases	Relapse EPTB cases	Total incident EPTB cases	Total incident cases	Proportion incident EPTB cases
2013	226,557	–	226,557	1,243,905	0.18
2014	275,502	–	275,502	1,609,547	0.17
2015	298,831	–	298,831	1,667,136	0.18
2016	281,162	–	281,162	1,763,876	0.16
2017	276,786	3,067	279,853	1,649,694	0.17
2018	380,904	5,622	386,526	1,908,683	0.20
2019	476051	3,862	479,913	2,162,323	0.22
2020	471,000	4,034	475,034	1,629,301	0.29

Abbreviations: EPTB = extrapulmonary tuberculosis

From the National tuberculosis prevalence survey India 2019–2021, the prevalence of microbiologically confirmed pulmonary tuberculosis among population aged ≥ 15 years in India was estimated at 316 (290–342) [This adjusted prevalence was estimated using a robust standard errors model with imputation and inverse probability weighting].[4] Averaging the proportion of incident EPTB cases column in Table S3.3 and dividing the estimates and bounds on the pulmonary tuberculosis prevalence estimates by (1- average of proportion of incident EPTB cases) we obtain the following as the estimates of the tuberculosis prevalence per 100,000 population:

$$\text{All ages tuberculosis prevalence in } 2015 = 315.1\ (210.8\text{–}529.0)$$

$$\text{Adult tuberculosis prevalence in } 2021 = 393.6\ (361.2\text{–}426.0)$$

iii. Adjusting the 2021 target bounds

The National Tuberculosis Prevalence Survey India 2019–2021 reports estimates for the prevalence of all forms of tuberculosis among all age groups in India (312.0 [286.0–337.0] per 100,000 population) and the prevalence of microbiologically confirmed pulmonary tuberculosis among adults aged ≥ 15 years in India (316.0 [290.0–342.0] per 100,000 population). As described in the previous section, we adjusted the estimate of the prevalence of pulmonary tuberculosis in adults for EPTB, giving a revised estimate for the prevalence of all forms of tuberculosis disease in adults of 393.6 (361.2–426.0). We subsequently increased the upper and lower bounds on the all age and adult targets by 30%, leading to estimates of 312.0 (218.4–405.6) and 393.6 (275.5–511.7) respectively. Rationale for adjusting the bounds on the targets is described below.

Rationale 1: Impact of the Covid-19 pandemic

Some state groups started and completed the survey before the COVID-19 pandemic, others during, others after the major pandemic waves had completed.[4] Depending on the impact of COVID-19 measures on tuberculosis, this could bias the estimates of the region either up or down, and bias the overall estimate of the tuberculosis prevalence for India, particularly as Delhi (the region with the highest estimated tuberculosis prevalence) started and completed the survey before the pandemic.[4]

Rationale 2: Differences between planned surveyed clusters and actual surveyed clusters

The National Tuberculosis Prevalence Survey India 2019–2021 compares the number of pulmonary tuberculosis cases notified at the state group level in 2019, 2020 and 2021 between those clusters who were surveyed and those who were not surveyed.[4] Although no statistically significant differences were observed between the surveyed and not-surveyed clusters, there are qualitative differences between the number of notifications of pulmonary tuberculosis between groups, where non-surveyed clusters consistently have a lower number of notifications.[4]

3.4.2 Tuberculosis infection prevalence

i. Adjusting the 2021 target bounds

The National Tuberculosis Prevalence Survey India 2019–2021 reports an estimate for the prevalence of tuberculosis infection in India among adults of 0.314 (0.272–0.353). We adjusted the bounds to give a revised estimate of 0.314 (0.114–0.514), with rationale described below.

Rationale 1: Oversampling from Gujarat with no adjustment

Of the 55 clusters where IGRA testing was done, 31 were in Gujarat and 24 were in the remaining 19 state groups. Gujarat had the lowest estimated tuberculosis prevalence per 100,000 population.[4] If we assume that prevalence of tuberculosis infection is correlated with prevalence of tuberculosis disease, then we would anticipate that the tuberculosis infection prevalence estimates from Gujarat would be correspondingly low. As more than half of the clusters were from Gujarat, and there is no indication of adjustment for oversampling from this region, it is possible that the reported country-level tuberculosis infection prevalence is an underestimate. If our assumption that prevalence of infection correlates with prevalence of disease was incorrect, the tuberculosis infection prevalence estimates may be overestimated. As such, we have adjusted the bounds to account for oversampling with no adjustment, but retained the central estimate, resulting in a calibration target of 0.314 (0.114–0.514).

3.4.3 Tuberculosis case notifications

i. Adjusting to account for the private sector contribution to reported case notifications

Treatment in India can occur in the public or private sector. While this varies by state, it is estimated that 60% of treatment is performed in the public sector, and the remaining 40% in the private sector. According to the WHO Global TB Report 2020, reported case notifications only included notifications from the public sector before 2013.[37] From 2013-2020, reported case notifications began to include the private sector (Figure S3.4). By 2020, approximately 31% of the total reported notifications were from the private sector.[47]

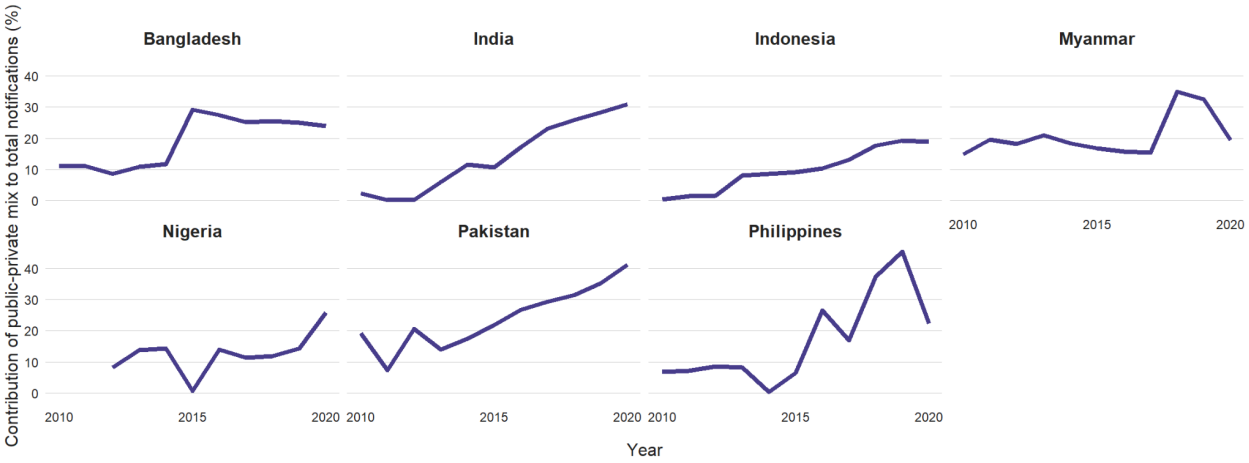


Figure S3.2 Contribution of the private sector to reported case notifications from WHO Global TB Report 2021[47]

The model represents case notifications as the number of tuberculosis treatment initiations. We want to calibrate the model to the *true* number of treatment initiations, as this is what the model will represent. Therefore, this involves adjusting the WHO reported case notifications to reflect underreporting from the private sector. To do this, we must calculate the fraction of total cases notifications (treatment initiations) that are reported, while accounting for both the private and public sector.

$\mathrm{RN}_{\mathrm{Total}}$ = Total Reported Notifications
$\mathrm{RN}_{\mathrm{Public}}$ = Public Sector Reported Notifications
$\mathrm{RN}_{\mathrm{Private}}$ = Private Sector Reported Notifications
$\mathrm{RN}_{\mathrm{Total}} = \mathrm{RN}_{\mathrm{Public}} + \mathrm{RN}_{\mathrm{Private}}$

Let: $f_{\mathrm{Private}} = \frac{\mathrm{RN}_{\mathrm{Private}}}{\mathrm{RN}_{\mathrm{Total}}}$ be the fraction of reported notifications that come from the private sector

Using the percent contribution of the private sector to the reported treatments, and the assumption that *all* treatments occurring in the public sector are reported, we can calculate the fraction of total notifications that are reported.

$\mathrm{N}_{\mathrm{Total}}$ = Total Notifications
$\mathrm{N}_{\mathrm{Public}}$ = Public Sector Notifications
$\mathrm{N}_{\mathrm{Private}}$ = Private Sector Notifications
$\mathrm{N}_{\mathrm{Total}} = \mathrm{N}_{\mathrm{Public}} + \mathrm{N}_{\mathrm{Private}}$

Let: $r_{f,k} = \frac{\mathrm{RN}_{\mathrm{Private}}}{\mathrm{N}_{\mathrm{Private}}}$ be the fraction of total private sector notifications reported in year k

$$\mathrm{RN}_{\mathrm{Total}} = \mathrm{N}_{\mathrm{Public}} + r_{f,k} \times \mathrm{N}_{\mathrm{Private}} \quad (1)$$

$$f_{\mathrm{Private}} \times \mathrm{RN}_{\mathrm{Total}} = r_{f,k} \times \mathrm{N}_{\mathrm{Private}} \quad (2)$$

$$\mathrm{RN}_{\mathrm{Total}} = \frac{r_{f,k} \times \mathrm{N}_{\mathrm{Private}}}{f_{\mathrm{Private}}} \quad (3)$$

Sub (3) into (1)

$$\frac{r_{f,k} \times \mathrm{N}_{\mathrm{Private}}}{f_{\mathrm{Private}}} = \mathrm{N}_{\mathrm{Public}} + r_{f,k} \times \mathrm{N}_{\mathrm{Private}}$$

Solve for $r_{f,k}$

$$r_{f,k} = \frac{\mathrm{N}_{\mathrm{Public}}}{\mathrm{N}_{\mathrm{Private}}(\frac{1}{f_{\mathrm{Private}}} - 1)}$$

$$\therefore r_{f,k} = \frac{60}{40(\frac{1}{f_{\mathrm{Private}}} - 1)}$$

Note: This calculation is valid for $f_{\mathrm{Private}} > 0$

We want to calculate f_T = fraction of total notifications reported

$$f_T = \frac{\mathrm{RN}_{\mathrm{Total}}}{\mathrm{N}_{\mathrm{Total}}}$$

$$f_T = \frac{\mathrm{RN}_{\mathrm{Public}} + \mathrm{RN}_{\mathrm{Private}}}{\mathrm{N}_{\mathrm{Total}}}$$

Assume:

$$\mathrm{RN}_{\mathrm{Public}} = \mathrm{N}_{\mathrm{Public}} = 60$$

$$N_{\mathrm{Total}} = 100$$

$$f_T = \frac{60 + r_{f,k} \times \mathrm{N}_{\mathrm{Private}}}{100}$$

Using the derived equation, we can calculate the fraction of total notifications reported from 2013–2020 (Table S3.4).

Table S3.4 The fraction of tuberculosis treatment notifications in India from the private sector and overall

Year (k)	Fraction of reported notifications that came from the private sector $f_{\text{Private},k}$	Fraction of total possible private sector notifications that were reported $r_{f,k}$	Fraction of total notifications reported $f_{T,k}$
≤ 2012	0	0	0.60
2013	0.05	0.08	0.63
2014	0.12	0.20	0.68
2015	0.10	0.17	0.67
2016	0.18	0.33	0.73
2017	0.22	0.42	0.77
2018	0.25	0.50	0.80
2019	0.28	0.58	0.83
2020	0.31	0.674	0.87

To adjust the WHO reported case notification estimates for underreporting, we divide the estimates by the fraction of total treatments reported (f_T), and assume 20% upper and lower uncertainty bounds. The reported and adjusted estimates of case notifications are provided in Table S3.5 and assume 20% upper and lower uncertainty bounds. The reported and adjusted estimates of case notifications are provided in Table S3.5.

Table S3.5 The WHO reported and adjusted tuberculosis case notification targets for India

Year	WHO reported case notification value	Adjusted case notification value	Low bound (Adjusted value × 0.8)	High bound (Adjusted value × 1.2)
2000	106	177	142	212
2020	118	136	109	163

3.4.4 Proportion of previously treated incident cases

i. Adjusting the proportion retreated bounds

The proportion retreated target is included to ensure that the disease tuberculosis incidence is derived from the correct source (i.e., to ensure that we do not overestimate the amount of incidence from fast-progression or reactivation without treatment).

The data available from the WHO are:

1. Number of case notifications (i.e., the notified treatment initiations), per year
2. Number of case notifications who are people who have been previously treated, per year

By dividing the number of notifications who are people who have been previously treated (2) by the total number of notifications (1), we get the proportion of notifications that have been previously treated.

$$= \frac{\text{Number of notifications who are people who have been previously treated per year}}{\text{Number of notifications per year}}$$

$$= \text{Proportion of notifications that have been previously treated}$$

We assume that at equilibrium, the proportion of notifications who have been previously treated will be equal to the proportion of incident disease cases who have been treated previously.

The estimate of the proportion of notifications that have been previously treated for India from the WHO dataset is 10.0% (4.3–14.7). However, country specific estimates may be subject to recall bias as they rely on patients to accurately report previous treatment. Additionally, studies have shown that approximately 11% of patients recorded as "new" have had some form of previous tuberculosis treatment.[52] Therefore, we adjusted the estimates from the WHO dataset, and calibrated to a target of 19.1% (13.9–24.1).

ii. Calculating the proportion retreated target in the model

The subsequent pages describe the methods used to calculate the proportion retreated target.

Definition 1: The number of notifications, per year is the flow from Dc and T = $\eta \times D_C$

Definition 2: Being "previously treated" implies that an individual arrived in the R compartment via the T compartment.

Definition 3: For an individual to count as a notification of a person who was previously treated (Definition 2), they must flow from T → R → Ds → Dc → T

Looking at the total number of notifications broken down to their origins, we see that:

$$\begin{aligned}&\text{Total number of notifications per year} = \\ &\text{Number of notifications of people who were in Ls per year} \\ &\quad + \text{Number of notifications of people who were in Lf per year} \\ &\quad + \text{Number of notifications of people who were in R per year}\end{aligned}$$

The "Notifications of people who were in R" term is further broken down into:

- People who entered R from T, per year
- People who entered R from Dc, per year
- People who entered R from Ds, per year

We can rewrite the total number of notifications per year equation as:

$$\begin{aligned}&\text{Total number of notifications per year} = \\ &\text{Number of notifications of people who were in Ls per year} \\ &+ \text{Number of notifications of people who were in Lf per year} \\ &+ \text{Number of notifications of people who were in R having entered R from Ds per year} \\ &+ \text{Number of notifications of people who were in R having entered R from Dc per year} \\ &+ \text{Number of notifications of people who were in R having entered R from T per year}\end{aligned}$$

Recall now what we are looking to calibrate to:

$$= \frac{\text{Number of notifications who are people who have been previously treated per year}}{\text{Number of notifications per year}}$$

The denominator is directly available from the model: the total number of notifications ($\eta \times D_C$). Using definitions 2 and 3 above, the "number of notifications who are people who have been previously treated per year" = "notifications of people who were in R having entered R from T per year". Therefore, we can redefine our calibration target as:

$$= \frac{\text{Number of notifications of people who were in R having entered R from T per year}}{\text{Total number of notifications per year}}$$

We do not have **notifications** disaggregated by source, but we do have **incidence** disaggregated by source. Incident cases are defined as the flow into Ds, which can be from R, from Ls, or from Lf.

$$\begin{aligned}&\text{Total number of incident cases per year} =\\&\text{Total number of incident cases of people from Lf per year}\\&+ \text{Total number of incident cases of people from Ls per year}\\&+ \text{Total number of incident cases of people from R per year}\end{aligned}$$

We obtain output on all these flows, so we can calculate the proportion of incident cases from each pathway (Lf, Ls, and R) easily by just dividing the total number of incident cases of people from Lf, Ls or R by the total number of incident cases.

The proportions of incidence from each pathway are:

$$\frac{\text{RD}}{(\text{RD} + \text{LsD} + \text{LfD})} \qquad \frac{\text{LfD}}{(\text{RD} + \text{LsD} + \text{LfD})} \qquad \frac{\text{LsD}}{(\text{RD} + \text{LsD} + \text{LfD})}$$

RD = flow from R to Ds = total number of incident cases of people from R, per year
LsD = flow from Ls to Ds = total number of incident cases of people from Ls, per year
LfD = flow from Lf to Ds = total number of incident cases of people from Lf, per year
RD + LsD + LfD = total number of incident cases, per year

Similarly, we can disaggregate the flow from R to Ds further into how the people in R entered R.

$$\begin{aligned}&\text{Total number of incident cases of people from R per year} =\\&\text{Total number of incident cases of people from R who entered R from T per year}\\&+ \text{Total number of incident cases of people from R who entered R from Dc per year}\\&+ \text{Total number of incident cases of people from R who entered R from Ds per year}\end{aligned}$$

Again, we don't have information on the disaggregated numbers of incident cases from R based on how they entered R, but we do have information on the entry to R.

$$\begin{aligned}\text{Total number entering into R per year} = \ &\text{Total number entering R from T per year}\\&+ \text{Total number entering R from Ds per year}\\&+ \text{Total number entering R from Dc per year}\end{aligned}$$

The proportion of the total flow into R from each of T, Ds, and Dc per year is:

$$\frac{\text{TR}}{(\text{TR+ DsR} + \text{DcR})} \qquad \frac{\text{DsR}}{(\text{TR+ DsR} + \text{DcR})} \qquad \frac{\text{DcR}}{(\text{TR+ DsR} + \text{DcR})}$$

TR = flow from T to R = total number entering R from T per year
DcR = flow from Dc to R = total number entering R from Dc per year
DsR = flow from Ds to R = total number entering R from Ds per year
TR + DsR + DcR = total number entering R per year

If we assume that the flows **INTO** R from each of T, Ds, and Dc are in the same proportions as the flows **OUT** of R, then we can disaggregate the outflow from R (which is the number of incident cases of people from R, per year, we called RD in the equation above) into incident cases of people from R who entered R from each of T, Ds, and Dc, per year by multiplying RD by the proportion from each of T, Ds, and Dc

Number of incident cases of people from R who entered R from T, per year
= (Number of incident cases of people from R, per year)×(Proportion of flow out of R that is from people who entered R from T, per year) etc.

We can rewrite RD in terms of the disaggregated pathways from T, Ds, and Dc:

$$\mathrm{RD} = \mathrm{RD} \times \frac{\mathrm{TR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \mathrm{RD} \times \frac{\mathrm{DsR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \mathrm{RD} \times \frac{\mathrm{DcR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})}$$

Subbing in the expression for RD above into the equation for the proportion of incident cases from R, we obtain:

$$\frac{\mathrm{RD} \times \frac{\mathrm{TR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \mathrm{RD} \times \frac{\mathrm{DsR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \mathrm{RD} \times \frac{\mathrm{DcR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})}$$

Factor, simplify and rewrite:

$$= \frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} * \left(\frac{\mathrm{TR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \frac{\mathrm{DsR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} + \frac{\mathrm{DcR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right)$$

$$= \left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{TR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right] + \left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{DsR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right] + \left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{DcR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right]$$

Proportion of incident cases from R =
(Proportion of incident cases from R who entered R from T)
+ (Proportion of incident cases from R who entered R from Dc)
+ (Proportion of incident cases from R who entered R from Ds)

The assumption we make here is that (at equilibrium) these proportions of incident cases will be equivalent for flows entering Ds (incident cases), entering Dc (progression from subclinical to clinical disease) and entering T (treatment initiation / case notifications).

$$\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \qquad \frac{\mathrm{LfD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \qquad \frac{\mathrm{LsD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})}$$

$$\left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{TR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right] \quad \left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{DsR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right]$$

$$\left[\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})} \right] \left[\frac{\mathrm{DcR}}{(\mathrm{TR} + \mathrm{DsR} + \mathrm{DcR})} \right]$$

Therefore, the proportion of notifications of people who were in R having entered R from T will be the same as the proportion of incidence from people who were in R having entered R from T.

Going back to the calibration target once again:

$$= \frac{\text{Number of notifications of people who were in R having entered R from T per year}}{\text{Total number of notifications per year}}$$

Although we do not know the number of notifications of people who were in R having entered R from T per year, this is equal to the proportion of notifications of people who were in R having entered R from T multiplied by the total number of notifications per year.

$$= \frac{\text{Total number of notifications per year} \times \text{Proportion of notifications of people who were in R having entered R from T}}{\text{Total number of notifications per year}}$$

We can cancel out the total number of notifications as it is in both the numerator and denominator.

$$= \frac{\text{Total number of notifications per year} \times \text{Proportion of notifications of people who were in R having entered R from T}}{\text{Total number of notifications per year}}$$

$$= \text{Proportion of notifications of people who were in R having entered R from T}$$

This value is calculated as the proportion of notifications of people who were in R multiplied by the proportion of the entry into R that came from T

$$= [\frac{\text{RD}}{(\text{RD} + \text{LsD} + \text{LfD})}][\frac{\text{TR}}{(\text{TR} + \text{DcR} + \text{DsR})}]$$

However, there may be some people who recently entered R from Dc or Ds, but who had also previously had treatment. Therefore, the previous equation is revised as:

$$= [\frac{\text{RD}}{(\text{RD} + \text{LsD} + \text{LfD})}][\frac{\text{TR} + (\text{DcR} + \text{DsR}) \times (\text{proportion of those in (DcR + DsR) who have been treated previously}}{(\text{TR} + \text{DcR} + \text{DsR})}]$$

We assume that the proportion of those in (DcR + DsR) who have been treated previously is the same as the proportion of those in DsR who have been treated previously.

We can then set the value:

$$\text{proportion of those in (DcR + DsR) who have been treated previously} =$$

$$[\frac{\text{RD}}{(\text{RD} + \text{LsD} + \text{LfD})}][\frac{\text{TR} + (\text{DcR} + \text{DsR}) \times (\text{proportion of those in (DcR + DsR) who have been treated previously}}{(\text{TR} + \text{DcR} + \text{DsR})}]$$

If we substitute in, we can see that the same term is repeated.

Let

$$\text{A} = \frac{\text{RD}}{(\text{RD} + \text{LsD} + \text{LfD})(\text{TR} + \text{DcR} + \text{DsR})}$$

Then we can rewrite the above as:

$$\text{A}[\text{TR} + (\text{Ds} + \text{Dc})[\text{A}[\text{TR} + (\text{Ds} + \text{Dc})[\text{A}[...]]]$$

Let $\text{B} = \text{TR}$ and $\text{C} = (\text{Ds} + \text{Dc})$

Substitute and expand:

$$\text{A}[\text{B} + \text{C}(\text{A}[\text{B} + \text{C}(\text{A}[...]))$$

$$\text{AB} + \text{AC}(\text{AB} + \text{AC}(\text{AB}[...]))$$

Let $\mathrm{X} = \mathrm{AB}$ and $\mathrm{Y} = \mathrm{AC}$.

Substitute and expand:

$$= \mathrm{X} + \mathrm{Y}(\mathrm{X} + \mathrm{Y}(\mathrm{X}[...]))$$

$$= \mathrm{X} + \mathrm{XY} + \mathrm{XY}^2 + \mathrm{XY}^3 ...$$

$$= \mathrm{X}\,(1 + \mathrm{Y} + \mathrm{Y}^2 + \mathrm{Y}^3 ...)$$

$$= \frac{X}{(1-Y)}$$

Substituting back in for X, Y, A, B, and C we obtain:

$$= \frac{\mathrm{AB}}{(1\text{-}\mathrm{AC})}$$

$$= \frac{\frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})(\mathrm{TR} + \mathrm{DcR} + \mathrm{DsR})} \times \mathrm{TR}}{(1 - \frac{\mathrm{RD}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})(\mathrm{TR} + \mathrm{DcR} + \mathrm{DsR})} \times (\mathrm{DcR} + \mathrm{DsR}))}$$

$$= \frac{\mathrm{RD} \times \mathrm{TR}}{(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD})(\mathrm{TR} + \mathrm{DcR} + \mathrm{DsR}) - \mathrm{RD}(\mathrm{DcR} + \mathrm{DsR})}$$

$$= \frac{\mathrm{RD} \times \mathrm{TR}}{\mathrm{TR}(\mathrm{RD} + \mathrm{LsD} + \mathrm{LfD}) + (\mathrm{DcR} + \mathrm{DsR})(\mathrm{LsD} + \mathrm{LfD})}$$

RD = flow from R to Ds = total number of incident cases of people from R, per year
TR = flow from T to R = total number entering R from T, per year
RD + LsD + LfD = total number of incident cases, per year

DcR = flow from Dc to R = total number entering R from Dc, per year
DsR = flow from Ds to R = total number entering R from Ds, per year
LsD = flow from Ls to Ds = total number of incident cases of people from Ls, per year
LfD = flow from Lf to Ds = total number of incident cases of people from Lf, per year

4. Policy scenarios

4.1 No-new-vaccine baseline

The primary no-new-vaccine simulated was the no-new-vaccine baseline, which assumed non-vaccine tuberculosis interventions continue at current levels into the future. As reported country-level data includes the high coverage levels of neonatal BCG vaccination, this was not explicitly modelled. We assumed that BCG vaccination would not be discontinued over the model time horizon.

4.2 Vaccine delivery scenarios

Two recently completed phase 2 trials have demonstrated encouraging efficacy results. The M72/AS01$_E$ candidate vaccine is a subunit vaccine for which results from a completed Phase IIb trial were published at the end of 2019.[13] After three years of follow-up, the efficacy of M72/AS01$_E$ at preventing disease in latently infected adults from South Africa, Zambia, and Kenya was estimated at 49.7% (95% confidence interval = 2.1–74.2).[13] To confirm this finding, a larger, Phase III follow-up study is needed, which includes participants who are uninfected, adolescents, as well as those living with HIV to assess safety and immunogenicity in these populations. This is being planned.

BCG-revaccination (administering a second dose of BCG to those who were vaccinated neonatally) was previously implemented in many countries, however evidence did not support the effectiveness of this practice. Interest in BCG-revaccination has recently been renewed following results from a trial for the vaccine candidate, H4:IC31. BCG-revaccination was assessed as a third parallel arm alongside H4:IC31 and a placebo in a pre-infection population in South Africa, and although neither vaccine appeared efficacious at preventing infection, BCG-revaccination appeared efficacious at preventing sustained infection (defined as three consecutive positive tests after day 84 of the trial) with an efficacy of 45.4% (6.4–68.1).[14] A larger trial of BCG-revaccination versus placebo in 1800 healthy adolescents from across South Africa is now underway to verify this finding.

We evaluated introducing vaccines with M72/AS01$_E$ and BCG-revaccination characteristics compared to the no-new-vaccine baseline as described in the subsequent sections.

4.2.1 Classifying tuberculosis vaccines

Before describing the specific characteristics for the vaccine scenarios that we investigated, we provide a brief overview on classifying tuberculosis vaccines (descriptions from Clark et al.[5]).

Tuberculosis vaccines are characterised on four key characteristics: the vaccine efficacy, the host infection status at the time of vaccination required for the vaccine to be efficacious, the mechanism of effect, and the duration of protection. Vaccine efficacy defines the magnitude of protection induced by the vaccine. Vaccine efficacy is assumed to be either “all or nothing”, where the vaccine offers full protection to a subset of individuals (equal to the vaccine efficacy) who were vaccinated, or “degree”, where the vaccine offers partial protection to all individuals who received the vaccine.

The host infection status at the time of vaccination required for the vaccine to be efficacious defines the *Mtb* infection status required of the population at the time they receive the vaccine for the vaccine to be efficacious. We divide the host infection status into No Current Infection (NCI), where the vaccine is efficacious in uninfected populations only, Current Infection (CI), meaning the vaccine is efficacious in populations with current infection with *Mtb* only, or Any Infection (AI) where the vaccine is efficacious in both pre- and post-infection populations.

The vaccine mechanism of effect type determines how the vaccine will offer protection. A prevention of infection (POI) vaccine protects individuals from initial or re-infection with *Mtb*, whereas a prevention of disease (POD) vaccine functions by preventing individuals who may be uninfected or infected with *Mtb* from progressing to active disease. A prevention of infection and disease vaccine (POI&D) prevents both infection and disease. Finally, the duration of protection represents the length of time following vaccination that individuals are protected.

4.2.2 M72/AS01$_E$ and BCG-revaccination scenarios

For each vaccine product, we established one "Basecase" vaccine scenario based on clinical trial data and expert opinion. We then varied vaccine product and delivery scenarios as univariate scenario analyses from the Basecase scenario as described in Table S4.1.

Table S4.1 M72/AS01$_E$ and BCG-revaccination scenarios evaluated in the analysis

Characteristic	M72/AS01$_E$		BCG-revaccination	
	Basecase	**Varied in univariate**	**Characteristic**	**Basecase**
Policy scenarios				
Age targeting	Campaign for ages 16-34, routine age 15	Older ages (campaign for ages 18-55) Elderly ages (campaign for ages 61+, routine age 60)	Campaign for ages 11-18, routine age 10	Older ages (campaign for ages 16-34, routine age 15) Elderly ages (campaign for ages 61+, routine age 60)
Vaccine characteristic and coverage scenarios				
Vaccine efficacy	50%	60% 70%	45%	70%
Duration of protection	10 years	5 years 15 years 20 years	10 years	5 years 15 years 20 years
Host infection status	AI	CI	NCI	AI
Mechanism of effect	Prevention of disease	Prevention of infection and disease	Prevention of infection	Prevention of infection and disease
Introduction year (years of any repeat campaigns)	2030 (2040)	2036 (2046)	2025 (2035, 2045)	2031 (2041)
Achieved vaccine coverage	Campaign = 70% / Routine = 80%	Campaign = 50% / Routine = 70% Campaign = 90% / Routine = 90%	80%	70% 90%

4.2.3 Vaccine delivery assumptions

Vaccine eligible population

In our modelling, we assume that there is no pre-vaccination infection testing. Therefore, even if a vaccine is only effective when delivered to uninfected individuals at the time of vaccination, we assume that both uninfected and

infected individuals will receive the vaccine, and only the uninfected individuals will receive protection. Our model structure allows for counting and tracking individuals who received the vaccine but do not receive any protection from it.

Efficacy
From trial data, the efficacy of M72/AS01$_E$ at preventing disease in latently infected adults was estimated at 49.7% (2.1–74.2).[13] Therefore, our Basecase vaccine efficacy was set at 50%, and based on expert opinion we evaluated 60% and 70% as scenario analyses. BCG-revaccination appeared efficacious at preventing *sustained* infection with an efficacy of 45.4% (6.4–68.1).[14] The Basecase efficacy was set to 45%, and 70% was evaluated in a scenario analysis.

Protection from repeat vaccinations
In the event that an individual who is currently protected with a vaccine receives another course, after consultation with an immunologist we have made some assumptions on the resulting level of vaccine protection:

BCG-revaccination: Based on expert advice, we assume that no additional protection is afforded if a second or third vaccine is administered while the individual is currently protected from the first.

M72/AS01$_E$: Based on expert advice, we assume that overall vaccine protection increases if a second vaccine is administered while the individual is currently protected by a first vaccine. We assume that this protection increases by (1-current protection) times vaccine efficacy, as in Table S4.2.

Table S4.2 Increase in protection for the number of vaccine courses

Number of vaccine courses currently protected by	Basecase	Efficacy variation 1	Efficacy variation 2
One	50.0%	60.0%	70.0%
Two	75.0%	84.0%	91.0%

Note that the number of vaccine courses refers to the number of vaccine courses that the individual is *currently* protected by, not that they have ever a) received, or b) been protected by. For example, if someone receives one vaccine, then wanes, then receives another one, they would only be currently protected by one, not two, vaccines, and so the efficacy would be either 50%, 60%, or 70% depending on the scenario.

Mechanism of effect
We assume that a vaccine that protects against infection will work by reducing the rate of infection for both initial and re-infection, and that a vaccine that protects against progression to disease will work by reducing the rate of progression to subclinical disease. If the vaccine protects against both infection and disease we assume that it has the same efficacy against preventing disease as it does infection. For example, if the vaccine is defined as a prevention of infection and disease vaccine with 50% efficacy, it reduces the rate of infection by 50% and the rate of progression to disease by 50%.

Introduction year
The Basecase introduction years, 2025 and 2030 for BCG-revaccination and M72/AS01$_E$ respectively, were determined based on considering when new trial data would become available, as well as incorporating time for licensure and policy change. The introduction year considered in scenario analyses, 2031 and 2036 for BCG-revaccination and M72/AS01$_E$ respectively, was based on applying IAVI/Full Value Assessment of Tuberculosis Vaccines analyses from Shelly Malhotra and expert advice to the earliest possible introduction year.[5]

Age targeting
The Basecase age was informed by ages of trial participants and expert advice. Additional scenarios were informed by work conducted by Pelzer et. al and expert advice.[58]

4.3 Vaccine model structure

Depending on the host infection status required at the time of vaccination for the vaccine to be efficacious, we implemented a different vaccine structure in the model to account for differences in Vaccinated Protected, Vaccinated Not Protected, and Vaccinated Waned. Each compartment in the vaccine structure is replicated for all tuberculosis natural history compartments, access-to-care strata, and ages.

4.3.1 No Current Infection vaccines

A No Current Infection (NCI) vaccine requires an individual to be uninfected at the time of vaccination in order for the vaccine to be efficacious. Implementation in the model of an NCI vaccine with the possibility of two repeat vaccine courses is provided in Figure S4.1. For our purposes, we assume that the level of protection remains the same regardless of the number of vaccine courses received (i.e. level of protection in "Vaccinated Protected (one vaccine course)" is equal to "Vaccinated Protected (two vaccine courses)" etc.). Additionally, because the vaccine is only efficacious for NCI, and in this model once you leave U_N (the state where the vaccine is effective) you never return, once you enter a "Vaccinated Not Protected" state you *never* have the opportunity to become "Vaccinated Protected" again.

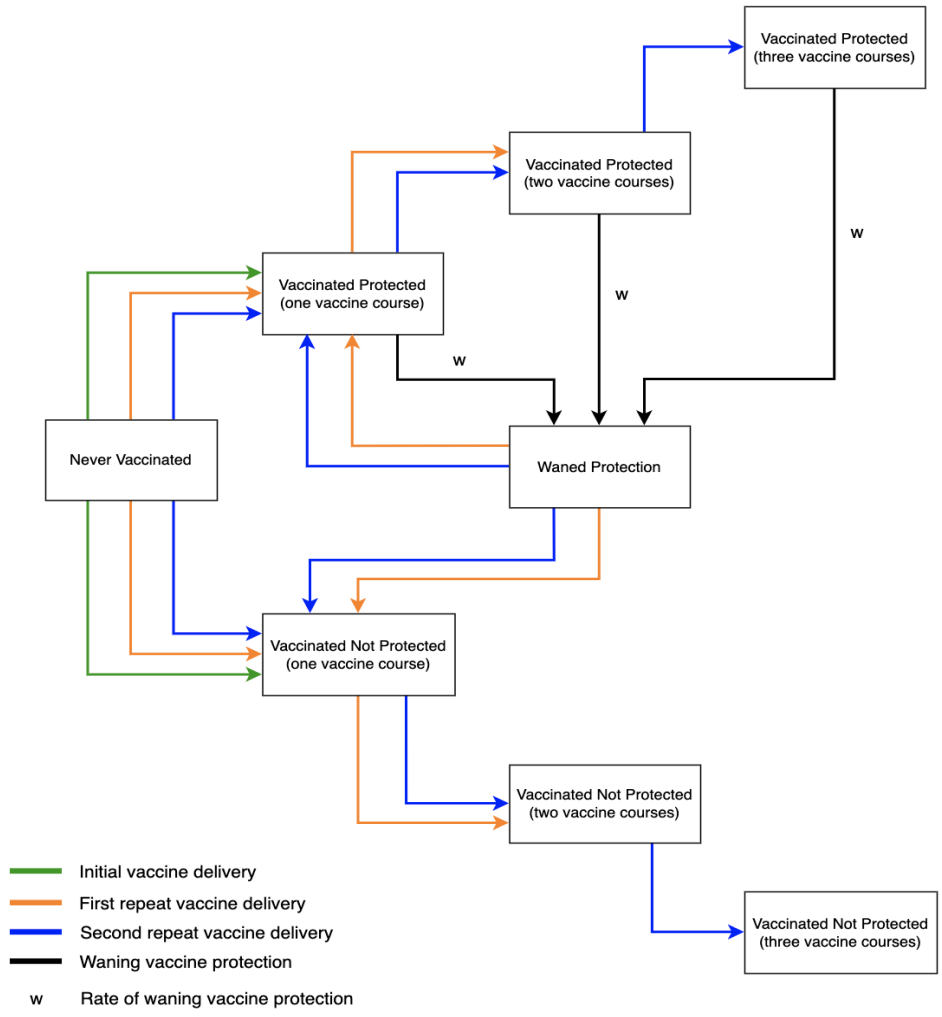


Figure S4.1 Vaccine structure for a NCI vaccine

4.3.2 Current Infection vaccines

A Current Infection (CI) vaccine requires an individual to be infected at the time of vaccination in order for the vaccine to be efficacious. Implementation in the model of a CI vaccine with the possibility of two repeat vaccine courses is provided in Figure S4.2. For our purposes, we assume that the level of protection builds with each vaccine course, with efficacy values as in Table S4.2.

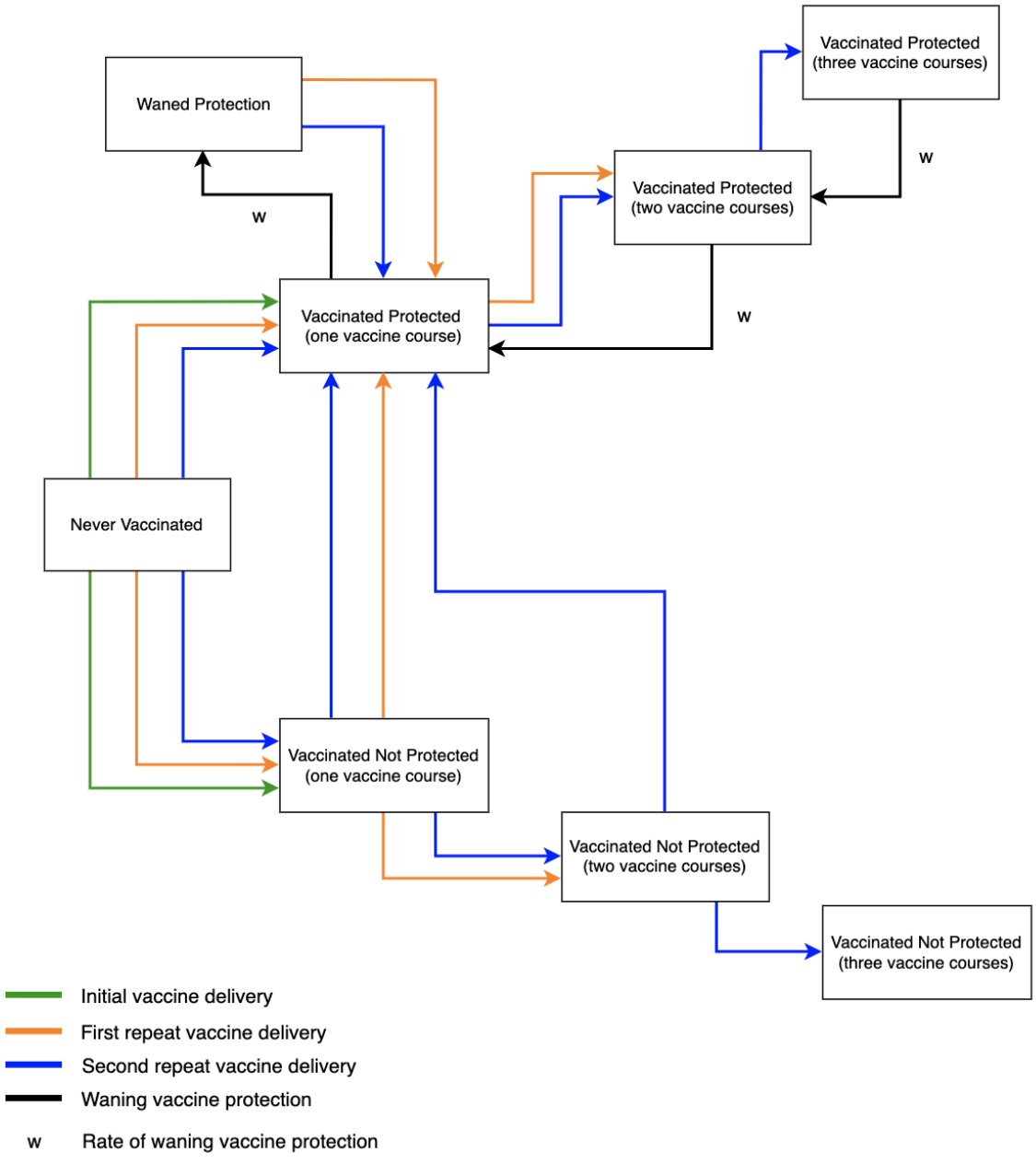


Figure S4.2 Vaccine structure for a CI vaccine (where protection builds with each vaccine course)

4.3.3 Any Infection vaccines

An Any Current Infection (AI) vaccine will be efficacious with any infection status (aside from current active disease) at the time of vaccination. The "Vaccine Not Protected" compartments remain as we assume that individuals with subclinical disease may be accidentally vaccinated and would not receive protection from the vaccine. However, we do want to keep track of the number of vaccinations for cost purposes.

AI-1 vaccines: With each vaccine course the level of protection remains the same (Figure S4.3). Waning occurs from any of the Vaccinated Protected compartments to the Waned Protection compartment.

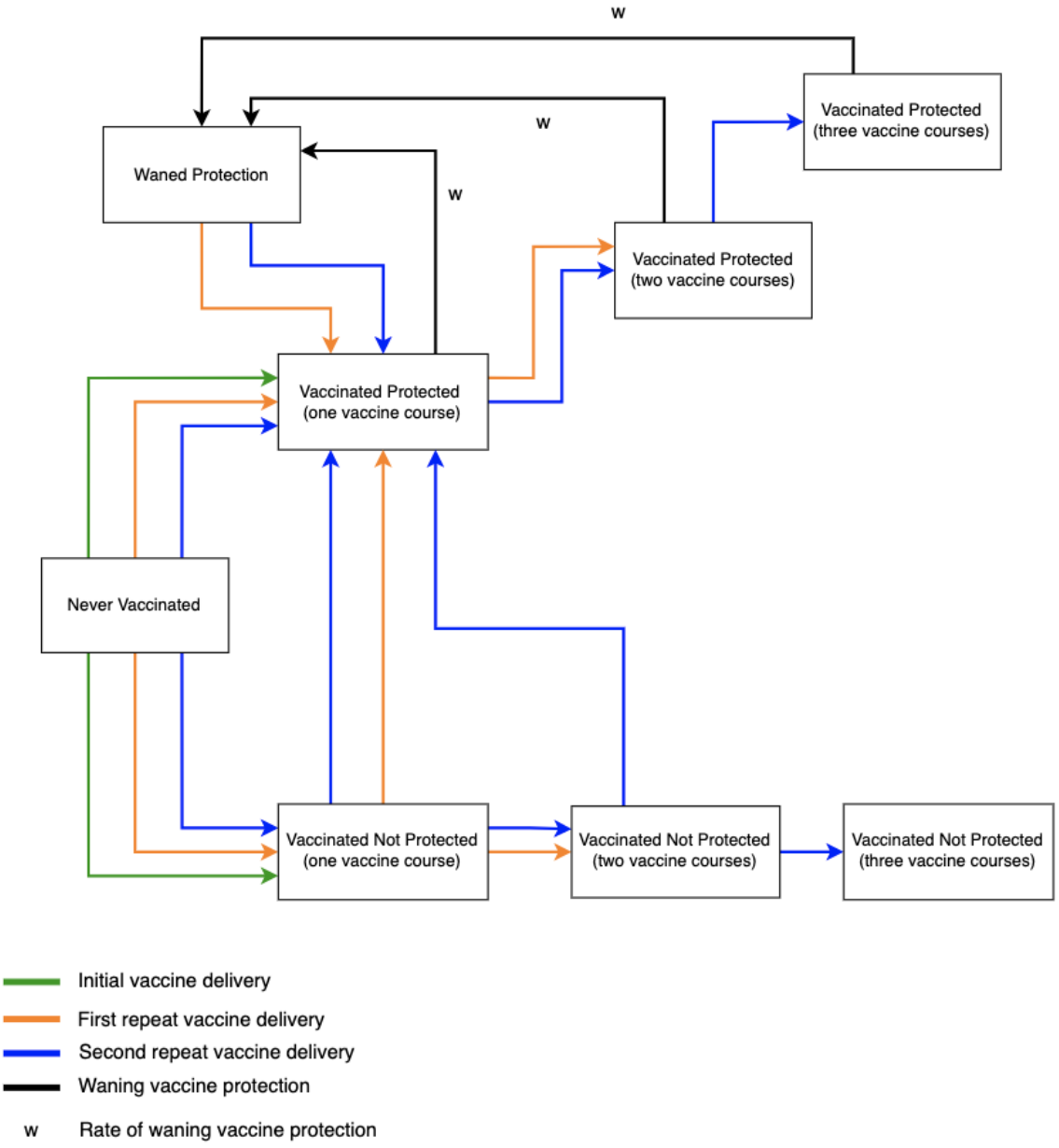


Figure S4.3 Vaccine structure for an AI vaccine (where protection does not build with each vaccine course)

AI-2 vaccines: With each vaccine course the level of protection builds if the recipient is currently in a Vaccinated Protected compartment (Figure S4.4). This is the same structure as the CI vaccine with protection building (Figure S4.2). Waning occurs from any of the Vaccinated Protected compartments to the Vaccinated Protected compartment one level below, or to the Waned Protection compartment for those with only one course of protection.

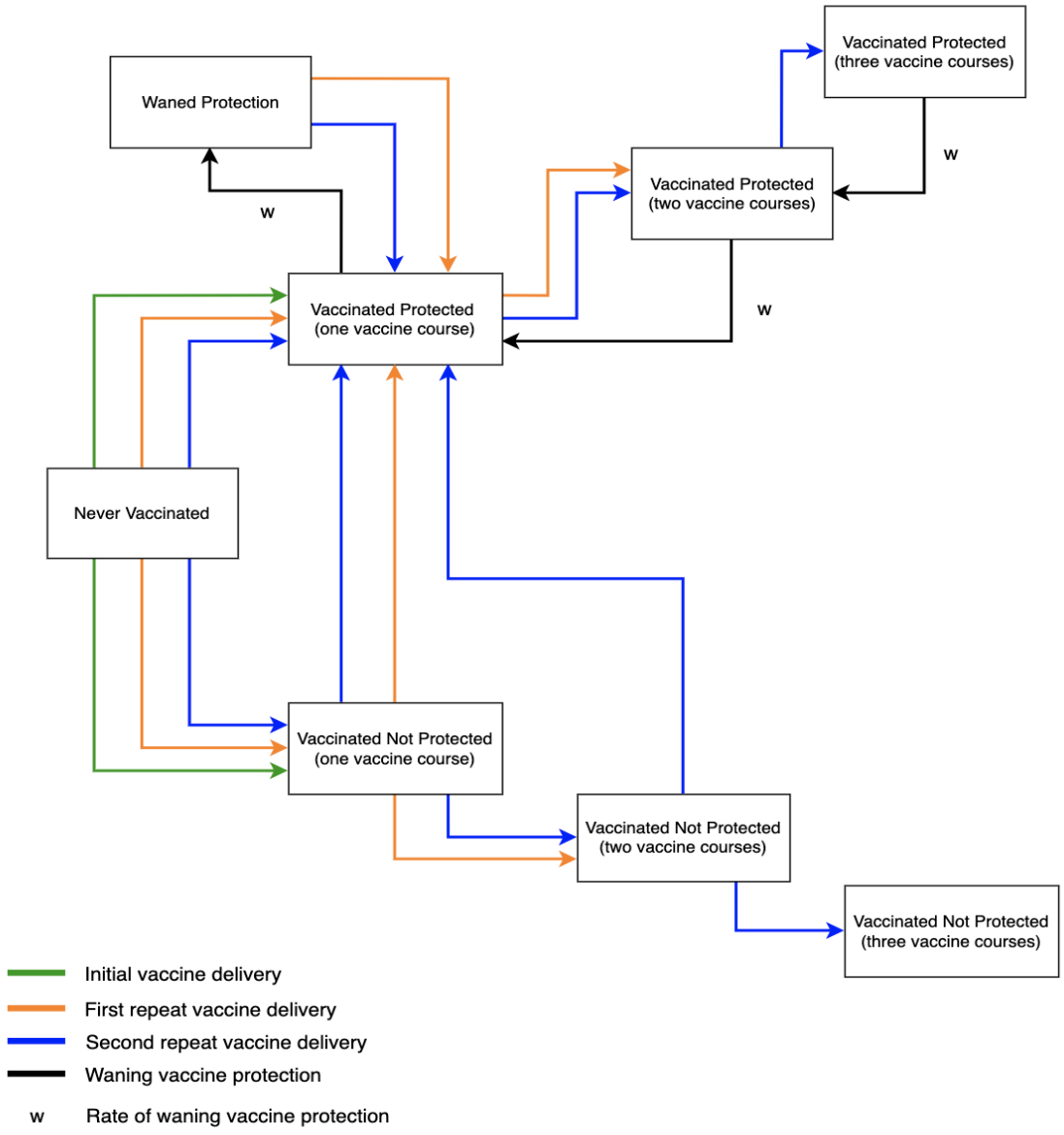


Figure S4.4 Vaccine structure for an AI vaccine (where protection builds with each vaccine course)

5. Economic analysis methods

Before undertaking this work, we established an economic analysis plan, involving stakeholders and government officials to ensure we had incorporated all necessary information and planned to report on all key outcomes, to outline the methods used in this work. This is summarised below.

5.1 Calculation of disability-adjusted life years

We calculated the difference in total disability-adjusted life years (DALYs) from vaccine introduction to 2050 for each scenario compared to the no-new-vaccine baseline. We used the disability weight for tuberculosis disease from the Global Burden of Disease 2019 study,[60] and country- and age-specific life expectancy estimates from the United Nations Development Programme.[61] To incorporate parameter uncertainty in years lost due to disability (YLD) weight estimates, we made 1000 draws from disability weight uncertainty ranges.

5.2 Tuberculosis-related cost model

We estimated health system unit costs, patient costs and productivity losses based on a scoping review of published literature. For the tuberculosis programme, we obtained unit costs for drug-susceptible (DS) and drug-resistant (DR) tuberculosis treatment and diagnostic costs. Uncertainty in cost estimates is characterised through gamma distributions around plausible unit cost estimates in a probabilistic sensitivity analysis. There was considerable uncertainty in the cost of delivering a vaccine, including the price of vaccine compounds and programmatic delivery among adolescents. Based on expert opinion from funders, for the M72/AS01$_E$ vaccine we assume a $2.50 per-dose vaccination price with two doses per course assumed in the Basecase. Based on the average estimated BCG price from 2020–2023 from UNICEF,[53] the vaccine price per dose for BCG-revaccination was set at $0.17, with one dose assumed per course.

5.3 Vaccine introduction

All cost inputs are given in Table S5.1.

Due to uncertainty in unit costs of vaccine supply and introduction among populations who may not typically receive large-scale mass vaccination, we make several assumptions around costs to supply and introduction of vaccines. Uncertainty in cost estimates is characterised through gamma distributions.

One-time vaccine introduction costs are included in years where there is a campaign and represent non-recurring costs such as establishing infrastructure and providing training for healthcare professionals. The costs were assumed to be $2.40 (1.20–4.80) per individual in the targeted age group (as opposed to the actual number of recipients) based on the vaccine introduction support policy of Gavi, the Vaccine Alliance.[54] Vaccine delivery was assumed to be $2.50 (1.00–5.00) per dose, with a further $0.11 (0.06–0.22) supply costs per dose.[55] The cost of recipient vaccination time was $0.94 (0.13–1.52), which was calculated by multiplying a wage proxy of GDP per capita for India by an estimate of the time required for vaccination.[56,57] We assume a 5% wastage rate.

For each year in the five-year scale up, the vaccination cost is calculated as:
Vaccination cost = (one time introduction costs) × (targeted age group population size) × 0.2 + (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For each year where there is a repeat campaign, the vaccination cost is calculated as:
Vaccination cost = (one time introduction costs) × (targeted age group population size) + (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For each year where there is only routine delivery of the vaccine, the vaccination cost is calculated as:
Vaccination cost = (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For the vaccination cost from the societal perspective, the patient time cost of vaccination was added as a multiplier to the number of doses, and therefore included in the equation along with vaccine price, vaccine supply costs, and the cost of delivery.

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 2025 (when vaccination began) at 3% per year, per guidelines.[59] We measured cost-effectiveness by 2050 against three India specific cost thresholds: 1x gross domestic product (GDP) per-capita (US$1,927.71),[57] and two country-level opportunity cost thresholds defined by Ochalek et al [the upper (US$363), and lower (US$264) bounds].[62]

5.5 Total costs from the health-system and societal perspectives

The following costs are included in the health-system perspective:

- Vaccine costs: One-time vaccine introduction costs, recurring vaccine delivery costs, vaccine price per dose, and supply costs
- Cost of testing and diagnosis for drug-susceptible and drug-resistant cases
- Cost of treatment for drug-susceptible and drug-resistant cases

In addition to the costs from the health-system perspective, costs from the societal perspective include:

- Vaccine costs: Patient time cost for vaccination
- Non-medical patient costs (including transportation) for drug-susceptible and drug-resistant cases
- Indirect patient costs for drug-susceptible and drug-resistant cases

Table S5.1 Tuberculosis testing, diagnostic, and vaccination related cost inputs

Unit Cost	Estimate	Lower Bound	Upper Bound	Sources
Unit cost of testing/diagnosis for DS cases per person	$22.45	$18.37	$26.53	63
Unit cost of testing/diagnosis for DR cases per person	$24.36	$5.04	$117.81	64
Unit cost of treatment for DS cases per person	$317.00	$254.00	$374.00	65
Unit cost of treatment for DR cases per person	$3,891.00	$3,382.00	$4,401.00	66
Non-medical patient cost per DS-TB disease episode (including transportation) per person	$51.25	$22.12	$76.94	67,68
Indirect patient cost per DS-TB disease episode (time spent on treatment and transport * wage) per person	$117.01	$24.04	$460.24	68,69
Non-medical patient cost per DR-TB disease episode (including transportation) per person	$143.49	$61.95	$215.42	67,68
Indirect patient cost per DR TB disease episode (time spent on treatment and transport * wage) per person	$327.63	$67.30	$1,288.66	68,69
Recurrent vaccine delivery cost per person per dose	$2.50	$1.00	$5.00	54
One-time vaccine introduction costs per targeted person	$2.40	$1.20	$4.80	54
Vaccine supply costs per person per dose	$0.11	$0.06	$0.22	55
Cost of vaccination time per person per dose	$0.94	$0.13	$1.52	56,57

6. Health impact outcomes

The following measures were calculated for each vaccine scenario as the median and 95% uncertainty range:

- Percent incidence rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Percent mortality rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Cumulative cases averted for each vaccine scenario between vaccine introduction (either 2025 or 2030) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative deaths averted for each vaccine scenario between vaccine introduction (either 2025 or 2030) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative treatments averted for each vaccine scenario between vaccine introduction (either 2025 or 2030) and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years

SUPPLEMENTARY RESULTS

7. No-new-vaccine baselines

7.1 *Status Quo* no-new-vaccine baseline calibration

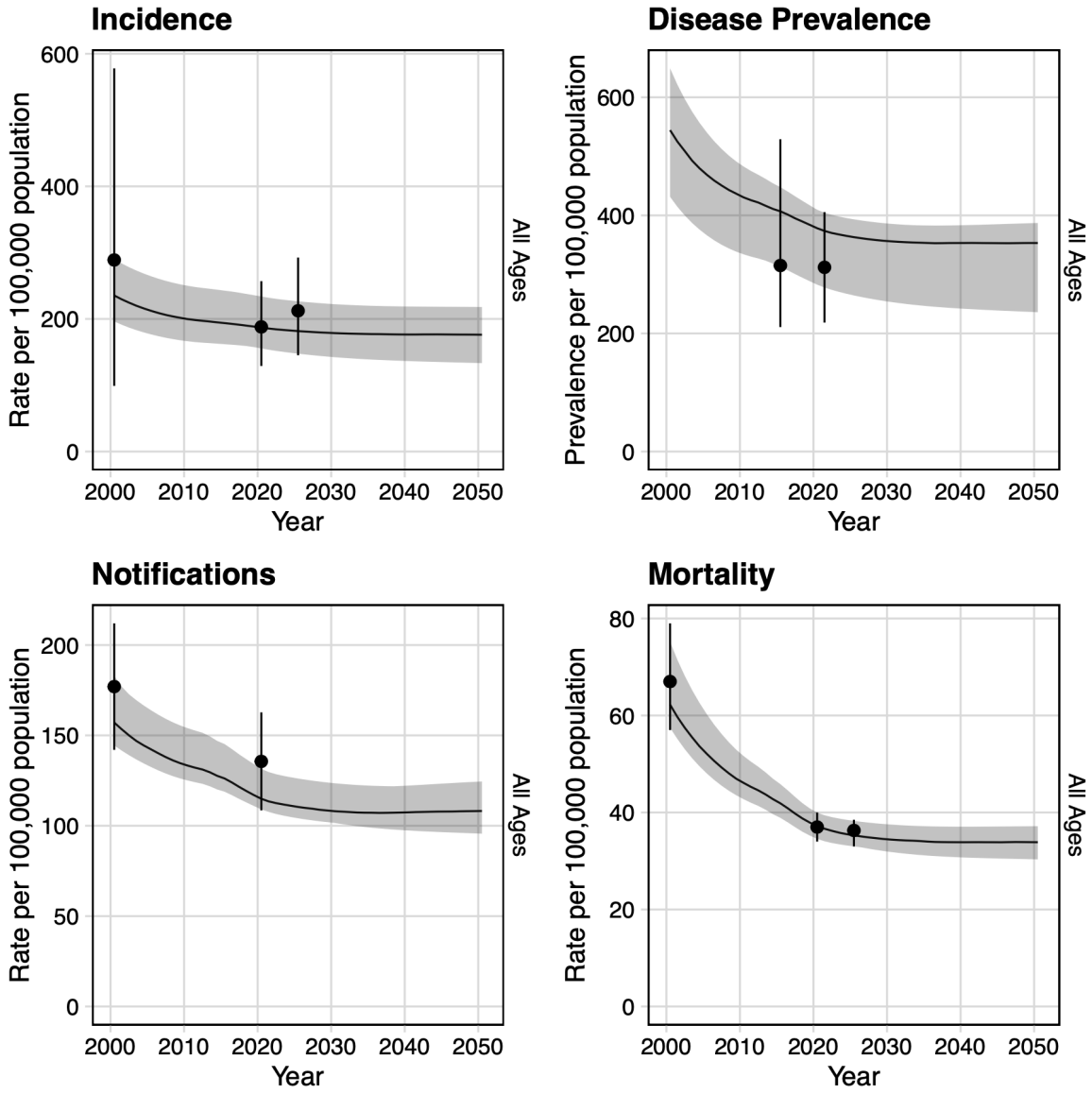


Figure S7.1 Tuberculosis incidence, disease prevalence, case notification and mortality rate trends from 2000–2050 for all ages

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

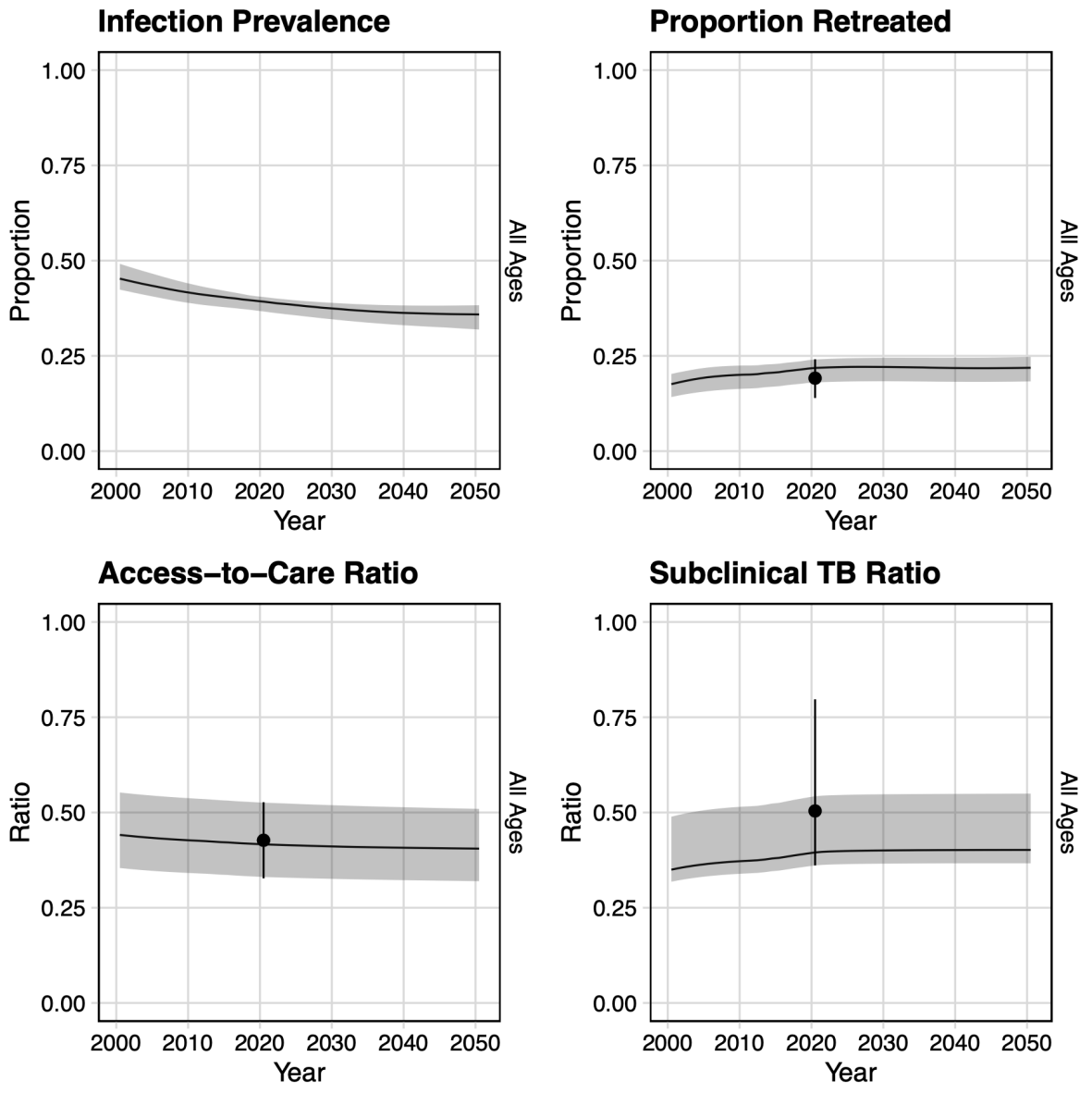


Figure S7.2 Tuberculosis infection prevalence, proportion retreated, access-to-care ratio and ratio of subclinical tuberculosis to total tuberculosis trends from 2000–2050 for all ages

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

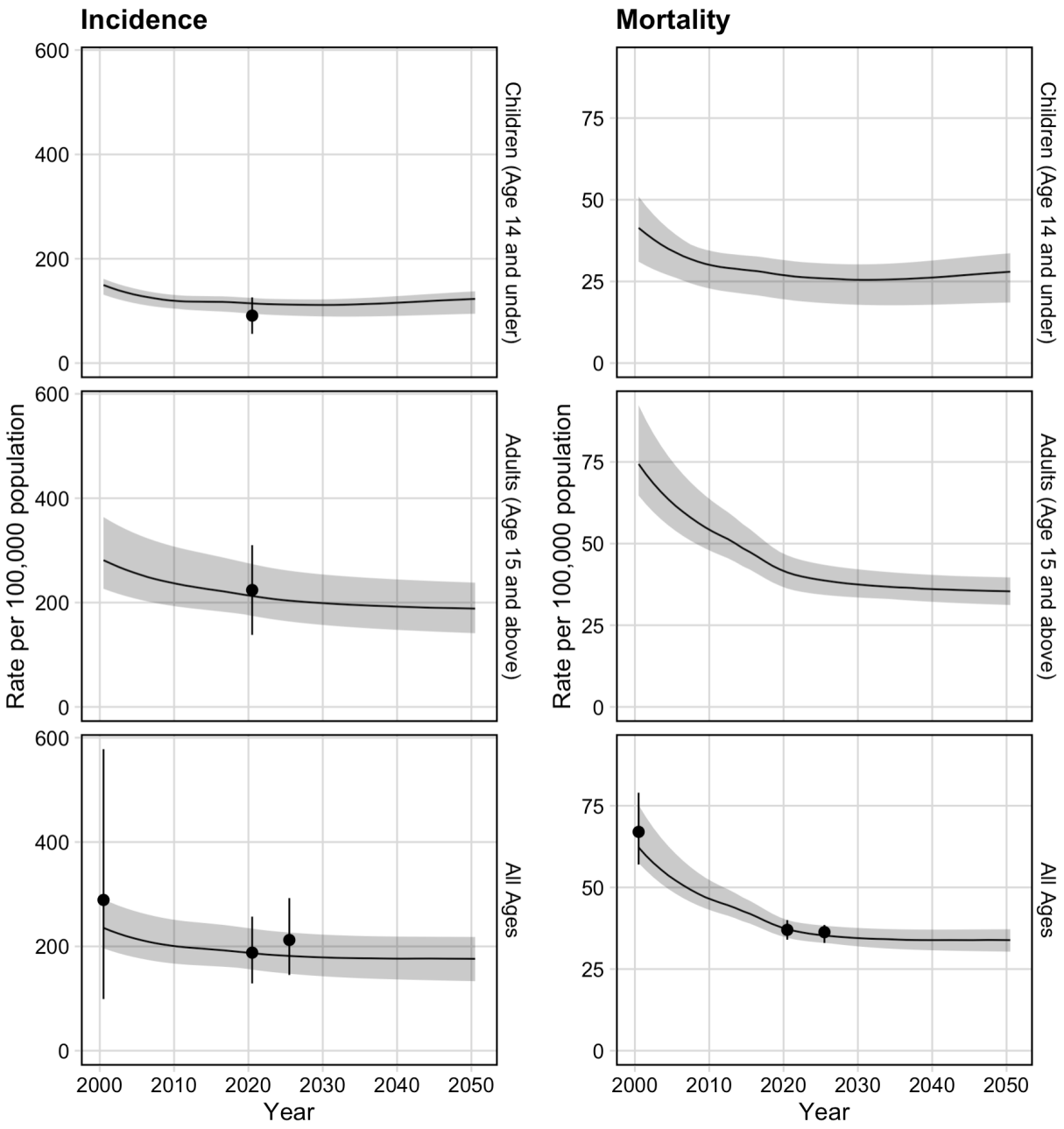


Figure S7.3 Tuberculosis incidence and mortality rate trends from 2000–2050 by age group

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

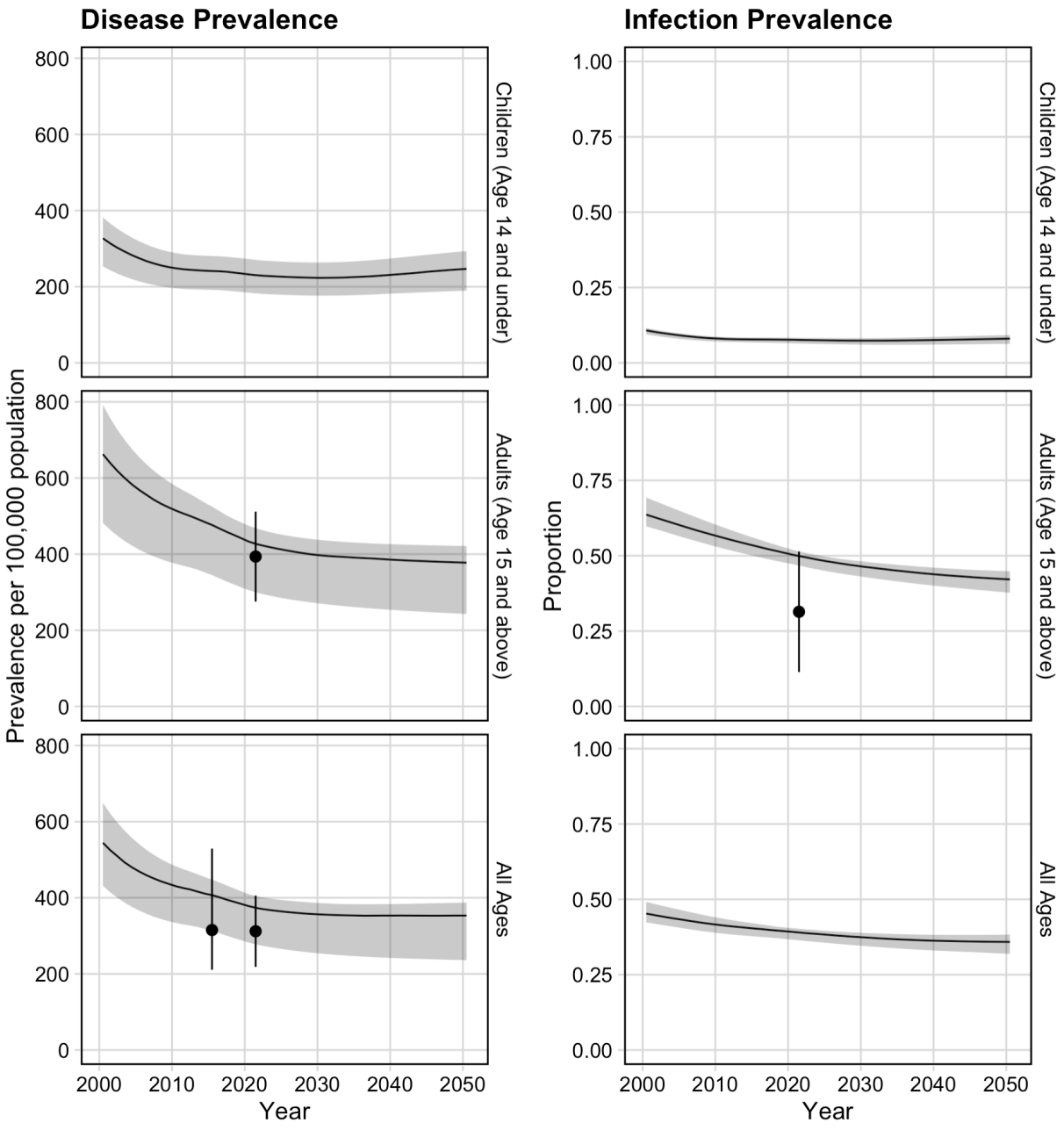


Figure S7.4 Tuberculosis disease and infection prevalence trends from 2000–2050 by age group

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

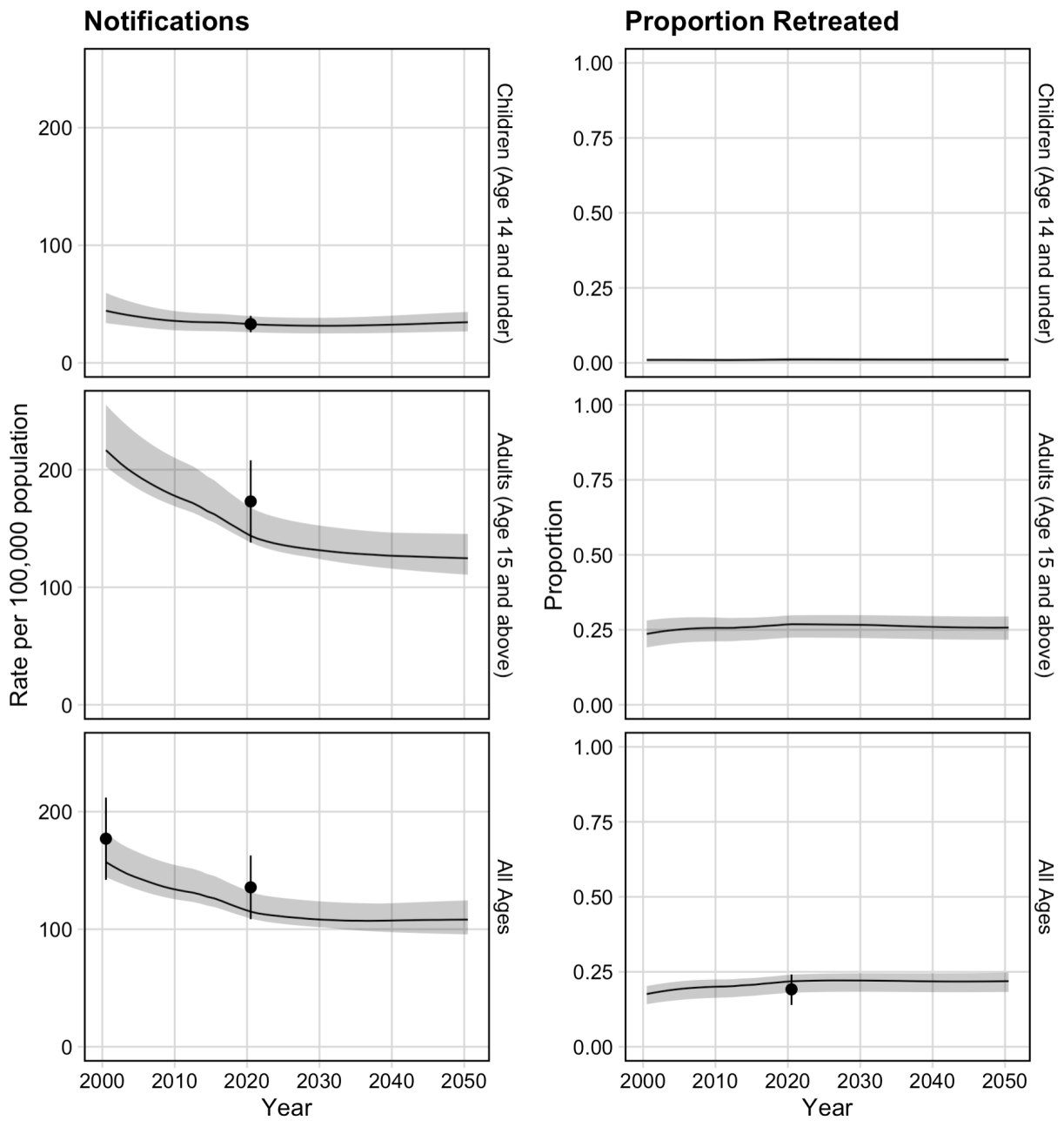


Figure S7.5 Tuberculosis case notification and proportion retreated trends from 2000–2050 by age group

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

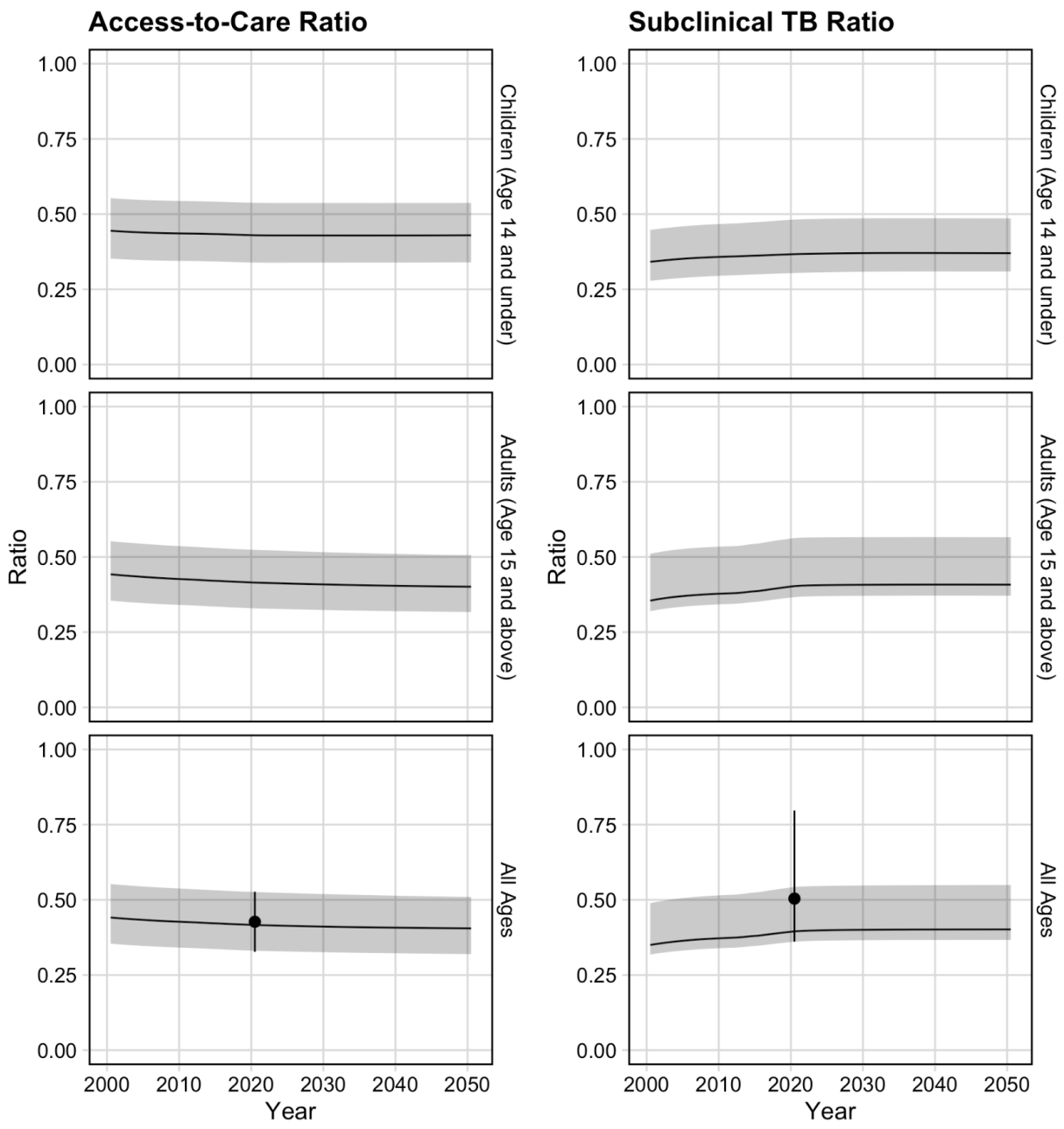


Figure S7.6 Access-to-care ratio and the ratio of subclinical tuberculosis to all active tuberculosis trends from 2000–2050 by age group

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical line is the calibration target from Table S3.1.

7.2 Posteriors distributions for model parameters

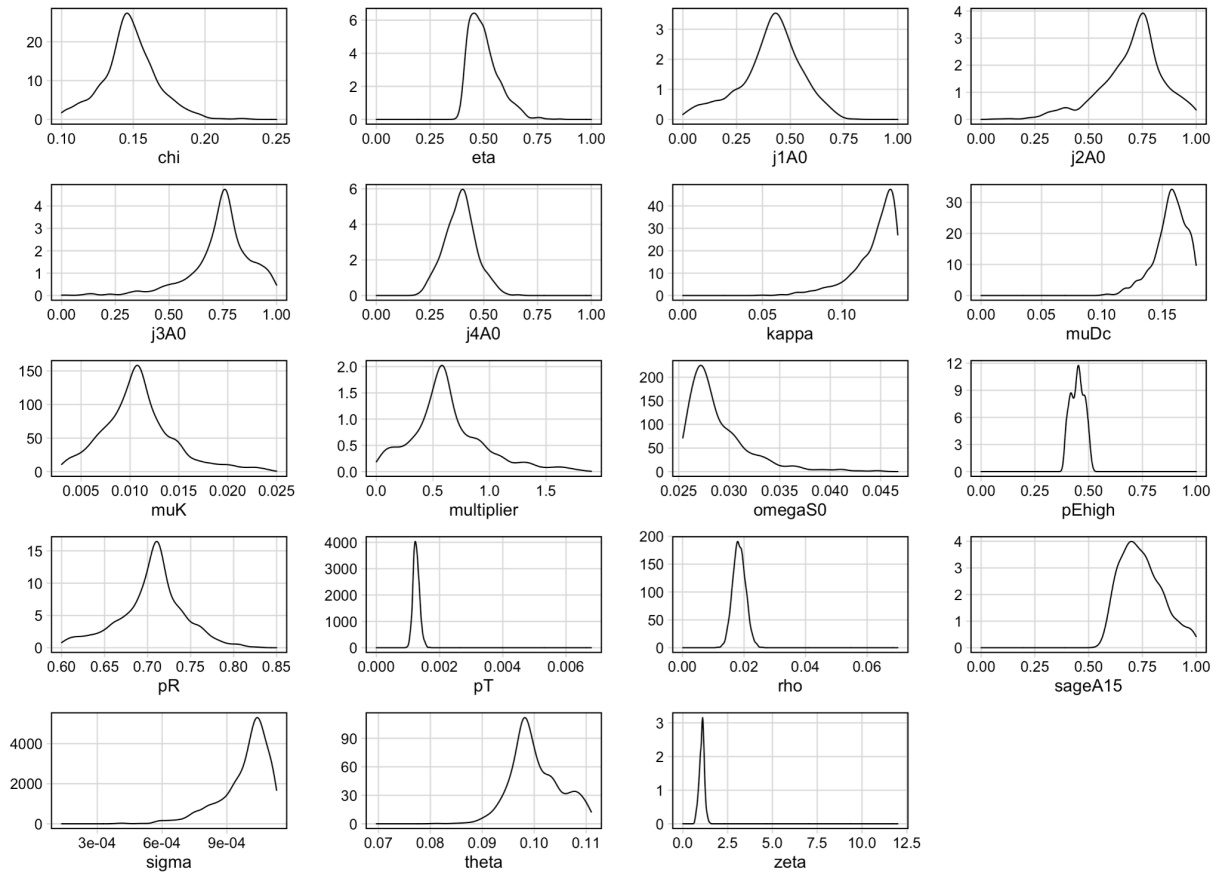


Figure S7.7 Posterior distributions for the 1000 parameter sets of the 19 parameters varied during calibration

Definitions: chi = rate of natural cure, eta = rate of treatment initiation, j1A0 = age multiplier for rate of fast progression (theta), j2A0 = age multiplier for rate of reactivation (sigma), j3A0 = age multiplier for rate of relapse (rho), j4A0 = age multiplier for rate of treatment initiation, kappa = on-treatment mortality fraction, muDc = rate of clinical disease mortality, muK = rate of background mortality for increased mortality rate from the Recovered compartment, multiplier = the multiplier to see the initial distribution of the population into the natural history compartments, omegaS0 = rate of progression between Latent-Slow and Latent-Zero, pEhigh = multiplier for high access-to-care relative to low access-to-care, pR = protection from reinfection for those in the Latency or Recovered compartments, pT = rate of transmission, rho = rate of relapse, sageA15 = age multiplier for mortality rates, sigma = rate of reactivation, theta = rate of fast progression following infection, zeta = rate of progression from subclinical to clinical disease compartments.

7.3 *Strengthened Current Interventions* no-new-vaccine baseline calibration

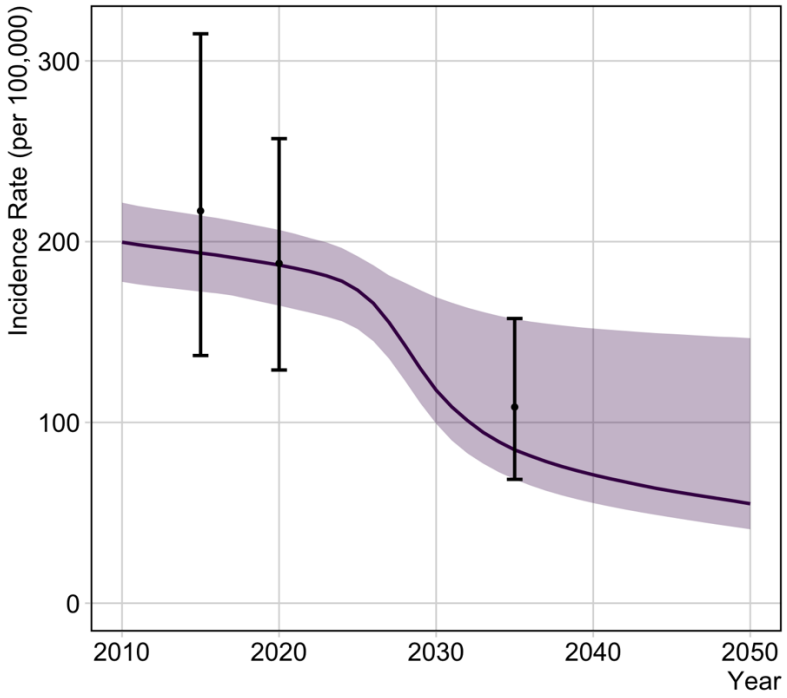


Figure S7.8 Tuberculosis incidence rate for the calibrated *Strengthened Current Interventions* no-new-vaccine baseline

The black trend line indicates the median modelled output with 95% uncertainty in shaded grey. The black dot and vertical lines are the targets as described below.

The targets indicated on the plot are (from left to right) the tuberculosis incidence rate per 100,000 population per year in the year:

- 2015 (not calibrated, but used to calculate the 2035 target)
- 2020 (the *Status Quo* baseline calibration target)
- 2035 (the *Strengthened Current Interventions* baseline calibration target—a 50% reduction compared to 2015 target)

8. Health impact results

8.1 M72/AS01$_E$ scenarios

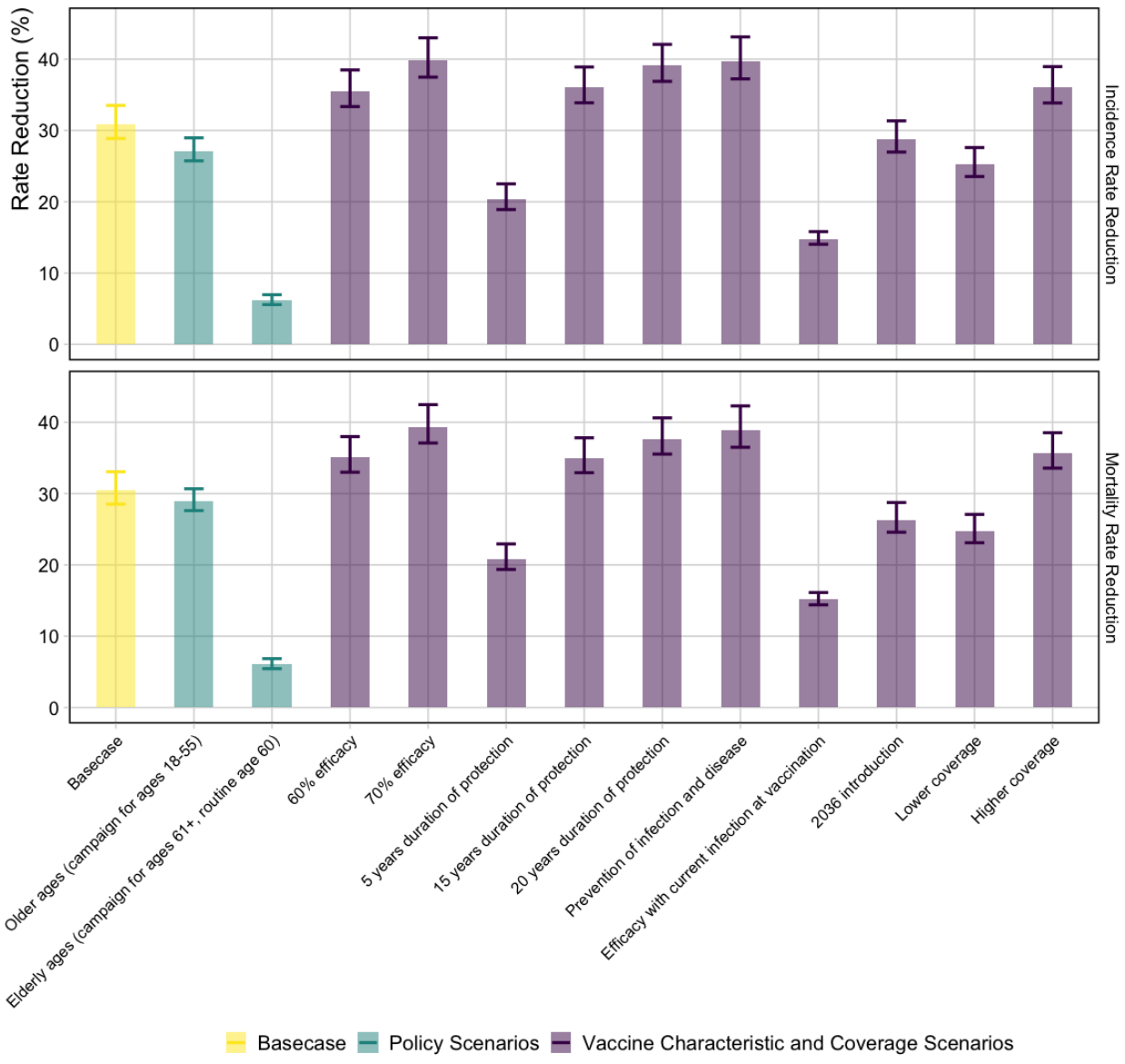


Figure S8.1 **Incidence and mortality rate reductions in 2050 for the M72/AS01$_E$ scenarios (*Status Quo* baseline)**

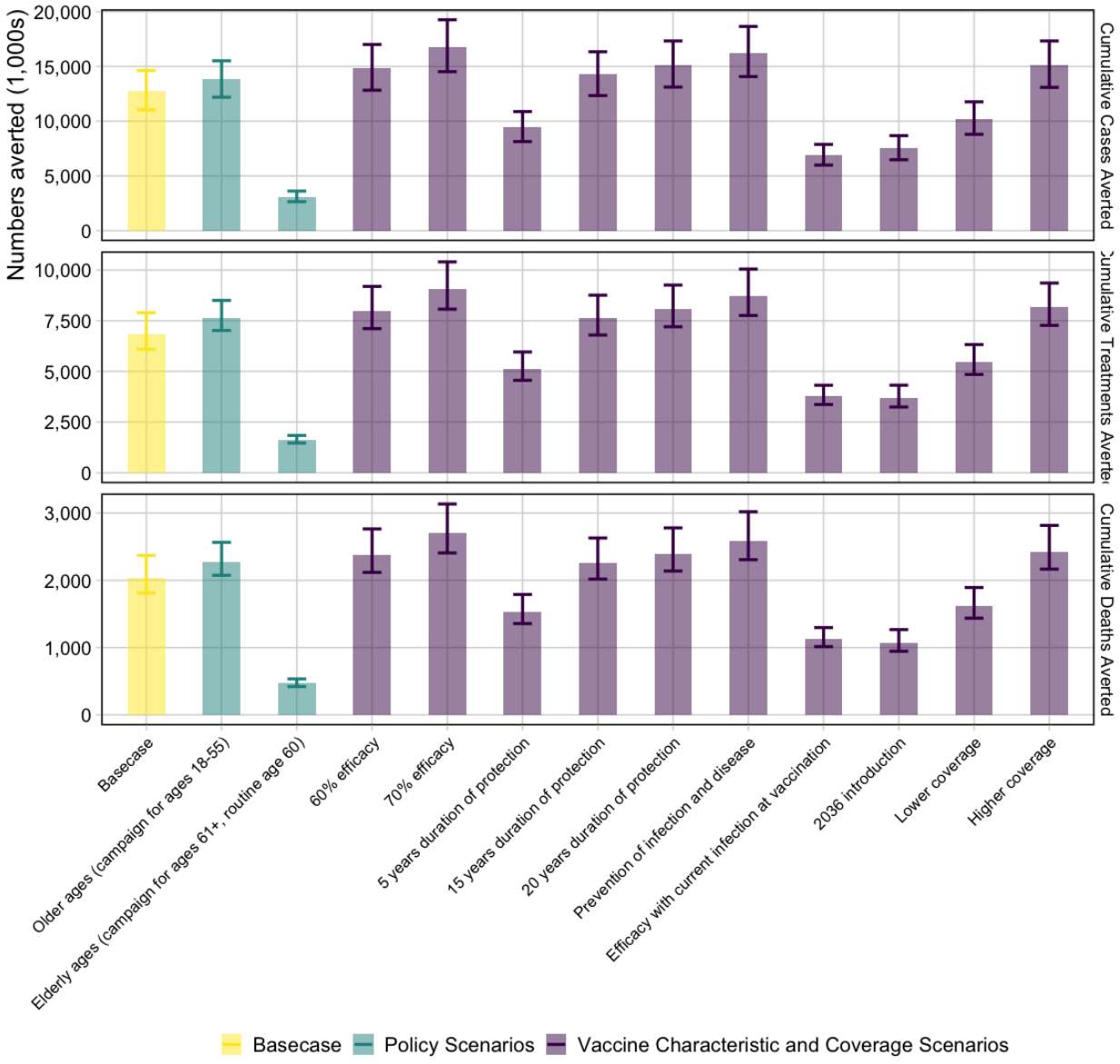


Figure S8.2 Cumulative tuberculosis cases, treatments, and deaths averted between 2030 and 2050 for the M72/AS01$_E$ scenarios (*Status Quo* baseline)

The horizontal line is the median value of the Basecase for each vaccine, and the vertical line separates vaccine profile and delivery scenarios.

Table S8.1 Health impact results for the M72/AS01$_E$ scenarios

Scenario	IRR in 2050 (%)	MRR in 2050 (%)	Cumulative cases averted 2030–2050	Cumulative treatments averted 2030–2050	Cumulative deaths averted 2030–2050
Basecase (*Status Quo* baseline)	30.9% (28.9–33.5)	30.4% (28.5–33.1)	12.7m (11.0–14.6)	6.9m (6.1–7.9)	2.0m (1.8–2.4)
Policy Scenarios (*Status Quo* baseline)					
Older ages (campaign for ages 18-55)	27.1% (25.7–29.0)	28.9% (27.6–30.7)	13.8m (12.2–15.5)	7.6m (7.0–8.5)	2.3m (2.1–2.6)
Elderly ages (campaign for ages 61+, routine age 60)	6.2% (5.6–7.0)	6.1% (5.4–6.9)	3.1m (2.6–3.6)	1.6m (1.5–1.8)	0.5m (0.4–0.5)
Vaccine Characteristic and Coverage Scenarios (*Status Quo* baseline)					
60% efficacy	35.6% (33.3–38.5)	35.1% (33.0–38.0)	14.8m (12.8–17.0)	8.0m (7.1–9.2)	2.4m (2.1–2.8)
70% efficacy	39.8% (37.5–43.0)	39.3% (37.1–42.5)	16.8m (14.5–19.3)	9.1m (8.1–10.4)	2.7m (2.4–3.1)
5 years protection	20.4% (18.9–22.5)	20.9% (19.4–22.9)	9.4m (8.1–10.9)	5.1m (4.6–6.0)	1.5m (1.4–1.8)
15 years protection	36.0% (33.9–38.9)	35.0% (32.9–37.8)	14.3m (12.3–16.3)	7.6m (6.8–8.8)	2.3m (2.0–2.6)
20 years protection	39.1% (36.9–42.1)	37.7% (35.5–40.6)	15.2m (13.1–17.3)	8.1m (7.2–9.3)	2.4m (2.1–2.8)
Prevention of infection and disease	39.7% (37.2–43.1)	39.0% (36.5–42.3)	16.2m (14.1–18.7)	8.7m (7.8–10.0)	2.6m (2.3–3.0)
Efficacious with current infection at vaccination	14.8% (14.0–15.8)	15.2% (14.4–16.1)	6.9m (6.0–7.9)	3.8m (3.4–4.3)	1.1m (1.0–1.3)
2036 introduction	28.8% (27.0–31.3)	26.3% (24.6–28.7)	7.5m (6.5–8.7)	3.7m (3.2–4.3)	1.1m (0.9–1.3)
Lower coverage	25.3% (23.5–27.6)	24.8% (23.1–27.1)	10.2m (8.8–11.8)	5.5m (4.8–6.3)	1.6m (1.4–1.9)
Higher coverage	36.0% (33.9–39.0)	35.7% (33.6–38.5)	15.1m (13.1–17.3)	8.2m (7.3–9.4)	2.4m (2.2–2.8)
***Strengthened Current Interventions* no-new-vaccine baseline**					
Basecase	16.1% (4.8–30.5)	17.1% (5.7–30.1)	3.0m (1.1–11.3)	1.7m (0.68–6.2)	0.51 (0.19–1.9)

Abbreviations: IRR = incidence rate reduction, MRR = mortality rate reduction.

8.2 BCG-revaccination scenarios

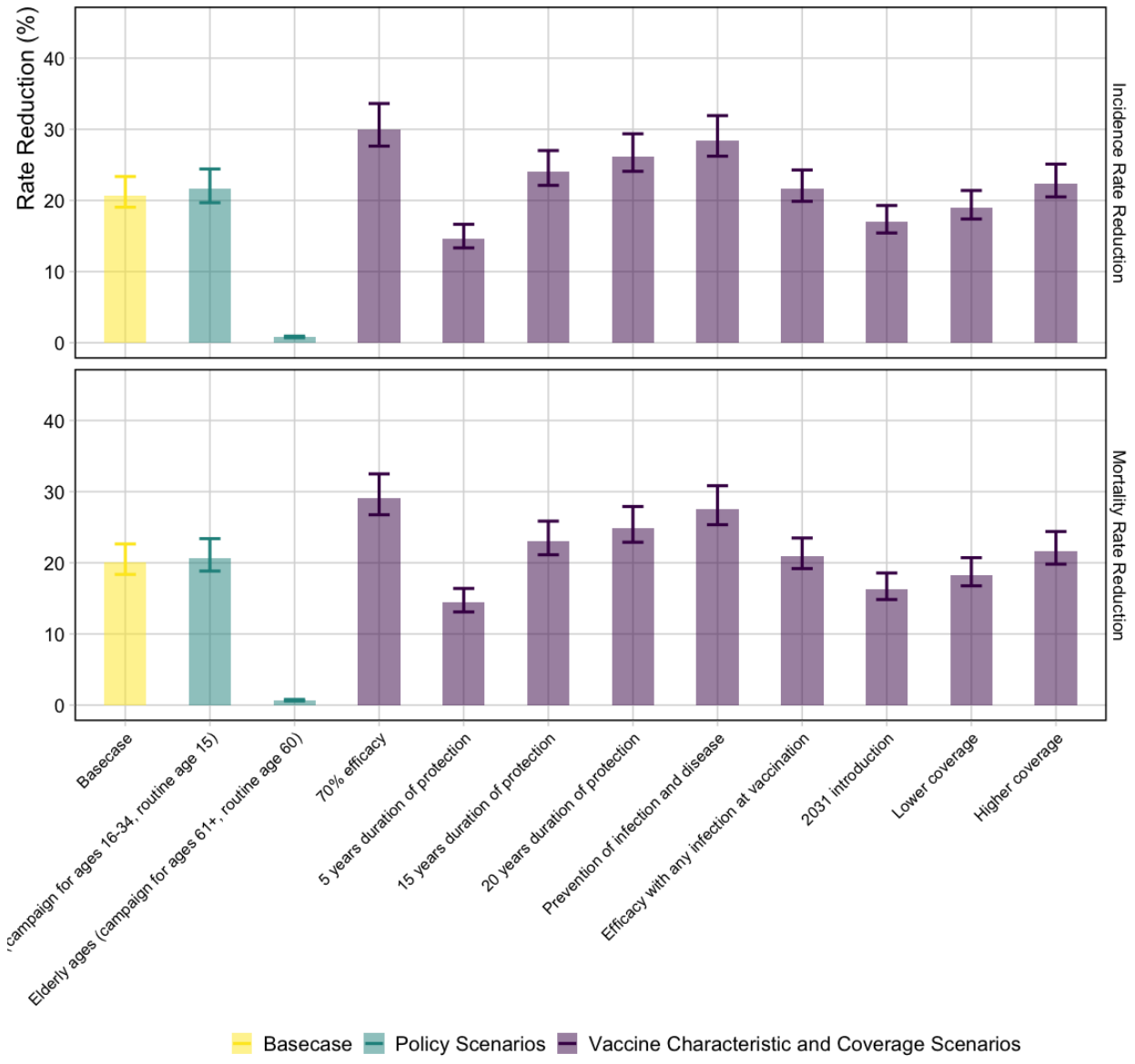


Figure S8.3 **Incidence and mortality rate reductions in 2050 for the BCG-revaccination scenarios (*Status Quo* baseline)**

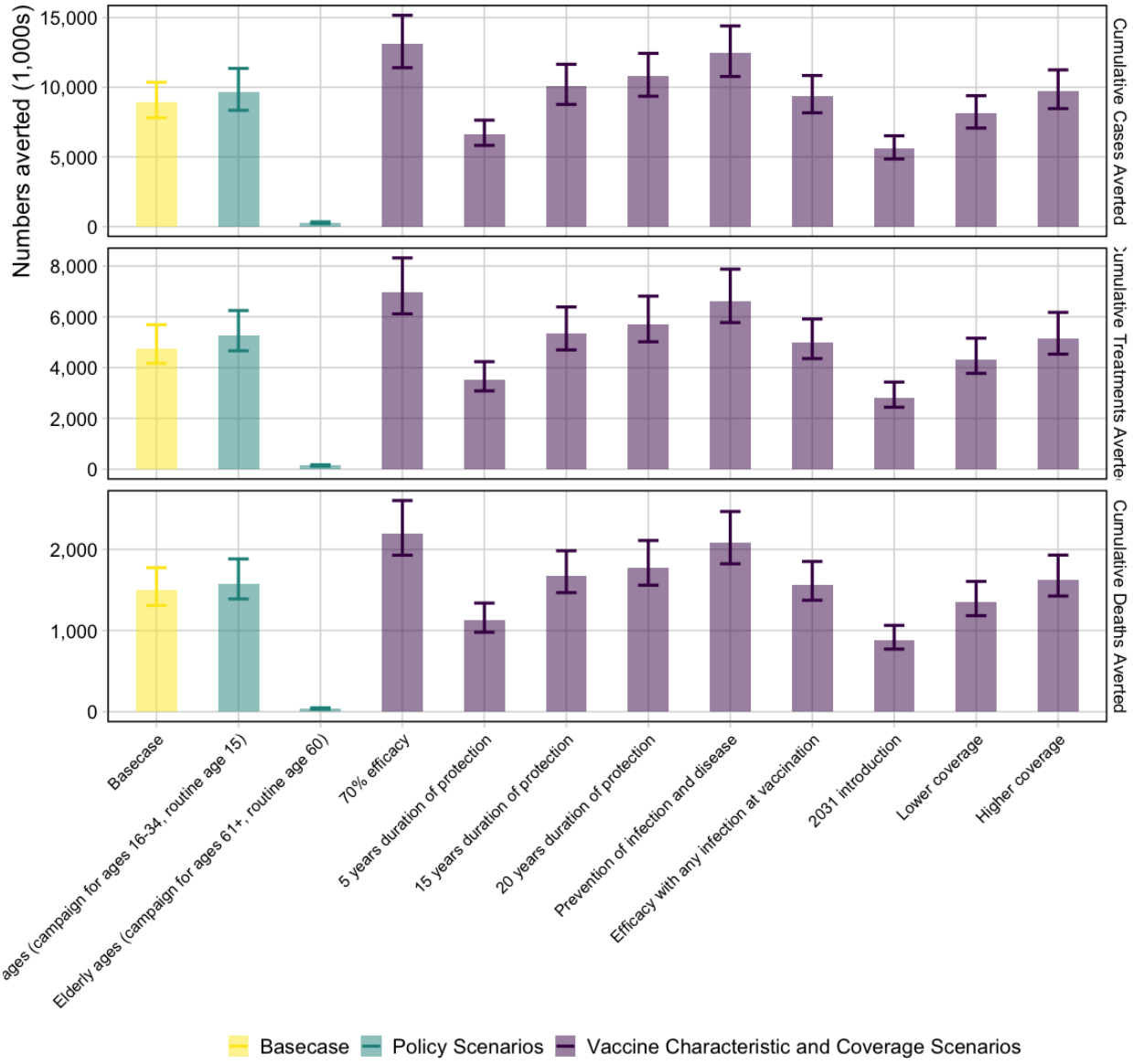


Figure S8.4 **Cumulative tuberculosis cases, treatments, and deaths averted between 2025 and 2050 for the BCG-revaccination scenarios (*Status Quo* baseline)**

The horizontal line is the median value of the Basecase for each vaccine, and the vertical line separates vaccine profile and delivery scenarios.

Table S8.2 Health impact results for the BCG-revaccination scenarios

Scenario	IRR in 2050 (%)	MRR in 2050 (%)	Cumulative cases averted 2025–2050	Cumulative treatments averted 2025–2050	Cumulative deaths averted 2025–2050
Basecase (*Status Quo* baseline)	20.7% (19.0–23.4)	20.0% (18.4–22.6)	9.0m (7.8–10.4)	4.8m (4.2–5.7)	1.5m (1.3–1.8)
Policy Scenarios (*Status Quo* baseline)					
Older ages (campaign for ages 16-34, routine age 15)	21.6% (19.7–24.4)	20.7% (18.8–23.4)	9.7m (8.3–11.4)	5.3m (4.7–6.2)	1.6m (1.4–1.9)
Elderly ages (campaign for ages 61+, routine age 60)	0.8% (0.7–0.9)	0.7% (0.6–0.8)	0.3m (0.2–0.3)	0.1m (0.1–0.2)	0.04m (0.03–0.05)
Vaccine Characteristic and Coverage Scenarios (*Status Quo* baseline)					
70% Efficacy	30.0% (27.6–33.6)	29.0% (26.7–32.5)	13.2m (11.4–15.2)	7.0m (6.1–8.3)	2.2m (1.9–2.6)
5 years protection	14.6% (13.3–16.6)	14.4% (13.1–16.4)	6.6m (5.8–7.6)	3.5m (3.1–4.2)	1.1m (1.0–1.3)
15 years protection	24.0% (22.1–27.0)	23.0% (21.1–25.9)	10.1m (8.8–11.6)	5.3m (4.7–6.4)	1.7m (1.5–2.0)
20 years protection	26.1% (24.1–29.4)	24.9% (22.9–27.9)	10.8m (9.4–12.4)	5.7m (5.0–6.8)	1.8m (1.6–2.1)
Prevention of infection and disease	28.4% (26.2–31.9)	27.5% (25.3–30.8)	12.4m (10.8–14.4)	6.6m (5.8–7.9)	2.1m (1.8–2.5)
Efficacious with any infection status at vaccination	21.6% (19.9–24.3)	20.9% (19.2–23.5)	9.4m (8.2–10.8)	5.0m (4.4–5.9)	1.6m (1.4–1.9)
2031 introduction	17.0% (15.4–19.3)	16.3% (14.8–18.6)	5.6m (4.9–6.5)	2.8m (2.4–3.4)	0.9m (0.8–1.1)
Lower coverage	19.0% (17.4–21.4)	18.3% (16.8–20.7)	8.1m (7.1–9.4)	4.3m (3.8–5.2)	1.4m (1.2–1.6)
Higher coverage	22.3% (20.5–25.1)	21.6% (19.8–24.4)	9.7m (8.5–11.2)	5.2m (4.5–6.2)	1.6m (1.4–1.9)
***Strengthened Current Interventions* no-new-vaccine baseline**					
Basecase	8.9% (1.0–20.8)	8.9% (1.0–20.1)	1.9m (0.42–8.0)	1.1m (0.25–4.4)	0.34m (0.08–1.4)

Abbreviations: IRR = incidence rate reduction, MRR = mortality rate reduction.

9. Economic results

9.1 M72/AS01$_E$ scenarios

Table S9.1 Cost-effectiveness analysis for M72/AS01$_E$ *Policy Scenarios*

Scenario	Total costs (USD, 1000s)	Total DALYs (1000s)	Total DALYs averted (1000s)	Incremental cost (USD, 1000s)	Incremental DALYs averted (1000s)	Cost (USD) per DALY averted
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Elderly ages (campaign for ages 61+, routine age 60)	17,523,764	3,986,463	5,256.71	–	–	*Weakly dominated*
Basecase (campaign for ages 16–34, routine age 15)	19,596,068	3,954,863	36,856.95	5,333,593	36,856.95	$144.71[+]
Older ages (campaign for ages 18–55)	21,456,380	3,953,202	38,517.91	1,860,312	1,660.96	$1,120.02[#]

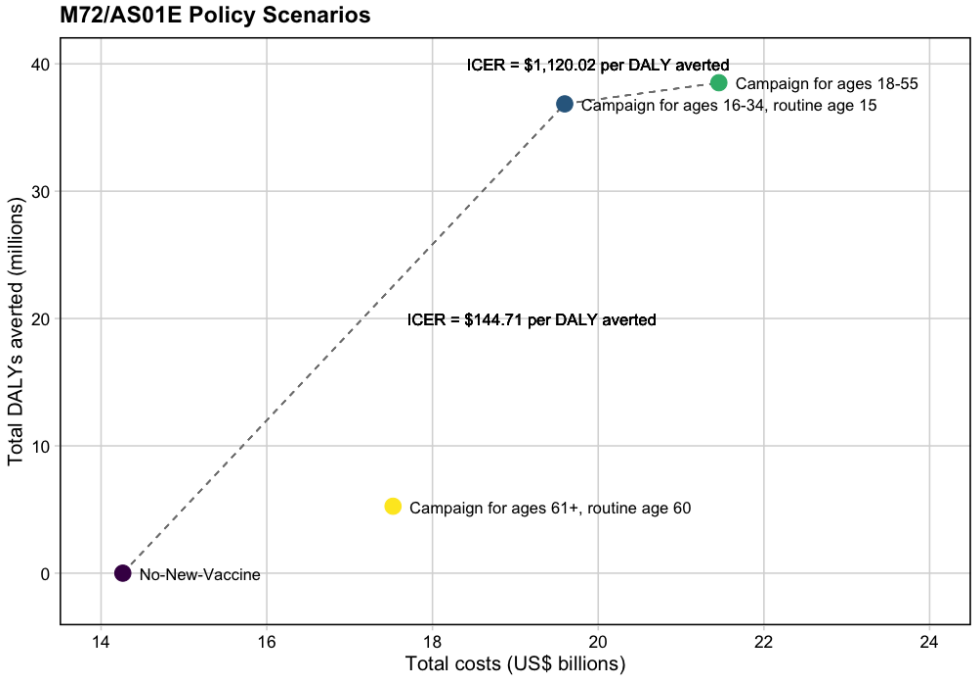


Figure S9.1 Efficiency frontiers for M72/AS01$_E$ *Policy Scenarios*

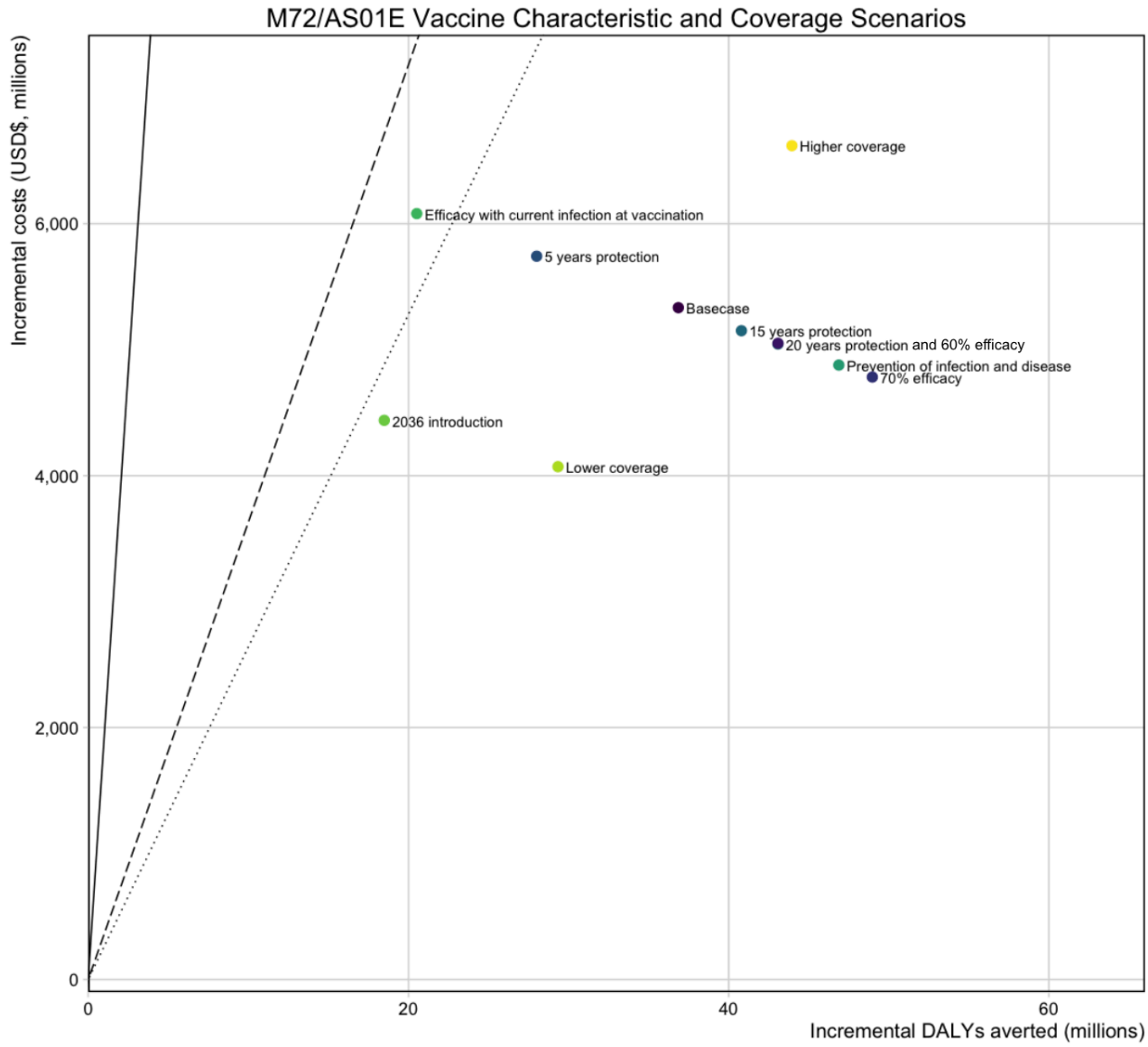


Figure S9.2 Comparison of ICERs for M72/AS01$_E$ *Vaccine Characteristic and Coverage* Scenarios

Abbreviations: DALYs = disability-adjusted life years, USD$ = United States Dollars.

Points are the mean incremental costs and mean incremental DALYs averted for each scenario compared to the costs and DALYs from the no-new-vaccine baseline. The solid line represents 1x GDP, the dashed line represents the country-level upper bound, and the dotted line represents the country-level lower bound. The 20 years protection and 60% efficacy scenarios for the M72/AS01$_E$ vaccine overlap and appear as one single point on the figure.

The Basecase M72/AS01$_E$ scenario assumes a 50% efficacy POD vaccine efficacious with any infection status at the time of vaccination, with 10 years duration of protection reaching 80% coverage for 15-year-olds and 70% coverage for those aged 16–34. Each M72/AS01$_E$ scenario is delivered routinely to those aged 15 and as a campaign for those aged 16–34. The scenarios on the figure are labelled with the difference in product characteristics for that scenario compared to the Basecase.

Table S9.2 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for the M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	36.9 (32.5, 42.9)	5 334 (3 036, 8 573)	145 (82, 236)	5 948 (3 242, 9 272)	161 (84, 259)
Vaccine Characteristic and Coverage Scenarios					
60% efficacy	43.1 (38.0, 50.1)	5 050 (2 752, 8 311)	117 (63, 196)	5 552 (2 807, 8 976)	129 (64, 213)
70% efficacy	49.0 (43.2, 56.9)	4 783 (2 483, 8 036)	98 (50, 167)	5 177 (2 336, 8 617)	106 (47, 180)
5 years protection	28.0 (24.6, 32.7)	5 742 (3 445, 9 046)	205 (122, 326)	6 519 (3 874, 9 853)	233 (132, 361)
15 years protection	40.8 (36.0, 47.4)	5 151 (2 852, 8 391)	126 (69, 209)	5 692 (2 993, 9 077)	140 (71, 228)
20 years protection	43.1 (38.0, 50.0)	5 045 (2 745, 8 305)	117 (63, 196)	5 544 (2 798, 8 970)	129 (64, 212)
Prevention of infection and disease	46.9 (41.3, 54.5)	4 878 (2 595, 8 119)	104 (54, 176)	5 310 (2 506, 8 744)	113 (52, 191)
Efficacy with current infection at vaccination	20.5 (18.2, 23.5)	6 080 (3 794, 9 429)	296 (184, 457)	6 992 (4 402, 10 256)	341 (211, 515)
2036 introduction	18.5 (16.2, 21.6)	4 439 (2 710, 6 930)	240 (145, 378)	5 070 (3 102, 7 553)	274 (162, 419)
Lower coverage	29.3 (25.8, 34.2)	4 071 (2 302, 6 555)	139 (77, 228)	4 525 (2 442, 7 087)	154 (79, 248)
Higher coverage	43.9 (38.8, 51.0)	6 620 (3 790, 10 626)	151 (85, 245)	7 403 (4 145, 11 508)	168 (88, 268)

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

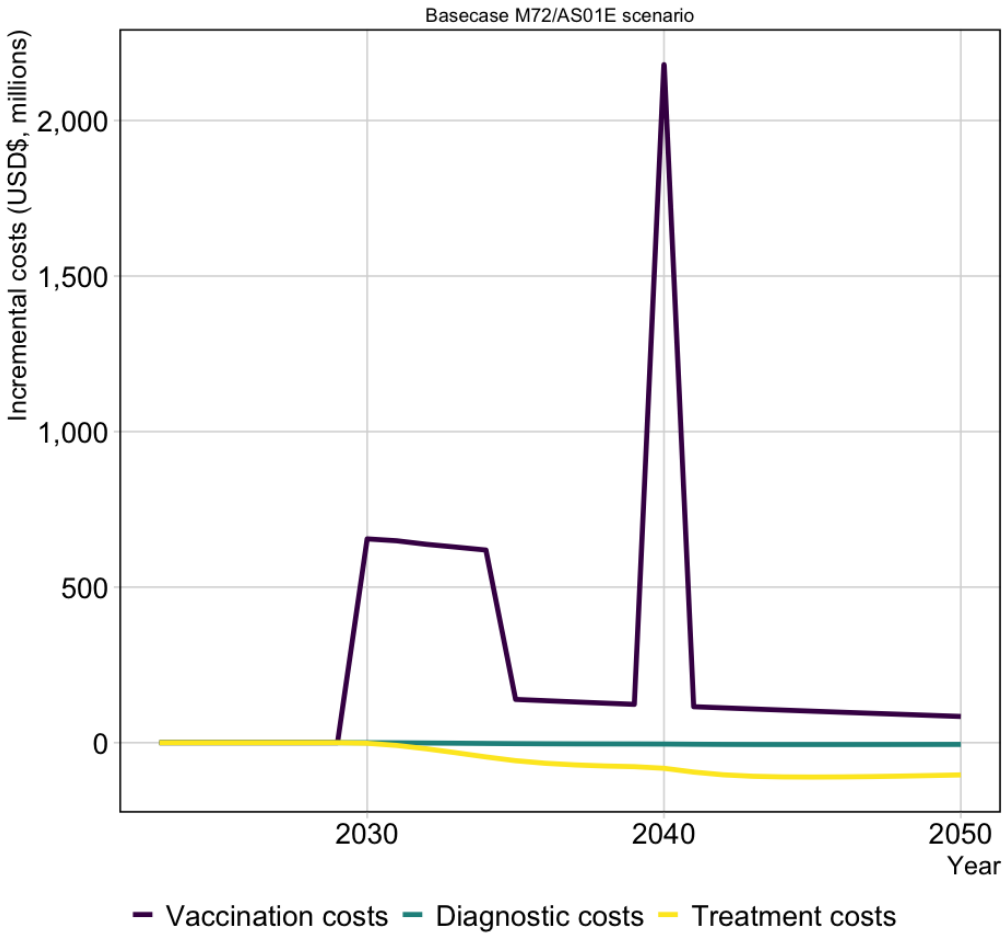


Figure S9.3 Basecase M72/AS01$_E$ scenario incremental discounted costs (USD$, millions) by year

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin-resistant tuberculosis, USD$ = United States dollars.

Table S9.3 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the health-system perspective

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	7 021 (4 758, 10 301)	-84 (-103, -67)	-3 (-10, -0.01)	-1 183 (-1 467, -941)	-418 (-500, -352)	5 334 (3 036, 8 573)
Policy Scenarios						
Older ages (campaign for ages 18–55)	9 097 (6 158, 13 365)	-94 (-114, -77)	-2.8 (-12, -0.01)	-1 334 (-1 610, -1 072)	-471 (-551, -402)	7 194 (4 220, 11 502)
Elderly ages (campaign for ages 61+, routine age 60)	3 663 (2 482, 5 362)	-20 (-24, -16)	-0.6 (-3, -0.003)	-282 (-348, -227)	-99 (-119, -84)	3 261 (2 068, 4 962)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	7 022 (4 758, 10 303)	-98 (-121, -78)	-3 (-12, -0.02)	-1 382 (-1 715, -1 099)	-488 (-584, -411)	5 050 (2 752, 8 311)
70% efficacy	7 023 (4 759, 10 304)	-111 (-137, -89)	-3 (-14, -0.02)	-1 571 (-1 945, -1 249)	-555 (-664, -467)	4 783 (2 483, 8 036)
5 years protection	7 020 (4 757, 10 300)	-63 (-79, -51)	-2 (-8, -0.01)	-896 (-1 115, -712)	-316 (-379, -266)	5 742 (3 445, 9 046)
15 years protection	7 021 (4 758, 10 302)	-93 (-115, -74)	-3 (-12, -0.02)	-1 312 (-1 625, -1 043)	-463 (-554, -390)	5 151 (2 852, 8 391)
20 years protection	7 022 (4 758, 10 302)	-98 (-121, -79)	-3 (-12, -0.02)	-1 386 (-1 717, -1 102)	-489 (-585, -413)	5 045 (2 745, 8 305)
Prevention of infection and disease	7 022 (4 759, 10 303)	-107 (-131, -85)	-3 (-13, -0.02)	-1 504 (-1 867, -1 196)	-531 (-635, -448)	4 878 (2 595, 8 119)
Efficacy with current infection at vaccination	7 019 (4 756, 10 298)	-47 (-57, -38)	-1 (-6, -0.01)	-658 (-806, -528)	-233 (-276, -195)	6 080 (3 794, 9 429)
2036 introduction	5 284 (3 583, 7 749)	-42 (-52, -34)	-1 (-5, -0.01)	-593 (-739, -470)	-209 (-253, -174)	4 439 (2 710, 6 930)
Lower coverage	5 413 (3 670, 7 929)	-67 (-82, -53)	-2 (-8, -0.01)	-941 (-1 171, -748)	-332 (-399, -279)	4 071 (2 302, 6 555)
Higher coverage	8 633 (5 844, 12 679)	-100 (-123, -80)	-3 (-12, -0.02)	-1 412 (-1 747, -1 123)	-499 (-596, -420)	6 620 (3 790, 10 626)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S9.4 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the societal perspective

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	8307 (5720, 11621)	-86 (-107, -69)	-1601 (-1957, -1303)	-209 (-349, -112)	-463 (-1559, -22)	5 948 (3 242, 9 272)
Policy Scenarios						
Older ages (campaign for ages 18–55)	10767 (7414, 15070)	-97 (-119, -79)	-1805 (-2151, -1493)	-236 (-388, -125)	-521 (-1715, -24)	8 108 (4 663, 12 431)
Elderly ages (campaign for ages 61+, routine age 60)	4327 (2969, 6025)	-21 (-25, -17)	-381 (-462, -314)	-50 (-82, -26)	-110 (-359, -5)	3 766 (2 403, 5 492)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	8308 (5721, 11623)	-101 (-125, -81)	-1871 (-2285, -1521)	-244 (-408, -130)	-541 (-1820, -25)	5 552 (2 807, 8 976)
70% efficacy	8309 (5721, 11624)	-115 (-142, -92)	-2125 (-2594, -1728)	-278 (-462, -148)	-614 (-2066, -29)	5 177 (2 336, 8 617)
5 years protection	8306 (5719, 11619)	-65 (-81, -52)	-1213 (-1486, -986)	-158 (-265, -85)	-351 (-1185, -16)	6 519 (3 874, 9 853)
15 years protection	8308 (5720, 11622)	-96 (-119, -77)	-1775 (-2169, -1444)	-232 (-387, -124)	-513 (-1726, -24)	5 692 (2 993, 9 077)
20 years protection	8308 (5721, 11622)	-101 (-125, -81)	-1876 (-2292, -1526)	-245 (-408, -131)	-542 (-1822, -25)	5 544 (2 798, 8 970)
Prevention of infection and disease	8309 (5721, 11624)	-110 (-136, -88)	-2035 (-2480, -1657)	-266 (-445, -142)	-588 (-1984, -28)	5 310 (2 506, 8 744)
Efficacy with current infection at vaccination	8305 (5718, 11617)	-48 (-60, -39)	-891 (-1078, -728)	-116 (-194, -62)	-257 (-855, -12)	6 992 (4 402, 10 256)
2036 introduction	6252 (4304, 8743)	-43 (-54, -34)	-802 (-990, -646)	-105 (-175, -56)	-232 (-783, -11)	5 070 (3 102, 7 553)
Lower coverage	6401 (4406, 8946)	-69 (-85, -55)	-1273 (-1561, -1034)	-166 (-278, -89)	-368 (-1243, -17)	4 525 (2 442, 7 087)
Higher coverage	10218 (7037, 14300)	-103 (-128, -83)	-1910 (-2330, -1554)	-250 (-416, -133)	-552 (-1857, -26)	7 403 (4 145, 11 508)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

9.2 BCG-revaccination scenarios

Table S9.5 Cost-effectiveness analysis for BCG-revaccination *Policy Scenarios*

Scenario	Total costs (USD, 1000s)	Total DALYs (1000s)	Total DALYs averted (1000s)	Incremental cost (USD, 1000s)	Incremental DALYs averted (1000s)	Cost (USD) per DALY averted
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Basecase (campaign for ages 11–18, routine age 10)	14,918,037	3,962,629	29,091.22	655,526	29,091.22	$22.53[+]
Older ages (campaign for ages 16–34, routine age 15)	15,819,567	3,961,671	30,049.06	901,530	957.84	$941.21[#]
Elderly ages (campaign for ages 61+, routine age 60)	15,922,705	3,991,270	449.83	–	–	*Strongly dominated*

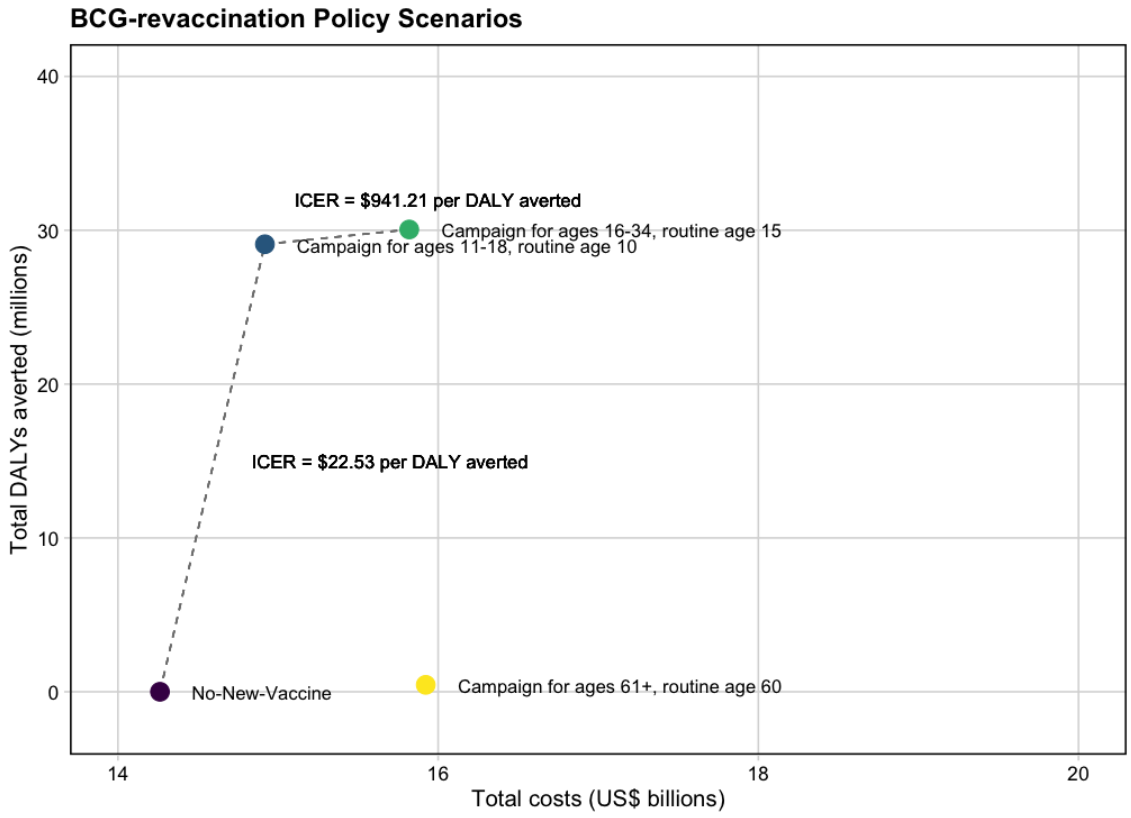


Figure S9.4 Efficiency frontiers for BCG-revaccination *Policy Scenarios*

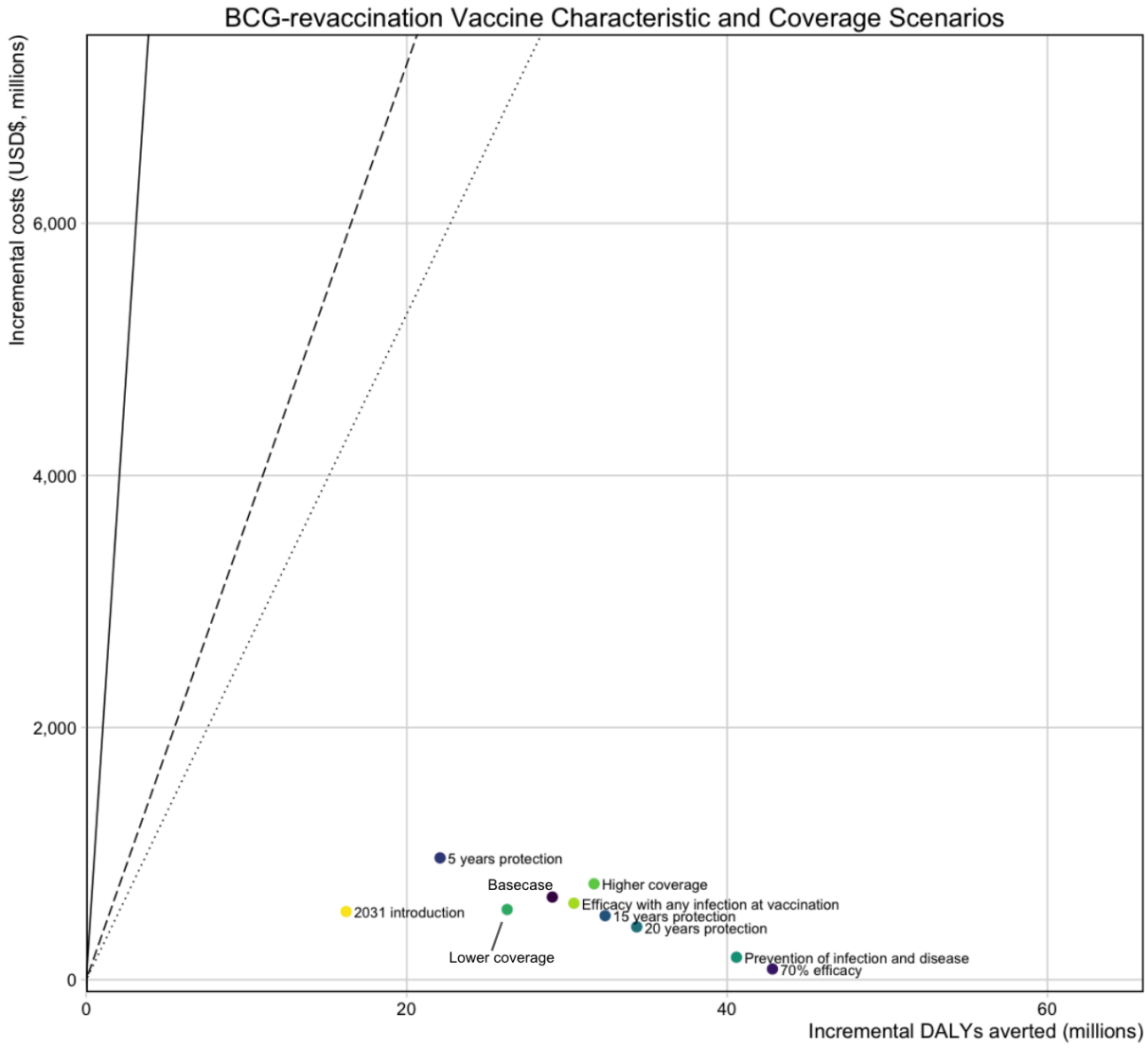


Figure S9.5 Comparison of ICERs for BCG-revaccination *Vaccine Characteristic and Coverage* Scenarios

Abbreviations: DALYs = disability-adjusted life years, USD$ = United States Dollars.

Points are the mean incremental costs and mean incremental DALYs averted for each scenario compared to the costs and DALYs from the no-new-vaccine baseline. The solid line represents 1x GDP, the dashed line represents the country-level upper bound, and the dotted line represents the country-level lower bound.

The Basecase BCG-revaccination scenario assumes a 45% efficacy POI vaccine efficacious with no current infection at the time of vaccination, with 10 years duration of protection and reaching 80% coverage. Each BCG-revaccination scenario is delivered routinely to those aged 10 and as a campaign for those aged 11–18. The scenarios on the figure are labelled with the difference in product characteristics for that scenario compared to the Basecase.

Table S9.6 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for BCG-revaccination *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	29.1 (25.1, 34.6)	656 (-442, 2 170)	23 (cost-saving, 78)	765 (-658, 2 405)	26 (-22, 86)
Vaccine Characteristic and Coverage Scenarios					
70% Efficacy	42.8 (37, 51)	85 (-1 058, 1 642)	2 (cost-saving, 39)	-33 (-1 759, 1 735)	cost-saving (cost-saving, 42)
5 years protection	22.1 (19, 26.3)	966 (-108, 2 465)	44 (cost-saving, 117)	1 199 (-116, 2 778)	54 (cost-saving, 131)
15 years protection	32.4 (27.9, 38.6)	508 (-605, 2 031)	16 (cost-saving, 65)	559 (-954, 2 232)	17 (cost-saving, 71)
20 years protection	34.4 (29.7, 40.9)	419 (-704, 1 947)	12 (cost-saving, 59)	435 (-1113, 2 135)	13 (cost-saving, 64)
Prevention of infection and disease	40.6 (35, 48.4)	178 (-958, 1 727)	4 (cost-saving, 44)	97 (-1556, 1 852)	2 (cost-saving, 47)
Efficacy with any infection status at vaccination	30.4 (26.4, 36.1)	607 (-494, 2 143)	20 (cost-saving, 73)	696 (-756, 2 360)	23 (cost-saving, 81)
2031 introduction	16.2 (13.9, 19.3)	541 (-162, 1 509)	33 (cost-saving, 98)	658 (-231, 1 700)	41 (cost-saving, 110)
Lower coverage	26.3 (22.6, 31.3)	557 (-414, 1 889)	21 (cost-saving, 75)	640 (-618, 2 085)	24 (cost-saving, 83)
Higher coverage	31.7 (27.3, 37.7)	761 (-461, 2 457)	24 (cost-saving, 82)	899 (-668, 2 736)	28 (cost-saving, 89)

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

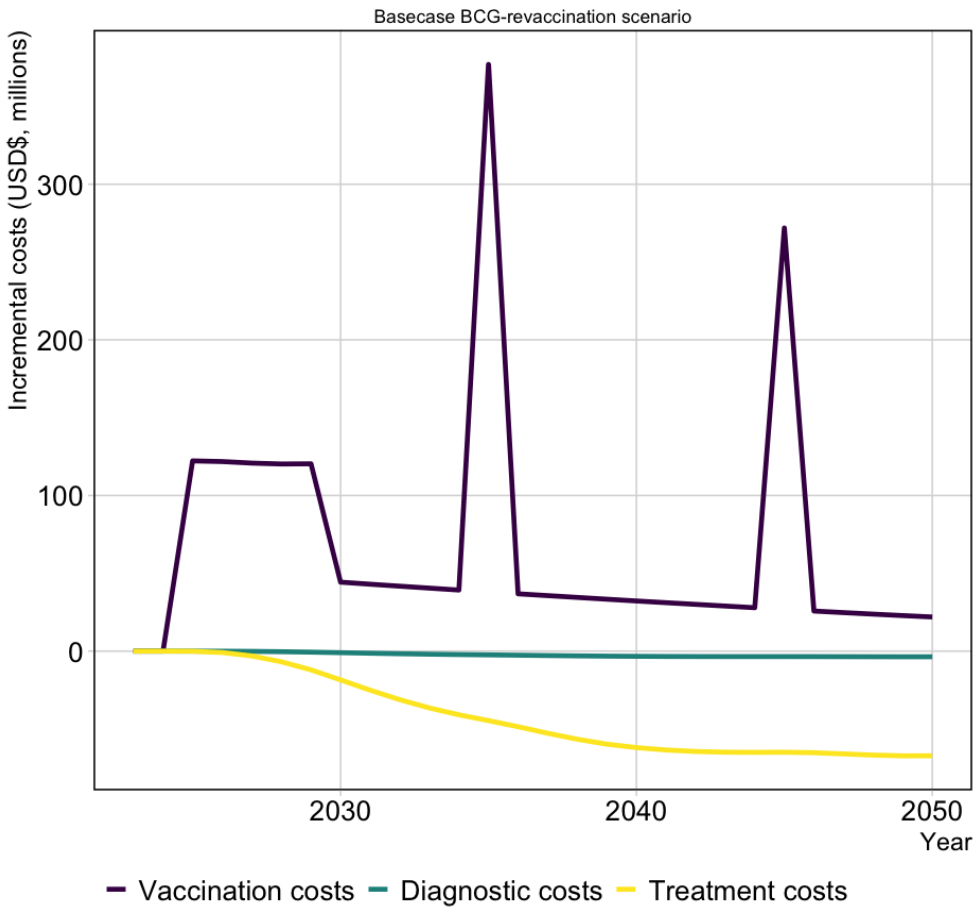


Figure S9.6 Basecase BCG-revaccination scenario incremental discounted costs (US$, millions) by year

Abbreviations: USD$ = United States dollars.

Table S9.7 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the health-system perspective

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	1 873 (804, 3 416)	-60 (-77, -48)	-2 (-8, -0.01)	-854 (-1 088, -674)	-301 (-368, -251)	656 (-442, 2 170)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	2 930 (1 234, 5 368)	-68 (-86, -54)	-2 (-8, -0.01)	-962 (-1 219, -755)	-340 (-414, -282)	1 557 (-142, 3 944)
Elderly ages (campaign for ages 61+, routine age 60)	1 695 (730, 3 080)	-2 (-2, -1)	-0.1 (-0.2, 0)	-24 (-31, -19)	-9 (-11, -7)	1 660 (695, 3 042)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	1 877 (805, 3 423)	-89 (-113, -71)	-3 (-11, -0.02)	-1 257 (-1 600, -994)	-444 (-540, -367)	85 (-1 058, 1 642)
5 years protection	1 876 (805, 3 420)	-45 (-57, -36)	-1 (-6, -0.01)	-638 (-811, -505)	-225 (-276, -187)	966 (-108, 2 465)
15 years protection	1 872 (803, 3 413)	-68 (-86, -54)	-2 (-8, -0.01)	-956 (-1 219, -754)	-338 (-411, -280)	508 (-605, 2 031)
20 years protection	1 871 (803, 3 412)	-72 (-91, -57)	-2 (-9, -0.01)	-1 018 (-1 296, -802)	-359 (-438, -298)	419 (-704, 1 947)
Prevention of infection and disease	1 874 (804, 3 417)	-84 (-107, -67)	-3 (-10, -0.01)	-1 189 (-1 517, -938)	-420 (-512, -348)	178 (-958, 1 727)
Efficacy with any infection at vaccination	1 881 (807, 3 428)	-63 (-80, -50)	-2 (-8, -0.01)	-893 (-1 141, -705)	-315 (-384, -262)	607 (-494, 2 143)
2031 introduction	1 213 (520, 2 212)	-33 (-43, -26)	-1 (-4, -0.01)	-471 (-605, -368)	-166 (-205, -137)	541 (-162, 1 509)
Lower coverage	1 657 (714, 3 010)	-55 (-69, -43)	-2 (-7, -0.01)	-772 (-983, -609)	-272 (-333, -226)	557 (-414, 1 889)
Higher coverage	2 086 (892, 3 810)	-66 (-83, -52)	-2.0 (-8, -0.01)	-929 (-1 184, -735)	-328 (-400, -273)	761 (-461, 2 457)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S9.8 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the societal perspective

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	2467 (1238, 4002)	-62 (-78, -49)	-1155 (-1451, -929)	-151 (-251, -80)	-334 (-1134, -16)	765 (-658, 2 405)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	3881 (1933, 6307)	-70 (-88, -55)	-1302 (-1624, -1049)	-170 (-286, -90)	-377 (-1282, -17)	1 962 (-61, 4 453)
Elderly ages (campaign for ages 61+, routine age 60)	2229 (1121, 3610)	-2 (-2, -1)	-33 (-42, -26)	-4 (-7, -2)	-10 (-31, 0)	2 181 (1 074, 3 563)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	2473 (1240, 4013)	-92 (-115, -72)	-1701 (-2137, -1374)	-222 (-368, -117)	-492 (-1672, -23)	-33 (-1 759, 1 735)
5 years protection	2471 (1239, 4009)	-47 (-59, -36)	-863 (-1080, -692)	-113 (-188, -60)	-250 (-846, -12)	1 199 (-116, 2 778)
15 years protection	2466 (1237, 3999)	-70 (-88, -55)	-1294 (-1629, -1039)	-169 (-281, -89)	-374 (-1270, -18)	559 (-954, 2 232)
20 years protection	2464 (1237, 3998)	-74 (-93, -58)	-1377 (-1730, -1106)	-180 (-299, -95)	-398 (-1353, -19)	435 (-1113, 2 135)
Prevention of infection and disease	2468 (1238, 4004)	-87 (-109, -68)	-1609 (-2022, -1296)	-210 (-348, -111)	-465 (-1582, -22)	97 (-1556, 1 852)
Efficacy with any infection at vaccination	2478 (1243, 4020)	-65 (-82, -51)	-1209 (-1513, -974)	-158 (-264, -83)	-350 (-1191, -16)	696 (-756, 2 360)
2031 introduction	1598 (801, 2593)	-34 (-44, -27)	-638 (-802, -509)	-83 (-140, -44)	-185 (-627, -9)	658 (-231, 1 700)
Lower coverage	2179 (1096, 3526)	-56 (-71, -44)	-1044 (-1311, -839)	-136 (-227, -72)	-302 (-1024, -14)	640 (-618, 2 085)
Higher coverage	2753 (1377, 4467)	-68 (-85, -53)	-1257 (-1580, -1013)	-164 (-273, -87)	-364 (-1234, -17)	899 (-668, 2 736)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

9.3 Economic results with the *Strengthened Current interventions* no-new-vaccine baseline

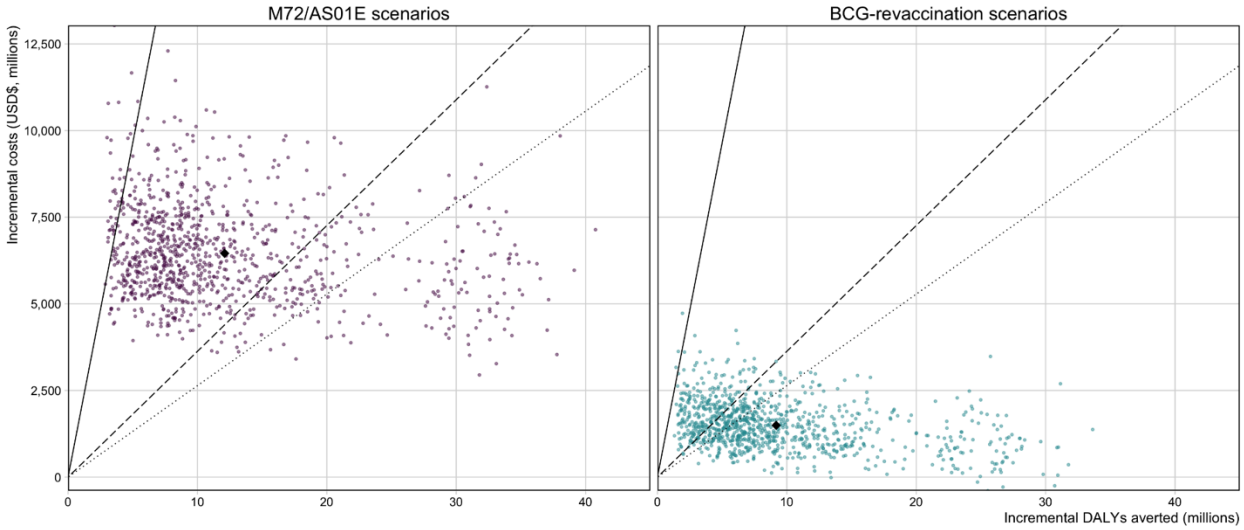


Figure S9.7 Cost-effectiveness planes for the M72/AS01$_E$ and BCG-revaccination Basecase scenarios with the Strengthened Current interventions no-new-vaccine baseline

Abbreviations: USD$ = United States dollars The Black triangle is the mean estimate for the scenario, and each individual parameter set is represented as a single dot.

The solid line represents 1x GDP, the dashed line represents the country-level upper bound, and the dotted line represents the country-level lower bound.

4.4 Comparison with Arinaminpathy et al., 2023

Shortly after Research Paper 2 was submitted, Arinaminpathy et al. published *The potential impact of vaccination on tuberculosis burden in India: A modelling analysis*.[8] As both studies are investigating a similar question, I summarise the results below, discuss the similarities and differences between the modelling and vaccination approaches, and describe the implications of the results for decision makers.

Comparison of key results

Arinaminpathy et al. estimated that 12% (4–28) of the cumulative tuberculosis incidence between 2023–2030 could be averted by delivering a vaccine preventing infection, compared to 29% (24–34) from delivering a vaccine preventing disease to 50% of the general population age 16+ each year.[8] The study also identified the importance of targeting vaccination to a vulnerable group with an increased risk of tuberculosis. Although only 16% of the population was included within a vulnerable group representing those with undernutrition, 40% of the cumulative burden averted by targeting the entire population age 16+ could be averted with only vaccinating the vulnerable group.[8]

Clark et al. also found that a vaccine preventing disease (M72/AS01$_E$) would avert more cases in India than a vaccine preventing infection (BCG-revaccination) over 2025–2050.[9] If introduced routinely to those aged 15 from 2030 and as a campaign for ages 16–34 in 2030 and 2040, the M72/AS01$_E$ vaccine could avert 17.6% of cases, and if introduced routinely to those aged 10 from 2025 and as a campaign for ages 11–18 in 2025, 2035, and 2045, BCG-revaccination could avert 12.5% of cases predicted between 2025 and 2050. Clark et al. calculated the economic impacts of the modelled scenarios and observed higher costs and cost-effectiveness ratios from M72/AS01$_E$ scenarios compared to BCG-revaccination, but all scenarios were cost-effective when compared to the US$363 per DALY averted opportunity cost-threshold.

Comparison of model and vaccine characteristics

The model and vaccine characteristics for each study are compared in Table 8 and described briefly below:

Table 8 Model and vaccine characteristics in Arinaminpathy et al. and Clark et al.

	Arinaminpathy et al., 2023[8]	Clark et al., 2023[9]
Model Characteristics		
Natural history model structure	Seven compartments: Uninfected, Latent-Fast, Latent-Slow, Active TB, Sought care & awaiting diagnosis, On TB treatment, Sought care & undiagnosed	Eight compartments: Uninfected-Naive, Latent-Fast, Latent-Slow, Latent-Zero, Subclinical disease, Clinical disease, On-treatment, Recovered
Age structure	Two categories: age ≤15 and age >15	Single ages from 0–79, one age group from 80–89, and one age group from 90–99
Calibration method	MCMC	History matching with emulation followed by ABC-MCMC
Calibration targets	Nine calibration targets: • Notification rate in 2020 • Mortality rate in 2019 • Disease prevalence in 2020 • TB infection prevalence (%) • % of prevalent TB on treatment • % of prevalent TB not seeking care • Relative risk of TB with undernutrition • Percent of population undernourished • Percent of population age ≤15	Nineteen calibration targets: • TB incidence rate (all ages/children/ adults in 2000, 2021, and 2025) • TB notification rate (all ages/children/ adults in 2000 and 2021) • TB mortality rate (all ages in 2000, 2021, and 2025) • TB disease prevalence (all ages in 2015 and 2021, adults in 2021) • TB infection prevalence (adults in 2021)
Risk groups	Risk strata for a vulnerable group	Access-to-care (low and high)
Vaccine Characteristics		
Vaccine product	Hypothetical vaccines	Vaccines with characteristics aligned with M72/AS01$_E$ and BCG-revaccination
Vaccine efficacy	50% efficacy (additional sensitivity analyses)	M72/AS01$_E$: 50%, 60%, 70% BCG-revaccination: 45%, 70%
Mechanism of effect	Separate POI and POD scenarios	M72/AS01$_E$: POD, POID BCG-revaccination: POI, POID
Host infection status required for efficacy	The vaccine was efficacious if administered to Uninfected, Latent-Fast, and Latent-Slow	M72/AS01$_E$: Any-infection, Current-infection BCG-revaccination: No-current-infection, Any-infection
Duration of protection	10 years (additional sensitivity analyses)	10 years, 5 years, 15 years, 20 years
Time horizon	2023–2030	2025–2050

Abbreviations: ABC = approximate bayesian computation, MCMC = markov chain monte carlo, POD = prevention of disease, POI = prevention of infection, POID = prevention of infection and disease, TB = tuberculosis.

Model Characteristics

Both studies used a compartmental model to represent tuberculosis natural history. Arinaminpathy et al. modelled a seven compartment structure, accounting for both fast and slow progression to tuberculosis disease from latency, and three compartments representing care seeking, but did not target or focus on this sophisticated care-seeking pathway in the results.[8] Similarly, Clark et al. accounted for both fast and slow progression from latency, but also disaggregated active tuberculosis into subclinical and clinical disease to align with prevalence survey data.[9] Anti-tuberculosis treatment was represented as one on-treatment compartment, with increased mortality informed by WHO estimates of treatment outcomes compared to the background mortality rate.

In Arinaminpathy et al., the model population was stratified into children (age ≤15) and adults (age > 15),[8] and fit to nine calibration targets, including point estimates of disease and infection prevalence from the recent national tuberculosis prevalence survey in India, but no time trends in calibration targets, or any age-specific calibration targets to represent differences in tuberculosis burden by age. Therefore, the study was limited with respect to the ages that could be targeted for vaccination. Clark et al. stratified the population into eighty-two age groups (single ages for 0–79, one group for 80–89 and one group for 90–99), and calibrated to nineteen targets, including age-specific estimates of tuberculosis incidence, notification and prevalence, which allowed for more specific age-targeting scenarios to be evaluated.[9]

A separate risk stratum was included in Arinaminpathy et al to represent a vulnerable population with a higher risk of tuberculosis, such as those with undernutrition. This group accounted for a fixed 16% of the population, and therefore may not represent any differences in the prevalence of undernutrition over time.[8] An additional structure was included in Clark et al. to represent the negative association between disease prevalence and access-to-care, but this was not used to evaluate vaccine targeting in this study.

Both studies calibrated to the disease prevalence estimate from the national tuberculosis prevalence survey in India and infection prevalence estimates. However, Clark et al. adjusted the bounds on the infection prevalence estimate to account for the possibility that oversampling from a lower disease prevalence area may have biassed the estimation. Therefore, Clark et al. simulated

a higher infection prevalence with a target of 31.4% (11.4–51.4) compared to 25% (20–30) in Arinaminpathy et al. The higher level of infection in the population could have resulted in differences in the dynamics of the epidemic between the studies, as well as the impact of vaccines which work for specific infection statuses.

Vaccine Characteristics

Arinaminpathy et al. modelled separate prevention of infection (POI) and prevention of disease (POD) vaccine scenarios.[8] Both vaccines primarily were assumed to have 50% efficacy with 10 years duration of protection and be efficacious with any infection status at the time of vaccination, but sensitivity analyses of higher and lower vaccine efficacies and durations of protection were performed.[8] Clark et al. modelled one vaccine which worked by preventing infection (BCG-revaccination, with a primary assumption of 45% efficacy which worked in those that were uninfected at the time of vaccination) and one which worked by preventing disease ($M72/AS01_E$, with a primary assumption of 50% efficacy which worked in any infection status) in the *Basecase* scenarios, and varied characteristics individually from the *Basecase* to assess the impact of uncertainty in vaccine profile.[9]

While the POD vaccine products were similar between both studies, differences in the POI vaccine scenarios would have resulted in an increased impact in Arinaminpathy et al. compared to Clark et al. Arinaminpathy et al. modelled a slightly higher efficacy of the POI vaccine and assumed efficacy with any infection status at the time of vaccination. In contrast, Clark et al. assumed the POI vaccine would only be efficacious in those that were uninfected at the time of vaccination, and as the model simulated a higher level of infection in the population, the vaccine would be effective in a lower proportion of the population eligible to receive it.

The vaccine introduction year for both the POI and POD vaccine modelled in Arinaminpathy et al. was 2023, with linear scale-up to target coverage by the end of 2025.[8] Both vaccines in Clark et al. were assumed to be introduced later, with the earliest introduction for $M72/AS01_E$ in 2030, and for BCG-revaccination in 2025, and linear scale-up to target coverage over 5 years.[9] The earlier and faster vaccine introduction in Arinaminpathy et al. is likely related to the increased vaccine impact.

The ages targeted did not vary between the POI and POD vaccine in Arinaminpathy et al. Delivery was either by vaccinating 50% of the general population aged 16+ per year who had not previously been vaccinated, or by vaccinating 50% of the vulnerable population per year who had not previously been vaccinated.[8] By 2029, one year before the impact measures were calculated, approximately 98% of the general population aged 16+ would have received a vaccine. The vaccines modelled in Clark et al. were based on characteristics from trials, and therefore different ages were targeted for the M72/AS01$_E$ and BCG-revaccination scenarios based on the trial eligible populations.[9–11] This resulted in the lower bound of the target population for M72/AS01$_E$ (age 15) being roughly aligned with Arinaminpathy et al. (age 16), while the BCG-revaccination scenario had a much younger target population (age 10–18).[9] The achieved coverage after five years for the *Basecase* M72/AS01$_E$ scenario was 80% for those aged 15 and 70% for ages 16–34, while the achieved coverage after five years for the Basecase BCG-revaccination scenario was 80%. The larger age group targeted in Arinaminpathy et al., combined with the higher achieved coverage, likely contributes to the larger health impact estimated compared to Clark et al.

Summary of comparison and implications for decision makers

Primarily, the differences in vaccine impact estimated by the studies were due to more optimistic assumptions surrounding vaccine delivery in Arinaminpathy et al., compared to the more conservative assumptions in Clark et al., including later introduction years aligning with anticipated vaccine licensure and delivery, longer scale-up pace and lower achieved coverage for a subset of the population. More novel natural history aspects were included in the model structure used in Clark et al., along with single age groups which allowed for more age-specific targeting of vaccines. Clark et al. calculated the economic impact of vaccines, which Arinaminpathy et al. did not, and therefore I was not able to compare the costs and cost-effectiveness of the scenarios between the studies. Arinaminpathy et al. evaluated the impact from targeting a specific population at a high risk of progression to disease for vaccination, and highlighted the benefits of vaccinating such a population at the beginning of the introduction period should a targeted approach be required. Both studies focussed on tuberculosis vaccination, but assumed no additional improvements in the health system that may have an impact on the tuberculosis burden, and therefore the impact of vaccines may have been overestimated. Overall, both studies estimated that introducing new tuberculosis vaccines in India could have a positive impact on the epidemic.

4.5 Scenario modelling for the National Tuberculosis Elimination Programme

During discussions with the Indian NTEP,[12] I was asked to generate additional health impact evidence considering their short-term decisions regarding the delivery of BCG as a booster. I used the calibrated country-level India model from Research Paper 2 to evaluate the health impact possible by 2030 of an additional scenario. This scenario assumed a prevention of infection vaccine with 40% efficacy and 10-years protection which would be efficacious with no current infection at vaccination. The vaccine was assumed to be introduced at the start of 2023 routinely to those aged 18 and as a campaign for ages 19 and above, with scale-up to 80% vaccine coverage over two years.

I found that introducing a vaccine to 80% of the population over 18 years of age (almost 800 million people over two years) could have a considerable impact averting cases and deaths before 2030. The NTEP scenario was estimated to avert approximately 1.4 (1.2–1.7) million cases and 160 (140–192) thousand deaths by 2030 (6.6% and 3.9% of the total cases and deaths estimated to occur between 2023 and 2030 respectively). The NTEP scenario could also reduce the tuberculosis incidence and mortality rates in 2030 by 8–10% compared to no-new-vaccine introduction. As the vaccine was assumed to be efficacious with no current infection at vaccination and would work by preventing infection, there was no impact on those who were already infected. Given that the time frame for analysis was only eight years (2023–2030), there was not enough time to observe the maximum impact of a POI vaccine as a significant proportion of the population already infected would continue to progress to disease during that time.

In Research Paper 2, I found that more cases and deaths could be averted with the assumed characteristics of M72/AS01$_E$ compared to BCG-revaccination in India.[9] However, M72/AS01$_E$ was not assumed to be available until at least 2030. While the overall impact was higher from M72/AS01$_E$ scenarios, given the anticipated year of introduction, there could be no impact on the 21.1 million cases and 4.1 million deaths that were estimated to occur in India between 2023 and 2030.[9] Therefore, in terms of measuring the potential impact of new vaccines by 2030, the BCG-revaccination scenarios in Research Paper 2 and the additional NTEP scenario demonstrate what could be possible with delivery of a vaccine that is already available, as opposed to waiting for a

new vaccine currently in trials. These results can contribute to the evidence used by decision makers regarding vaccine introduction in the near future.

4.6 Summary

In Chapter 4, I addressed thesis **Aim 2**, country-level modelling of M72/AS01$_E$ and BCG-revaccination in India to provide evidence for country-level decision makers, through **Objectives 1** and **3**. To address **Objective 3**, I adapted the multi-country tuberculosis model from **Objective 1a** to develop a sophisticated country-level model for India, incorporating differences in public and private sector treatment outcomes. I calibrated this model to nineteen country-specific calibration targets, and simulated the introduction of M72/AS01$_E$ and BCG-revaccination under varying delivery strategies. Finally, I estimated the health, costs, cost-effectiveness, and budget impacts of each vaccine scenario compared to no-new-vaccine introduction.

Both M72/AS01$_E$ and BCG-revaccination were estimated to have a positive health impact. More cases and deaths could be averted by 2050 with M72/AS01$_E$ (12.7 [11.0–14.6] million cases and 2.0 [1.8–2.4] million deaths) than with BCG-revaccination (9.0 [7.8–10.4] million cases and 1.5 [1.3–1.8] million deaths) due to assumed vaccine product characteristics. The annual average cost of vaccination in the *Basecase* M72/AS01$_E$ scenario was approximately US$251 million, compared to US$67 million in the *Basecase* BCG-revaccination scenario. Cost-effectiveness ratios for M72/AS01$_E$ scenarios were around four times larger than those for BCG-revaccination scenarios, due to the higher vaccine price for M72/AS1$_E$ (US$2.50 per dose vs. US$0.17) and requiring two doses per vaccine course.

Country-level modelling suggested that introducing M72/AS01$_E$ and BCG-revaccination could have a large health and economic impact by 2050 in India. Uncertainty remains surrounding what the realised vaccine characteristics will be, but within the range of product characteristics modelled, my results suggest that positive health and economic impacts are likely. Using the detailed country-level model, the evidence I have generated can directly support the Indian government with decisions regarding policy recommendations and vaccine delivery. However, as demonstrated in Chapter 2, the regional burden and epidemiology of tuberculosis varies substantially across India, which may impact the effectiveness of vaccine delivery strategies.

Subnational modelling of M72/AS01$_E$ and BCG-revaccination for specific regions within India could help investigate potential differences in impact.

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CHAPTER 5 Subnational modelling: Comparing the impact of introducing novel tuberculosis vaccines in Delhi and Gujarat, India

This chapter contains Research Paper 3 in section 5.2 addressing thesis **Aim 3** and thesis **Objective 4**. The supplementary material for Research Paper 3 is in section 5.3 addressing thesis **Objective 1**.

5.1 Introduction

Results of the country-level modelling from Chapter 4 suggest that M72/AS01$_E$ and BCG-revaccination could have a large health impact in India and would be cost-effective regardless of the modelled product characteristics.[1] Previous work has suggested that the benefits of novel vaccines may vary based on underlying tuberculosis burden and age distribution in a population, but no studies have quantified and compared potential vaccine impact at the regional level in India.

The India tuberculosis prevalence survey conducted between 2019 and 2021 found wide variation in tuberculosis prevalence throughout the country, with some high burden regions having over five times the estimated tuberculosis prevalence as others.[2] Delhi and Gujarat have the highest and lowest estimates of adult tuberculosis prevalence in India respectively and also differ substantially in population size, demographics, and tuberculosis care provision. As vaccine effectiveness may depend on whether the recipient is uninfected or infected with *Mtb*, differences in tuberculosis infection prevalence may drive differences in the absolute and relative impact of M72/AS01$_E$ and BCG-revaccination between Delhi and Gujarat. Estimates of the impact of M72/AS01$_E$ and BCG-revaccination could inform vaccine introduction and delivery decisions at the regional level.

In Research Paper 3 of this thesis, I generated subnational models of Delhi and Gujarat to assess the influence of differences in disease burden on the impact of M72/AS01$_E$ and BCG-revaccination introduction. Research Paper 3 is included in Section 5.2 as a draft ahead of submission.

5.2 Research paper – The potential health and economic impacts of new tuberculosis vaccines under varying delivery strategies in Delhi and Gujarat, India: a modelling study

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Student ID Number	1804462	**Title**	Ms
First Name(s)	Rebecca Anne		
Surname/Family Name	Clark		
Thesis Title	Mathematical modelling of the impact of adolescent/adult tuberculosis vaccines to inform global, national, and subnational policy and delivery		
Primary Supervisor	Richard 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?			
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Please list the paper's authors in the intended authorship order:	Rebecca A Clark, Allison Portnoy, Chathika K Weerasuriya, Tom Sumner, Roel Bakker, Rebecca C Harris, Kirankumar Rade, Sanjay Kumar Mattoo, Dheeraj Tumu, Nicolas A Menzies, Richard G White
Stage of publication	Not yet submitted

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 developed the natural history and vaccine model structures. I researched and selected the subnational regions to model, and I collected the epidemiological data to parameterise and calibrate the regions. I organised discussions with collaborators to verify assumptions, and develop vaccine delivery scenarios. I calibrated the models for both regions, and generated the required impact results. I prepared the results and shared them with collaborators for input. I wrote the first full draft of the paper and revised the paper based on comments from co-authors. I am in the process of preparing the manuscript for submission.

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

The potential health and economic impacts of new tuberculosis vaccines under varying delivery strategies in Delhi and Gujarat, India: a modelling study

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Word count: 3500 words

Abstract (346/350 words)

Background

India has the largest tuberculosis burden globally, but this burden varies nationwide. All-age tuberculosis prevalence in 2021 ranged from 747/100,000 in Delhi to 137/100,000 in Gujarat. Previous modelling has demonstrated the benefits and costs of introducing novel tuberculosis vaccines in India overall. However, no studies have compared the potential impact of tuberculosis vaccines in regions within India with differing tuberculosis disease and infection prevalence. We used mathematical modelling to investigate how the health and economic impact of two potential tuberculosis vaccines, M72/AS01$_E$ and BCG-revaccination, could differ in Delhi and Gujarat under varying delivery strategies.

Methods

We applied a compartmental tuberculosis model separately for Delhi (higher disease and infection prevalence) and Gujarat (lower disease and infection prevalence), and projected epidemiological trends to 2050 assuming no new vaccine introduction. We simulated M72/AS01$_E$ and BCG-revaccination scenarios varying target ages and vaccine characteristics. We estimated cumulative cases, deaths, and disability-adjusted life years averted between 2025–2050 compared to the no-new-vaccine scenario and compared incremental cost-effectiveness ratios to three cost-effectiveness thresholds.

Results

M72/AS01$_E$ averted a higher proportion of tuberculosis cases than BCG-revaccination in both regions (Delhi: 16·0% vs 8·3%, Gujarat: 8·5% vs 5·1%) and had higher vaccination costs (Delhi: USD$118 million vs USD$27 million, Gujarat: US$366 million vs US$97 million). M72/AS01$_E$ in Delhi could be cost-effective, or even cost-saving, for all modelled vaccine characteristics. M72/AS01$_E$ could be cost-effective in Gujarat, unless efficacy was assumed only for those with current infection at vaccination. BCG-revaccination could be cost-effective, or cost-saving, in both regions for all modelled vaccine scenarios.

Discussion

M72/AS01$_E$ and BCG-revaccination could be impactful and cost-effective in Delhi and Gujarat. Differences in impact, costs, and cost-effectiveness between vaccines and regions were determined partly by differences in disease and infection prevalence, and demography. Age-specific regional estimates of infection prevalence could help to inform delivery strategies for vaccines that may only be effective in people with a particular infection status. Evidence on the mechanism of effect of M72/AS01$_E$ and its effectiveness in uninfected individuals, which were important drivers of impact and cost-effectiveness in Gujarat, are also key to improve estimates of population-level impact.

Research in Context

Evidence before this study

The National Tuberculosis (TB) Prevalence Survey in India conducted between 2019–2021 estimated an overall disease prevalence of 312 per 100,000, but also indicated that this burden varied widely across the country. The National Capital Territory of Delhi was estimated to have the highest prevalence of disease for all ages (747 per 100,000), while Gujarat was estimated to have the lowest (137 per 100,000). New tuberculosis vaccines are likely to play a key role in tuberculosis elimination and, in particular, promising results were reported from Phase IIb trials of M72/AS01$_E$ and BCG-revaccination. It is unknown how the impact of delivery of specific vaccine candidates in India may vary depending on differences in subnational demography or burden of disease.

We searched PubMed with no date or language restrictions for all studies modelling the impact of specific tuberculosis vaccine candidates in Delhi or Gujarat using the search terms ((“tuberculosis”) OR (“Mtb”)) AND ((“M72/AS01”) OR (“BCG”)) AND (“India”) AND ((“Delhi”) OR (“Gujarat”) OR (“subnational”)). Studies have estimated that introducing new tuberculosis vaccines could have a positive impact on the epidemic and be cost-effective in India overall, but there were no studies that estimated the impact of new tuberculosis vaccines for regions within India with differing demography and disease burden.

Added value of this study

We used mathematical modelling to investigate how the health impact and cost-effectiveness of M72/AS01$_E$ and BCG-revaccination could vary between high- and low-tuberculosis burden areas in India—represented by Delhi and Gujarat—under varying delivery strategies. We fit each model to the regional disease prevalence estimated by the National TB Prevalence survey, and, assuming disease prevalence correlated with infection prevalence, modelled a higher infection prevalence in Delhi than in Gujarat.

This was the first study to estimate and compare the impact of introducing novel tuberculosis vaccines for two subnational regions within India which represented high and low burdens of

disease. M72/AS01$_E$ scenarios were estimated to avert a larger number of cases and deaths in both Delhi and Gujarat compared to BCG-revaccination due to the assumed vaccine characteristics, and more cases and deaths were averted in Delhi compared to Gujarat for both vaccines due to the higher burden of disease. We showed how vaccine impact is closely tied to infection prevalence, given assumptions surrounding vaccines that will be effective only if people are uninfected or if they are infected. As BCG-revaccination was assumed to only be efficacious in those that are uninfected, we estimated a higher relative impact of the vaccine in Gujarat with the lower modelled infection prevalence. Given the assumed vaccine and delivery characteristics, M72/AS01$_E$ and BCG-revaccination scenarios were likely to be cost-effective (or even cost-saving) in Delhi. BCG-revaccination scenarios were also estimated to be cost-effective in Gujarat, but M72/AS01$_E$ scenarios were likely to be cost-effective only if, given the lower prevalence of infection, we assumed that vaccine efficacy was not restricted to current infection at the time of vaccination.

Implications of all the available evidence

Evidence from this study, combined with previous evidence for India overall, continued to show that new tuberculosis vaccines could be impactful and cost-effective when introduced. Moving forward, age-specific regional estimates of *Mtb* infection prevalence are needed to better inform vaccine impact estimation for vaccines that will only be effective if individuals are either uninfected or infected. Determining whether M72/AS01$_E$ is able to prevent both infection and disease, and if it is efficacious in those that are uninfected at the time of vaccination, remain additional areas for continued research to reduce unknowns.

Background

India has the highest global burden of tuberculosis, but this burden varies widely across the country. In the National Tuberculosis (TB) Prevalence survey conducted from 2019–2021, the estimated tuberculosis prevalence was 312 per 100,000 for all ages in India overall.[1] The National Capital Territory of Delhi was estimated to have the highest regional tuberculosis prevalence of 747 per 100,000, whereas Gujarat was estimated to have the lowest regional tuberculosis prevalence [137 per 100,000].[1]

Tuberculosis elimination is a key focus for the Indian government, and prevention strategies, including tuberculosis vaccines and preventive treatment, are considered within the National Strategic Plan for Elimination of Tuberculosis 2017–2025.[2] As of July 2023, there were sixteen tuberculosis vaccine candidates in clinical trials. Results are eagerly anticipated from an upcoming Phase III trial of the vaccine candidate M72/AS01$_E$ and the ongoing confirmatory Phase IIb trial for BCG-revaccination, as both products have demonstrated promising results in previous Phase IIb trials.[3,4]

Earlier modelling studies have found that the introduction of new tuberculosis vaccines could have a positive impact worldwide [5–10] and in India.[11–15] However, it is unknown how or if the impact of tuberculosis vaccines will vary regionally within India, given the varying burdens of disease. The Indian government is set to undertake a study to investigate the impact of delivering BCG to household contacts aged 6–18 compared to offering preventive therapy.[16] Variation in disease and infection prevalence may influence the impact of these interventions by region.

We used mathematical modelling to investigate how the health impact and cost-effectiveness of M72/AS01$_E$ and BCG-revaccination could vary between high- and low-tuberculosis burden areas of India—represented by Delhi and Gujarat—under varying delivery strategies.

Methods

Data

Data to inform calibration was obtained from the National TB Prevalence survey in India,[1] the India TB Report 2022 and 2023,[2,17] and Ni-kshay—an online tuberculosis reporting and surveillance system developed by the National TB Elimination Program.[18] We combined available demographic data and extrapolated to obtain single age and year projections of population size for each region.[19]

Model structure and calibration

We adapted a tuberculosis natural history model structure and parameterisation from previous studies.[5,11] We used history matching with emulation through the hmer R package to calibrate the model to each region.[20] We fit each model to three targets to represent the higher tuberculosis burden in Delhi, and the lower tuberculosis burden in Gujarat. We assumed a uniform distribution between lower and upper bounds, and adjusted each target as described in the Supplementary Material sections 2 and 3. We fit to the 2021 disease prevalence per 100,000 [Delhi: 747 (510–984), Gujarat: 137 (76–198)][1], the 2021 notification rate per 100,000 [Delhi: 536 (429–644), Gujarat: 137 (110–165)][17], and the 2020 proportion of active tuberculosis that was subclinical [0·564 (interquartile range = 0·428–0·685)][21]. The model for Gujarat was also fit to the estimated adult tuberculosis prevalence in 2011 [383 (315–451) per 100,000].[22]

Scenarios

i. No-new-vaccine baseline

We used the calibrated models for Delhi and Gujarat to project baseline epidemiology to 2050 in each setting, assuming the coverage and quality of non-vaccine tuberculosis services continued at 2019 levels, with no new vaccine introduction.

ii. Vaccine scenarios

We established a *Basecase* vaccine scenario for each vaccine product. *Basecase* vaccine characteristics were informed by trial characteristics and expert opinion, and we assumed that each vaccine would be delivered to an age group aligned with the clinical-trial-eligible ages.[3,4] The *Basecase* M72/AS01$_E$ scenario assumed a 50% efficacy prevention of disease vaccine effective

with any infection status at vaccination and ten years average protection, introduced in 2030 routinely to those aged 15 (achieving 80% coverage over five years) and as a campaign for ages 16–34 (achieving 70% coverage over five years) in 2030 and 2040. The *Basecase* BCG-revaccination scenario assumed a 45% efficacy prevention of infection vaccine effective in individuals with no current infection at the time of vaccination and ten years average protection, introduced in 2025 routinely to those aged 10 (achieving 80% coverage over five years) and as a campaign for ages 11–18 (achieving 80% coverage over five years), in 2025, 2035, and 2045.

We evaluated age-targeting *Policy Scenarios* for both vaccine products. We met with in-country partners in the Government of India to discuss preferred ages to target for tuberculosis vaccine delivery. We ensured that our modelled scenarios captured this information to provide the most useful estimates to decision makers. The *Older Ages: M72/AS01$_E$* scenario assumed routine delivery to those aged 17 and a campaign for ages 18–55, and the *Older Ages: BCG-revaccination* scenario assumed routine delivery to those aged 15 and a campaign for ages 16–34. For both vaccine products, we evaluated an *All-Adults* scenario with routine delivery for those aged 18 and a campaign for everyone aged 19 and older.

To investigate uncertainty in vaccine product characteristics, we evaluated *Vaccine Characteristic and Coverage Scenarios* by varying individual features of the vaccine profile from the *Basecase* (Table 1).

We assumed vaccine delivery costs of \$2·50 (1·00–5·00) per dose, supply chain costs of \$0·11 (0·06–0·22) per dose and a vaccine price of \$2·50 per dose for M72/AS01$_E$ (assuming two doses per course) and \$0·17 per dose for BCG-revaccination (assuming one dose per course). For vaccine campaigns, we included a one-time vaccine introduction cost of \$2·40 (1.20–4·80) per individual in the targeted age group to represent non-recurring start-up costs.

Outcomes

We estimated the cumulative number of tuberculosis cases and deaths averted between vaccine introduction and 2050 for each scenario compared to the predicted numbers in the no-new-vaccine baseline. We estimated incidence and mortality rate reductions in 2050 for each scenario compared

to the estimated rates in 2050 for the no-new-vaccine baseline. We calculated incremental vaccination, diagnostic, and treatment costs for each scenario compared to the no-new-vaccine baseline in 2020 US dollars.

We performed cost-effectiveness analysis comparing the *Policy Scenarios* for each vaccine product and region. Costs and benefits were discounted to 2025 at 3% per year as per guidelines.[23] We estimated incremental costs and disability-adjusted life years (DALYs) averted for each scenario between 2025–2050, using the disability weight for tuberculosis from the Global Burden of Disease 2019 study,[24] and India-specific life expectancy estimates from the United Nations Development Programme.[25] We calculated incremental cost-effectiveness ratios (ICERs) as mean incremental costs divided by mean incremental DALYs averted for each scenario. We evaluated the resulting ICERs against three cost-effectiveness thresholds: 1 times gross domestic product (GDP) per capita for India (US$1,928), and two opportunity cost thresholds defined by Ochalek et al: the country-level upper (US$443) and lower (US$328) bounds.[26]

To investigate if the decision to introduce a vaccine would change based on the assumed vaccine characteristics, we calculated ICERs for the *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline. We assumed each vaccine product was delivered using the *Basecase* age-targeting assumptions (M72/AS01$_E$: routine for age 15, campaign for ages 16–34; BCG-revaccination: routine for age 10, campaign for ages 11–18).

Results

Calibrated trends for Delhi and Gujarat are shown in Figure 1. Between 2025 and 2050, the no-new-vaccine baseline predicted 4·1m (95% uncertainty interval: 3·7–4·4) cases and 533 (349–761) thousand deaths in Delhi, and 2·2m (2·0–2·5) cases and 210 (100–325) thousand deaths in Gujarat. Consistent with findings from the National TB Prevalence Survey, a higher burden of disease was predicted in Delhi than in Gujarat. A lower and declining trend in tuberculosis infection prevalence was predicted in Gujarat compared to Delhi.

Key results are described below, with full results in Supplementary Material sections 8 and 9. The *Basecase* M72/AS01$_E$ scenario averted 655 (587–730) thousand cases, or 16·0% of the total predicted cases, and 77 (49–112) thousand deaths, or 14·4% of the total predicted deaths between 2025 and 2050 in Delhi (Table 2). The *Basecase* M72/AS01$_E$ scenario averted 186 (155–228) thousand cases (8·5% of the total predicted cases) and 16 (7–27) thousand deaths (7·6% of the total predicted deaths) in Gujarat between 2025–2050 (Table 2). The number of cases and deaths averted was increased in both Delhi and Gujarat with delivery to a larger and older population (Table 2). The *All-Adults* scenario averted more cases and deaths than the *Older Ages* scenario, which similarly averted more than the *Basecase* M72/AS01$_E$ scenario (Figure 2).

If M72/AS01$_E$ was able to prevent both infection and disease, the number of cases and deaths averted could increase by 23–25% in Delhi and 25–28% in Gujarat compared to the *Basecase* M72/AS01$_E$ scenario (Table 2). However, if M72/AS01$_E$ was only efficacious with current infection at vaccination, the number of cases and deaths averted could decrease by 28–29% in Delhi and 44–46% in Gujarat compared to the *Basecase* M72/AS01$_E$ scenario (Table 2).

The *Basecase* BCG-revaccination scenario averted 359 (305–402) thousand cases (8·8% of total predicted cases) and 44 (29–65) thousand deaths (8·3% of total predicted deaths) in Delhi, and 113 (91–143) thousand cases (5·1% of total predicted cases) and 10 (5–17) thousand deaths (4·8% of total predicted deaths) in Gujarat between 2025–2050 (Table 2). Due to differences in modelled infection prevalence, delivering BCG-revaccination to an older population (*Older Ages* and *All-Adults* scenarios) decreased the number of cases and deaths averted in Delhi, but increased the impact in Gujarat compared to the *Basecase* BCG-revaccination scenario (Figure 2).

If BCG-revaccination was able to prevent infection and disease, the number of cases and deaths averted could increase by 52–53% in Delhi and 36–40% in Gujarat compared to the *Basecase* BCG-revaccination scenario (Table 2). If BCG-revaccination worked in any infection status as opposed to only those who were uninfected, the number of cases and deaths averted could increase by 21–23% in Delhi, but could only increase the number of cases and deaths averted in Gujarat by 0–1% compared to the *Basecase* BCG-revaccination scenario (Table 2).

In both regions, M72/AS01$_E$ resulted in a higher number of cases and deaths averted than BCG-revaccination: approximately 1.8 times in Delhi and 1.6 times in Gujarat (Table 2). For both vaccine products, more cases and deaths were averted in Delhi compared to Gujarat: 3·5–4.8 times for M72/AS01$_E$ and 3·2–4.4 times for BCG-revaccination (Table 2).

The total vaccination cost for the M72/AS01$_E$ *Basecase* was US$118m (80–173) in Delhi and was US$366m (248–536) in Gujarat, compared to the BCG-revaccination Basecase vaccination total cost of US$27m (12–49) in Delhi and US$97m (42–178) in Gujarat (Tables S10.2, S10.5, S10.8, S10.11). Larger vaccination costs were predicted for introducing M72/AS01$_E$ compared to BCG-revaccination in both regions: 4·4 times more in Delhi and 3·8 times more in Gujarat. Incorporating cost-savings in treatment and diagnostic costs, the total incremental programme cost for the M72/AS01$_E$ *Basecase* in Delhi was US$5m (minus 37–63) and in Gujarat was US$332m (213–505) (Tables S10.2, S10.8). The *Basecase* BCG-revaccination scenario led to cost-savings of US$38m (58–13) in Delhi (Table S10.5). The total programme cost for the *Basecase* BCG-revaccination scenario in Gujarat was US$77m (21–158) in Gujarat (Table S10.11).

In Delhi, introducing M72/AS01$_E$ was potentially cost-effective for all *Policy Scenarios*. The *Basecase* M72/AS01$_E$ scenario (ICER = US$4), *Older Ages* scenario (ICER = US$126) and *All-Adults* scenario (ICER = US$317) were cost-effective at the country-level upper and lower bounds, and the 1xGDP threshold (Table 3, Figure 3). The incremental cost of the *Basecase* M72/AS01$_E$ scenario was US$5m (minus 37–63), averting 1·5m (1·0–2·1) DALYs between 2025–2050 compared to the no-new-vaccine baseline (Table 3, Figure 3). In Gujarat, only the *All-Adults* scenario was considered potentially cost-effective for M72/AS01$_E$ at the 1xGDP threshold (ICER = US$975) (Table 3, Figure 3). The cost of the *All-Adults* scenario compared to the no-new-vaccine

baseline was US$624m and 640 thousand DALYs were averted between 2025–2050 (Table 3, Figure 3).

In Delhi, the *Older Ages* and *All-Adults* BCG-revaccination scenarios were dominated by the *Basecase* BCG-revaccination scenario. The *Basecase* BCG-revaccination scenario was considered cost-effective at all thresholds (ICER = cost-saving), with cost savings of US$37m and averting 938 thousand DALYs between 2025–2050 compared to the no-new-vaccine baseline. In Gujarat, the *Basecase* BCG-revaccination scenario was cost-effective at the country-level upper bound (ICER = US$351), with an incremental cost of US$77m compared to the no-new-vaccine baseline and averting 219 thousand DALYs between 2025–2050. The *Older Ages* scenario was cost-effective at 1xGDP per capita (ICER = US$868) (Table 3, Figure 3).

When comparing the ICERs from the *Vaccine Characteristic and Coverage Scenarios* in Delhi, regardless of the assumed product characteristics, introducing M72/AS01$_E$ routinely to those aged 15 and as a campaign for ages 16–34 could be cost-effective, and in some cases, cost-saving, at the country-level lower bound (Figure 4). Similarly, introducing BCG-revaccination routinely to those aged 10 and as a campaign for ages 11–18 could be cost-saving in Delhi (Figure 4). In Gujarat, delivering M72/AS01$_E$ routinely to those aged 15 and as a campaign for ages 16–34 could be cost-effective at a 1xGDP per capita threshold, except if the vaccine was only efficacious with current infection at vaccination (Figure 4). Introducing BCG-revaccination in Gujarat could be cost-effective regardless of the modelled product characteristics (Figure 4).

In both regions, there were larger ICERs for M72/AS01$_E$ scenarios compared to BCG-revaccination and, for both vaccine products, larger ICERs for Gujarat compared to Delhi (Figure 4). Full impact results for all vaccine scenarios for both regions are provided in the Supplementary Material sections 8 and 9.

Discussion

Our modelling suggests that M72/AS01$_E$ and BCG-revaccination could have a substantial impact in Delhi and Gujarat. M72/AS01$_E$ scenarios resulted in a higher number of cases and deaths averted than BCG-revaccination in both regions, and more cases and deaths were averted in Delhi compared to Gujarat. We found that, given the assumed characteristics, both vaccine products were likely to be cost-effective or cost-saving in Delhi. In Gujarat, M72/AS01$_E$ was likely to be cost-effective unless it only worked in those with current infection at the time of vaccination. M72/AS01$_E$ scenarios had higher vaccination costs than BCG-revaccination, and higher vaccination costs were estimated in Gujarat overall than in Delhi.

For all modelled scenarios, M72/AS01$_E$ would have a larger and faster impact on the tuberculosis burden than BCG-revaccination. We assumed that M72/AS01$_E$ would be effective in anyone regardless of the presence or absence of infection and would work by preventing disease. Therefore, those with current infection who received the vaccine would have an immediately lower rate of disease progression. We assumed that BCG-revaccination would only be effective in those who were uninfected at vaccination and would work by preventing infection. Therefore, the impact from BCG-revaccination would be delayed by the time to infection, and the time from infection to disease.

Several findings were related to the lower infection prevalence modelled in Gujarat compared to Delhi. For M72/AS01$_E$ scenarios, the relative decrease in the number of cases and deaths averted if M72/AS01$_E$ was only effective in individuals with current infection was much larger in Gujarat compared to Delhi. If M72/AS01$_E$ vaccine efficacy was restricted to those with current infection, a larger proportion of the population would no longer benefit from vaccination in Gujarat compared to Delhi, due to the lower infection prevalence in Gujarat. BCG-revaccination was estimated to have a larger relative impact in Gujarat than in Delhi for strategies targeting an older and larger proportion of the population (*Older Ages* or *All-Adults* scenarios compared to the *Basecase*). As we modelled a higher infection prevalence for all ages in Delhi and assumed that BCG-revaccination would only be effective if administered to people who were uninfected, there was a higher proportion of the population who were uninfected and would receive protection from the vaccine in Gujarat than in Delhi.

Across the range of assumptions we examined for vaccine product characteristics, M72/AS01$_E$ and BCG-revaccination were likely to be cost-effective (and even cost-saving) in Delhi compared to the thresholds evaluated. In Gujarat, M72/AS01$_E$ could be cost-effective unless efficacy was restricted to those with current infection at time of vaccination, and BCG-revaccination was likely to be cost-effective regardless of the modelled characteristics. Understanding the mechanism of effect of M72/AS01$_E$ and confirming whether it works in all populations is a key area for future research, particularly in Gujarat and other areas with a low prevalence of infection.

M72/AS01$_E$ was predicted to have higher vaccination costs than BCG-revaccination in both regions: 4·4 times as high in Delhi (US$118m vs US$27m) and 3·5 times as high in Gujarat (US$366m vs US$97m), due to the higher price per dose for M72/AS01$_E$, ($2·50 per dose compared to $0·17 per dose for BCG) and the requirement for two doses per course. Higher costs for both products were predicted in Gujarat compared to Delhi due to the larger population size.

There are limitations associated with this work. Firstly, this is a mathematical modelling study, and therefore limitations associated with models apply. We represented tuberculosis natural history with a compartmental model accounting for multiple infection states. If our assumptions around how the latency structure or aspects such as subclinical tuberculosis interact with vaccines were incorrect, we may have over- or under-protected the population, leading to incorrect vaccine impact estimates. We assumed that bounds of certain natural history parameters would not vary between regions, and therefore used posterior ranges from the previously published national-level India model as priors for Delhi and Gujarat calibration.[11] If this was an incorrect assumption, or if the assumptions on the national India model prior ranges were incorrect, our projections may inaccurately represent Delhi and Gujarat.

Our model includes an on-treatment compartment but assumed that the only people who are treated are those with tuberculosis. The reported notification rate in Gujarat was greater than the prevalence estimate, implying more people were treated per year than those with prevalent disease. While Gujarat has excellent tuberculosis treatment services, only 35% of the reported notifications were bacteriologically confirmed. Therefore, there could be treatment of individuals who did not

have tuberculosis, which we did not represent, but could be investigated with future adaptations to the model.

A key limitation of this work was the availability of region-specific data to inform calibration. The National TB Prevalence Survey in India provided estimates of the tuberculosis prevalence for each region for one year, allowing us to model a higher burden of tuberculosis in Delhi compared to Gujarat, but this did not allow us to incorporate a data-driven time trend. There were no region-specific calibration targets to constrain mortality, and therefore we found large uncertainty on the number of cumulative deaths averted due to large uncertainty around trends in mortality. Additionally, there were no region-specific estimates of infection prevalence, which was a key determiner of vaccine impact. We assumed differences in mortality and infection prevalence between Delhi and Gujarat would align with the differences observed in disease prevalence and modelled a higher mortality rate and infection prevalence in Delhi. To continue modelling subnational regions, more region-specific data to inform model predictions is urgently needed.

We represented population size and age structure for Delhi and Gujarat by utilising all available demographic data and projections for the regions and extrapolated forward to 2050 where no data was available. As the risk of tuberculosis is age-dependent, if we incorrectly represented the demographic structure of the regions, we may have over or underestimated the health impact possible with new vaccines.

The no-new-vaccine baseline assumed that the current quality and coverage of services would continue. We did not consider improvements in social determinants which may occur over the time-period. The burden projected in the no-new-vaccine baseline may be higher than what is realised in the future, and therefore may be overestimating the health benefit and cost-effectiveness of vaccines. We introduced vaccines into the population independently, and did not integrate with other services, such as tuberculosis preventive therapy, which may alter future outcomes.

Conclusions

Our study has demonstrated that M72/AS01$_E$ and BCG-revaccination are likely to be impactful and cost-effective if introduced in Delhi and Gujarat. Delhi and Gujarat were selected as the modelled regions to represent a high and low burden setting respectively. There were differences in vaccine impact between regions, which were only revealed through subnational modelling and considering differences in disease and infection prevalence. While national models are beneficial to demonstrate potential impact overall, if there are distinct epidemiological differences within the country, the impact can vary.

Our results support the need for more infection prevalence surveys. If vaccines may only work in those who are either uninfected or infected, modelled projections of infection prevalence of each region may be a particularly important driver of impact. Age-specific regional estimates of infection prevalence would help to inform delivery strategies for vaccines only effective in people with a particular infection status and improve vaccine impact estimates. Another key area for future research is investigating the mechanism of effect of M72/AS01$_E$, and confirming effectiveness in uninfected individuals, which was an important driver of impact and cost-effectiveness in Gujarat. Further research to reduce vaccine characteristic uncertainty and generate subnational models for additional regions is needed to maximise success of vaccine delivery in India.

Data sharing statement

No individual level participant data was used for this modelling study. Analytic code will be made available at https://doi.org/10.5281/zenodo.6421372 immediately following publication indefinitely for anyone who wishes to access the data for any purpose.

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Conception: RAC, AP, CKW, RCH, NAM, RGW
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Data analysis: RAC, AP, TS, CKW, NAM, RGW
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Manuscript drafting and revisions: RAC, AP, RGW, NAM, TS, KR, SKM, DT, CKW, RB, RCH
All authors had the opportunity to access and verify the data and were responsible for the decision to submit the manuscript for publication.

Declaration of interests

RCH reports employment by Sanofi Pasteur, unrelated to tuberculosis and outside the submitted work. NAM received consulting fees from The Global Fund to Fight AIDS, Tuberculosis and Malaria, and WHO, and reports funding to their institution from the U.S. Centers for Disease Control and Prevention, the Bill & Melinda Gates Foundation, NIH, and U.S. Council of State and Territorial Epidemiologists. RGW is also funded for other work by the Wellcome Trust (218261/Z/19/Z), NIH (1R01AI147321-01), EDCTP (RIA208D-2505B), UK MRC (CCF 17-7779 via SET Bloomsbury), ESRC (ES/P008011/1), BMGF (OPP1084276, OPP1135288 & INV-001754), and WHO. All other authors declare no conflicts of interest.

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Tables and Figures

Table 1 Vaccine scenarios

Characteristic	M72/AS01$_E$		BCG-revaccination	
	Basecase	**Univariate scenario analyses**	**Basecase**	**Univariate scenario analyses**
Policy Scenarios				
Age targeting	Routine for age 15, campaign for ages 16–34	*Older Ages* (routine for age 17, campaign for ages 18–55) *All-Adults* (routine for age 18, campaign for ages 19+)	Routine for age 10, campaign for ages 11–18	*Older Ages* (routine for age 15, campaign for ages 16–34) *All-Adults* (routine for age 18, campaign for ages 19+)
Vaccine Characteristic and Coverage Scenarios				
Efficacy	50%	60%, 70%	45%	70%
Mechanism of effect	Prevents disease	Prevents infection and disease	Prevents infection	Prevents infection and disease
Infection status at time of vaccination required for efficacy	Any infection (current / no current infection)	Current infection only	No current infection only	Any infection (current / no current infection)
Duration of protection	10 years	5, 15, 20	10 years	5, 15, 20
Introduction year	2030	2036	2025	2031
Coverage	Medium: 80% routine, 70% campaign	Low: 70% age 15, 50% campaign High: 90% age 15, 90% campaign	Medium: 80% routine, 80% campaign	Low: 70% routine, 70% campaign High: 90% routine, 90% campaign

Figure 1 Calibrated epidemiological trends for Delhi and Gujarat

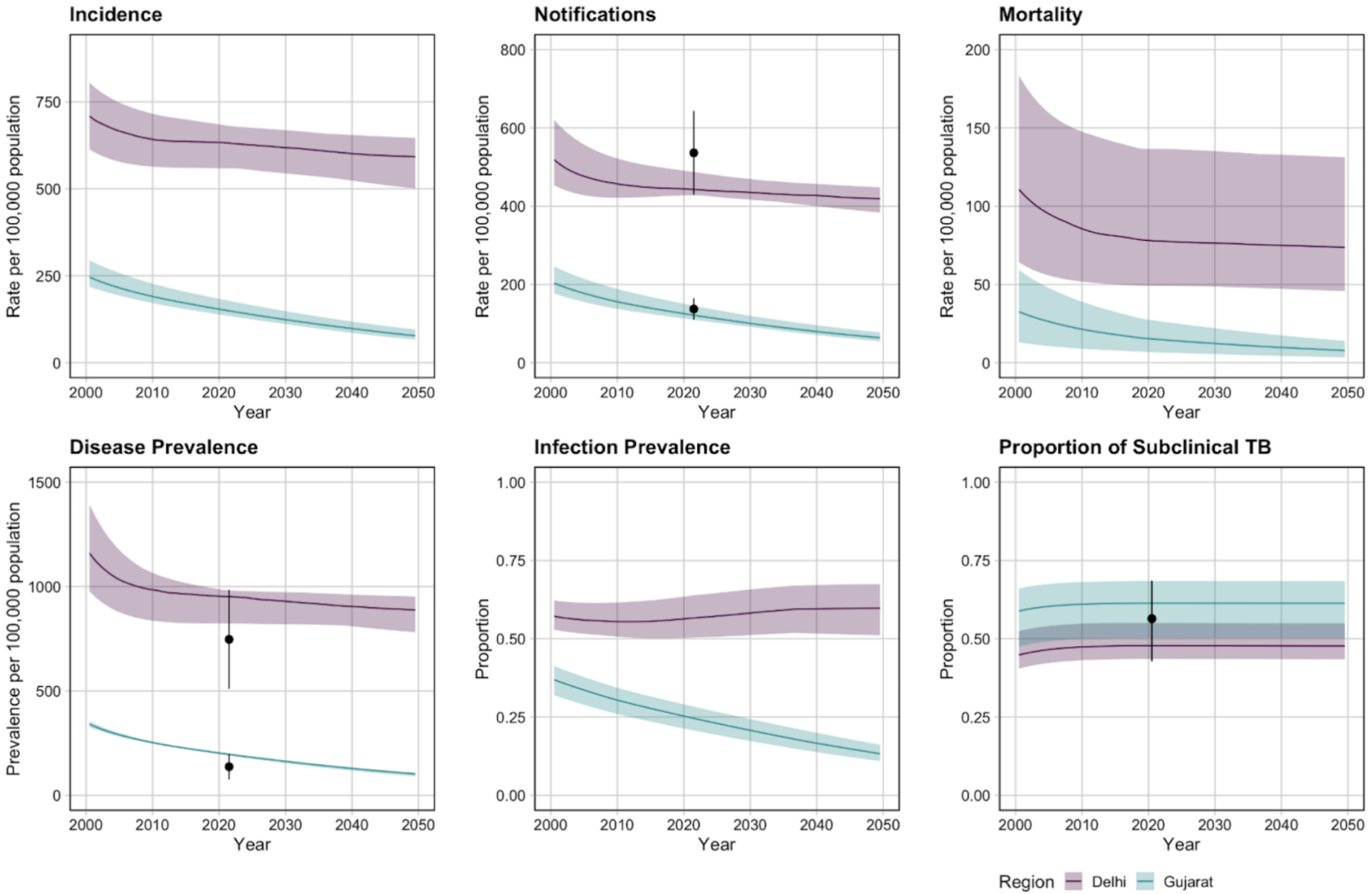
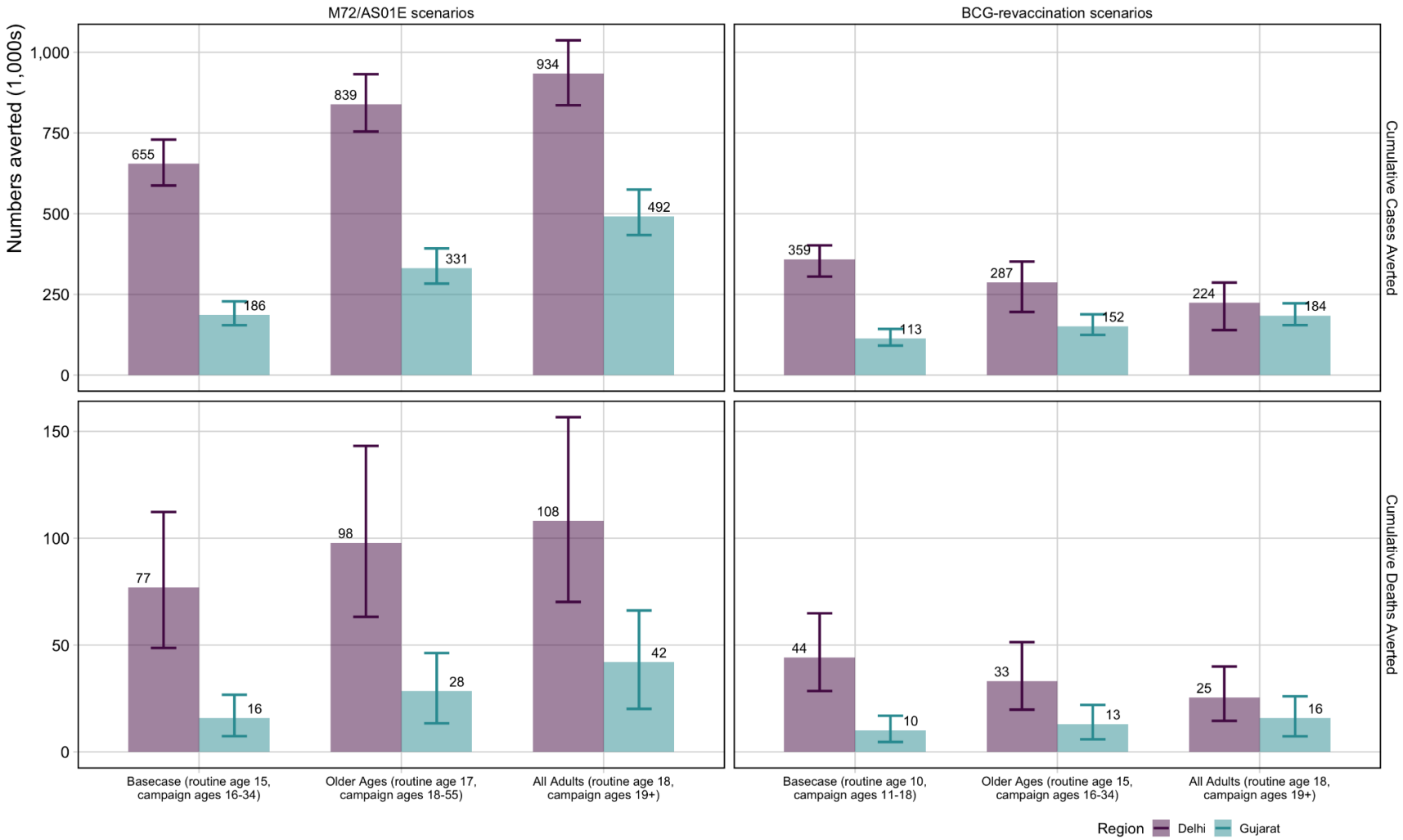


Table 2 Health impact results for M72/AS01$_E$ and BCG-revaccination in Delhi and Gujarat

Scenario	Cumulative cases averted between 2025–2050 (1000s)		Cumulative deaths averted between 2025–2050 (1000s)		Incidence rate reduction in 2050 (%)		Mortality rate reduction in 2050 (%)	
	Delhi	Gujarat	Delhi	Gujarat	Delhi	Gujarat	Delhi	Gujarat
M72/AS01$_E$ scenarios								
Basecase (routine age 15, campaign ages 16-34)	655 (587–730)	186 (155–228)	77 (49–112)	16 (7–27)	26 (23–29)	16 (15–19)	27 (23–30)	17 (15–19)
Policy Scenarios								
Older ages (routine age 17, campaign ages 18–55)	839 (755–932)	331 (284–393)	98 (63–143)	28 (13–46)	29 (25–33)	25 (23–27)	31 (26–34)	26 (24–28)
All-adults (routine age 18, campaign ages 19+)	935 (836–1,037)	492 (434–575)	108 (70–157)	42 (20–66)	31 (26–34)	32 (30–34)	32 (27–36)	34 (32–36)
Vaccine Characteristic and Coverage Scenarios								
Efficacy with current infection at vaccination	471 (403–535)	101 (84–124)	55 (34–82)	9 (4–15)	17 (16–19)	8 (7–9)	18 (16–20)	8 (7–9)
Prevention of infection and disease	817 (730–914)	238 (198–293)	95 (61–140)	20 (9–34)	33 (29–37)	22 (19–25)	34 (29–38)	22 (20–25)
BCG-revaccination scenarios								
Basecase (routine age 10, campaign ages 11-18)	359 (305–402)	113 (92–143)	44 (29–65)	10 (5–17)	13 (10–16)	10 (9–12)	14 (10–16)	10 (9–12)
Policy Scenarios								
Older ages (routine age 15, campaign ages 16–34)	287 (196–352)	152 (125–188)	33 (20–51)	13 (6–22)	10 (6–14)	13 (11–15)	10 (6–14)	9 (8–11)
All-adults (routine age 18, campaign ages 19+)	224 (139–287)	184 (155–222)	25 (15–40)	16 (7–26)	8 (4–11)	15 (13–17)	8 (4–11)	11 (10–13)
Vaccine Characteristic and Coverage Scenarios								
Efficacy with any infection at vaccination	434 (390–494)	114 (92–145)	54 (34–80)	10 (5–17)	16 (13–19)	10 (9–12)	17 (14–19)	10 (9–12)
Prevention of infection and disease	544 (490–601)	154 (125–195)	67 (43–98)	14 (6–23)	21 (17–24)	14 (12–16)	21 (18–24)	13 (12–16)

Estimates are provided as the median and 95% uncertainty intervals

Figure 2 Cumulative cases and deaths averted between 2025–2050 for *Policy Scenarios* for both vaccines and regions



Cases and deaths averted are compared to the predicted number of cases and deaths that would occur between 2025 and 2050 with the no-new-vaccine baseline: 4·1 (3·7–4·4) million cases and 533 (349-761) thousand deaths in Delhi, and 2·2 (2·0–2·5) million cases and 210 (100–325) thousand deaths in Gujarat.

Table 3 Competing choice cost-effectiveness analysis for Delhi and Gujarat

Scenario	Total costs (USD, 1000s)	Total DALYs averted (1000s)	Incremental cost (USD, 1000s)	Incremental DALYs averted (1000s)	Cost (USD) per DALY averted
Delhi					
M72/AS01$_E$ policy scenarios					
No-new-vaccine	977,788	–	–	–	–
Basecase (routine age 15, campaign for ages 16–34)	982,966	1,465	5,178	1,465	4
Older ages (routine age 17, campaign for ages 18–55)	1,023,279	1,786	40,313	321	126
All-adults (routine age 18, campaign for ages 19+)	1,050,875	1,873	27,596	87	317
BCG-revaccination policy scenarios					
No-new-vaccine	977,788	–	–	–	–
Basecase (routine age 10, campaign for ages 11–18)	940,220	938	-37,568	938	*Cost-saving*
Older ages (routine age 15, campaign for ages 16–34)	973,930	693	–	–	*Strongly dominated*
All-Adults (routine age 18, campaign for ages 19+)	1,032,616	521	–	–	*Strongly dominated*
Gujarat					
M72/AS01$_E$ policy scenarios					
No-new-vaccine	584,609	–	–	–	–
Basecase (routine age 15, campaign for ages 16–34)	917,077	308	–	–	*Weakly dominated*
Older ages (routine age 17 campaign for ages 18–55)	1,097,770	505	–	–	*Weakly dominated*
All-Adults (routine age 18, campaign for ages 19+)	1,208,573	640	623,965	640	975
BCG-revaccination policy scenarios					
No-New-Vaccine	584,609	–	–	–	–
Basecase (routine age 10, campaign for ages 11-18)	661,265	219	76,656	219	351
Older ages (routine age 15, campaign ages 16–34)	708,672	273	47,407	55	868
All-Adults (routine age 18, campaign ages 19+)	844,338	312	135,666	39	3,486

Figure 3 Competing choice cost-effectiveness analysis for Delhi and Gujarat *Policy Scenarios* for both vaccine products

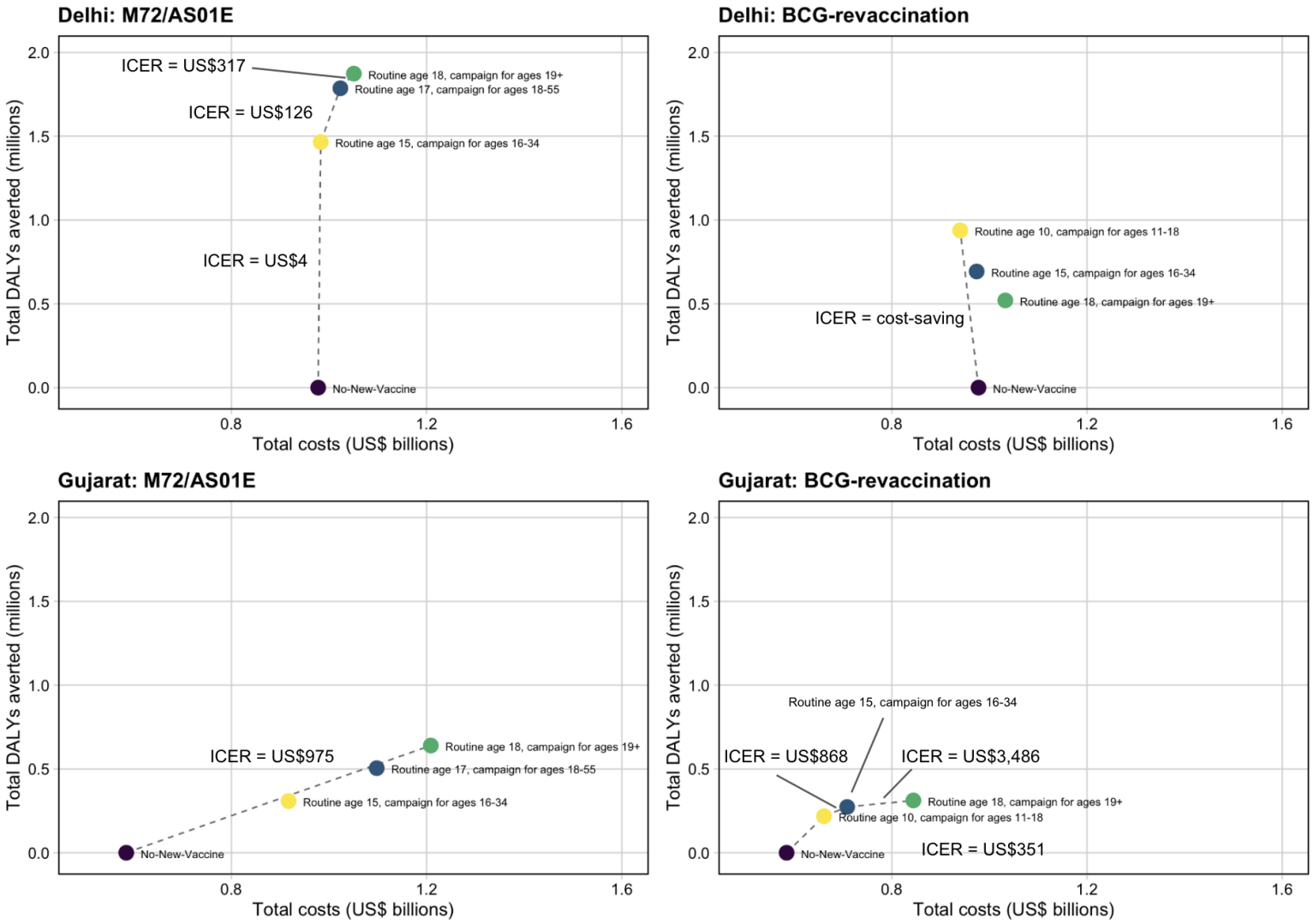
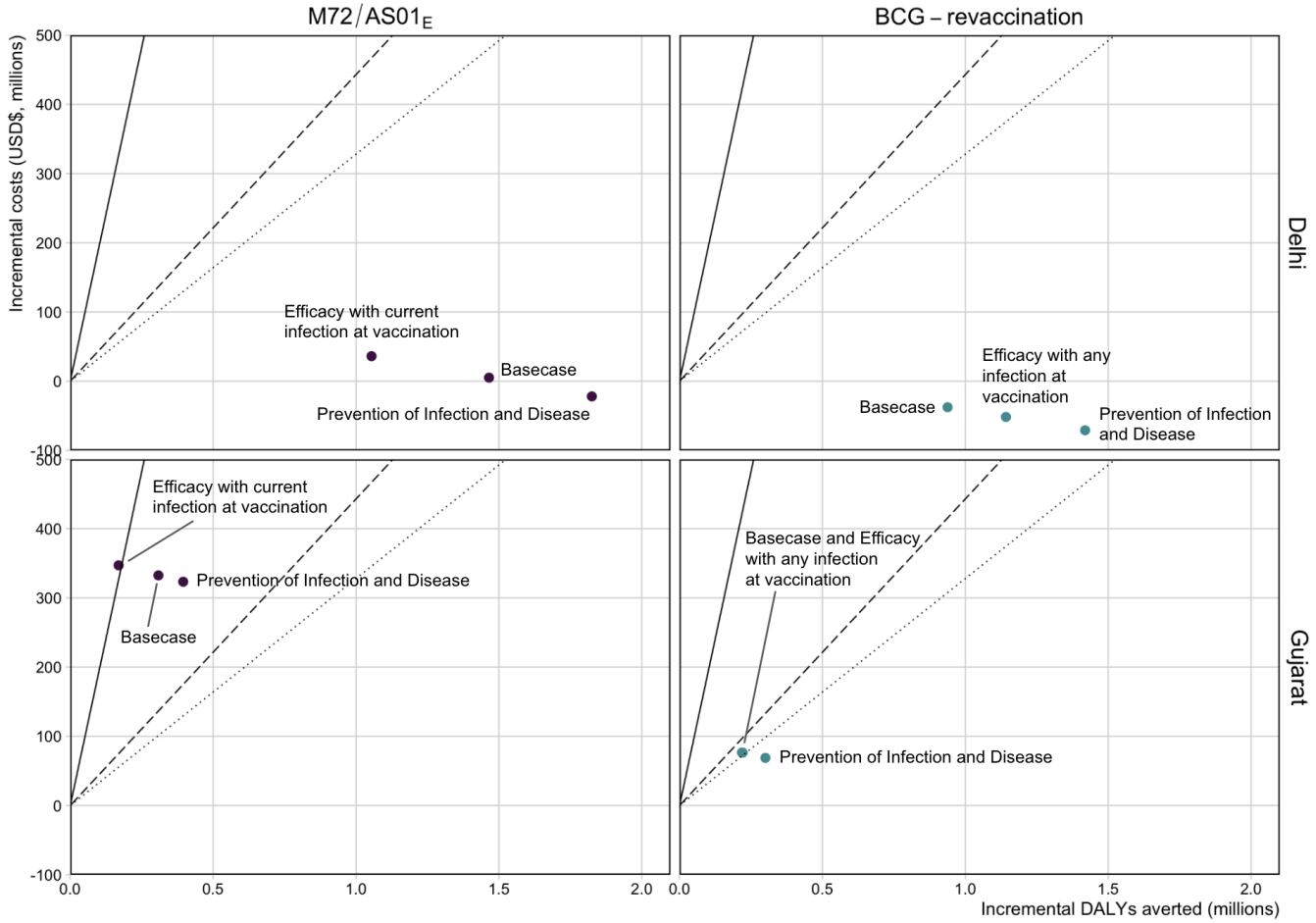


Figure 4 Comparison of ICERs for select *Vaccine Characteristic and Coverage Scenarios*



The cost-effectiveness thresholds are indicated as follows: solid line = 1xGDP per capita (US$1,928), dashed line = country-level upper bound (US$443), and dotted line = country-level lower bound (US$328). The Basecase M72/AS01$_E$ scenario assumes a 50% efficacy POD vaccine efficacious with any infection status at the time of vaccination, with 10 years duration of protection reaching 80% coverage for 15-year-olds and 70% coverage for those aged 16–34. Each M72/AS01$_E$ scenario is delivered routinely to those aged 15 and as a campaign for those aged 16–34. The Basecase BCG-revaccination scenario assumes a 45% efficacy POI vaccine efficacious with no current infection at the time of vaccination, with 10 years duration of protection and reaching 80% coverage. Each BCG-revaccination scenario is delivered routinely to those aged 10 and as a campaign for those aged 11–18. The scenarios on the figure are labelled with the difference in product characteristics for that scenario compared to the Basecase.

5.3 Supplementary Material – The potential health and economic impacts of new tuberculosis vaccines under varying delivery strategies in Delhi and Gujarat, India: a modelling study

The Supplementary Material for Research Paper 3 will be submitted alongside Research Paper 3. It is reproduced here with no modifications or adaptations from the version which will be submitted.

Supplementary Material for *The potential health and economic impacts of new tuberculosis vaccines under varying delivery strategies in Delhi and Gujarat, India: a modelling study*

Rebecca A. Clark et al

Table of Contents

SUPPLEMENTARY METHODS

1. Summary of tuberculosis in India, Delhi, and Gujarat

India is classified as one of the WHO top 30 high tuberculosis burden countries for 2021–2025, in addition to appearing on the high tuberculosis/HIV and drug-resistant tuberculosis lists.[1] The incidence rate of new tuberculosis cases in India in 2021 was estimated at 210 per 100,000 population per year.[2] India is divided into 28 states and 11 union territories, with a total population of over 1.3 billion estimated in 2020 (Figure S1.1).[3] The state with the largest population size is Uttar Pradesh, accounting for approximately 17% of the total population in 2020.[3,4] The rurality of each state varies across India, with almost 90% of the population in 2011 living in a rural area in Himachal Pradesh and Bihar, compared to less than 3% in Delhi and Chandigarh (Figure S1.2).[5]

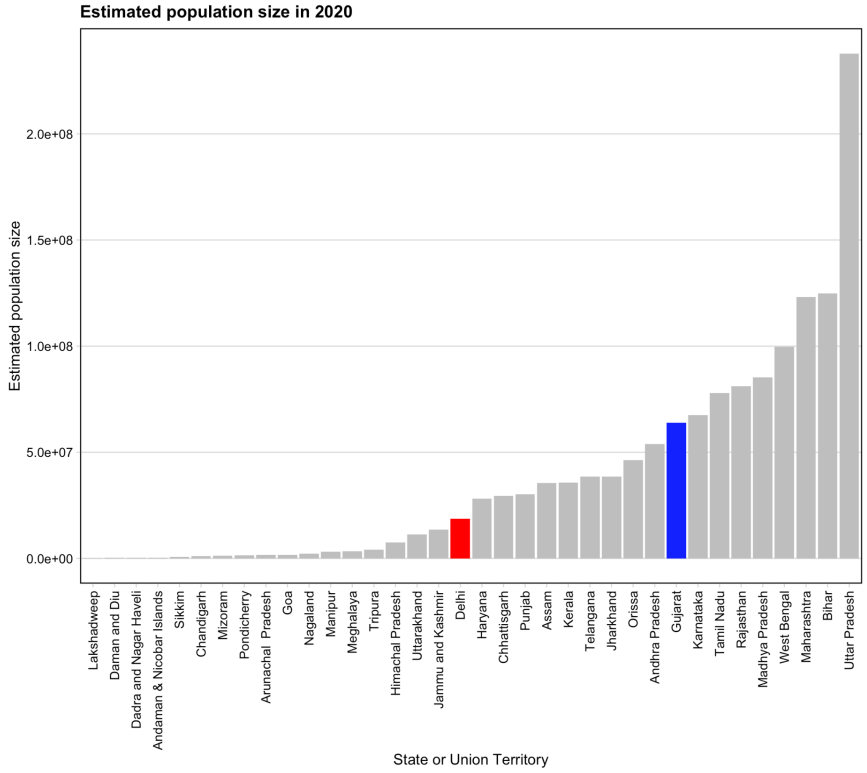


Figure S1.1 Estimated population size in 2020 by state and union territory. Delhi is highlighted in red, and Gujarat is highlighted in blue.[4]

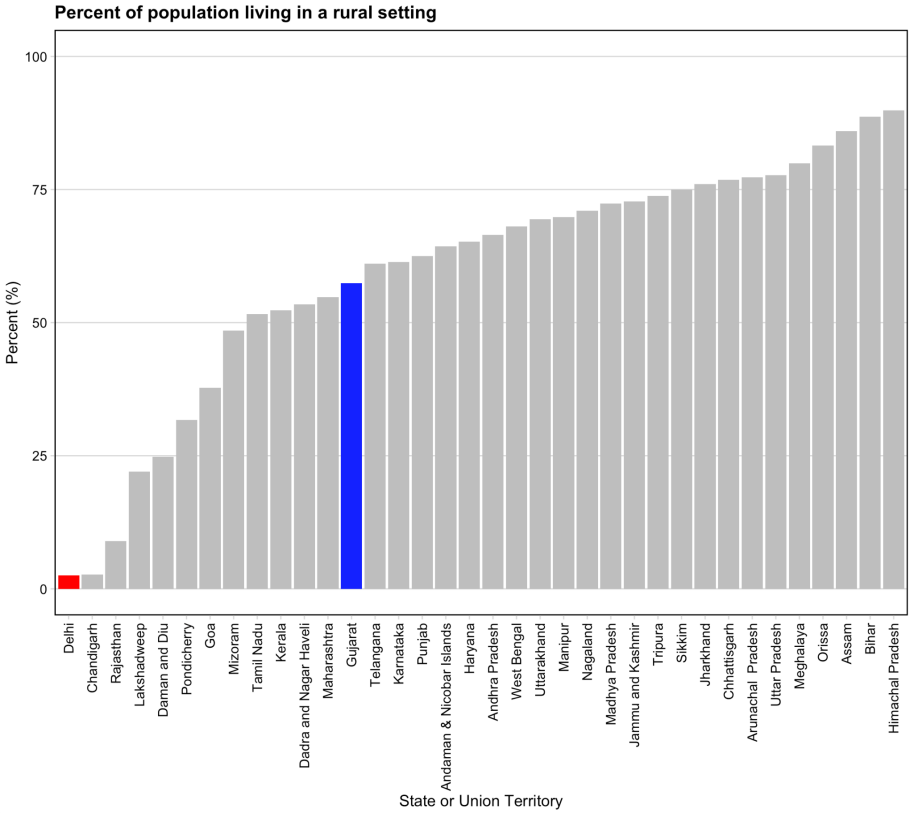


Figure S1.2 Percent of the population of each state and union territory living in a rural setting in 2011. Delhi is highlighted in red, and Gujarat is highlighted in blue.[5]

Financial and policy responsibility for the healthcare system falls to the federal government, while the state government is responsible for healthcare delivery.[6] Although tuberculosis treatment is freely available from the public sector, evidence has shown a large proportion of patients are choosing to access care from the private sector.[7–9] A 2019 study from Arinaminpathy et al. estimated that nationally, the percent of treatment months completed in the public sector was 36.0% (33.0, 39.0), ranging from 22.0% (17.0, 25.0) in Bihar to 73.0% (63.0, 79.0) in Himachal Pradesh.[7]

In terms of access to healthcare, there are large variations between and within states depending on the relative proportions of urban and rural communities.[10] States with an increased level of urbanisation have access to options in both the public and private sectors, whereas states are restricted by the limited availability of local healthcare options when rurality is increased.[10] For healthcare services specific to tuberculosis, a systematic review from 2015 investigated the quality of tuberculosis care provided in India, and found that they were often lacking in major areas, including baseline knowledge of tuberculosis symptoms and standard treatment protocol.[11]

The tuberculosis burden varies widely across India (Figure S1.3). The tuberculosis disease prevalence estimate for all ages was estimated at 312 (286–337) per 100,000 in India overall, but ranged by state from 137 (76–198) per 100,000 to 747 (510–984) per 100,000 (almost 5.5 times greater).[12]

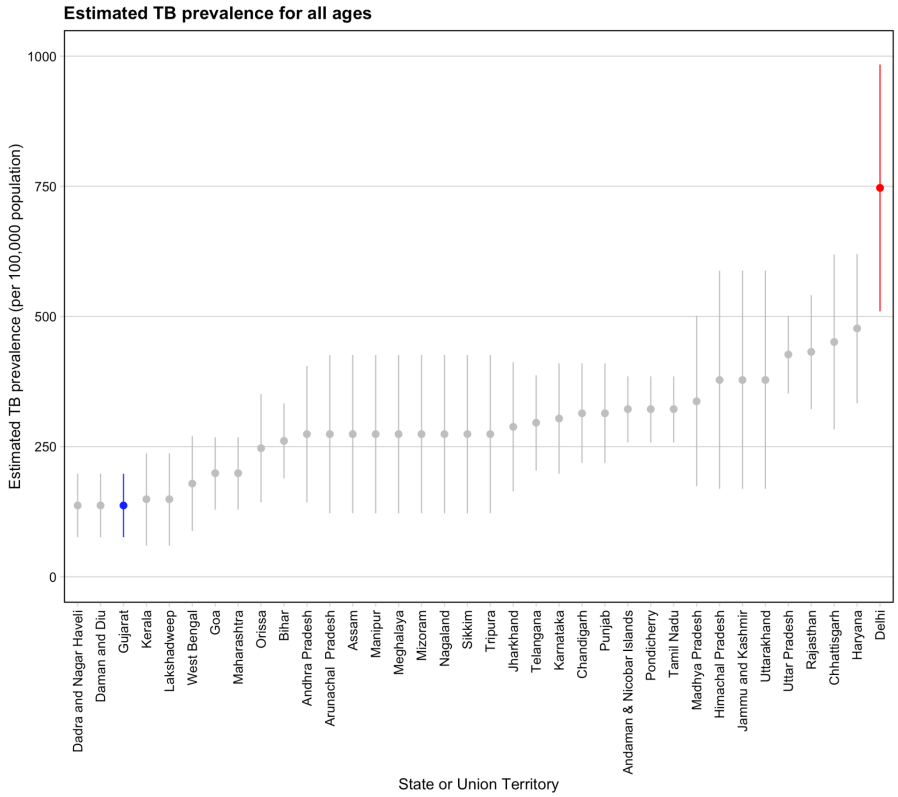


Figure S1.3 Estimated TB prevalence (per 100,000 population) for all ages by state and union territory.[12] Delhi is highlighted in red, and Gujarat is highlighted in blue.

[+] *Gujarat, Dadra and Nagar Haveli, and Daman and Diu were grouped together as one state group for estimating TB prevalence, and therefore have the same estimated value.*

Specifically modelling states and union territories within India will help to support the National Tuberculosis Elimination Program (NTEP) Sub-National Certification of Disease Free Status initiative introduced by the Government of India, which incentivises states and districts to reduce tuberculosis incidence rates. We chose to model Delhi and Gujarat to represent regions with extremes of the wide variation in epidemiology across India (highest and lowest prevalence estimate from the survey respectively), as well as additional distinct characteristics such as population sizes and levels of urbanisation to assess the possible influence of heterogeneity on proposed delivery strategies, as well as to extrapolate to other similar regions.

Delhi

The National Capital Territory of Delhi, or "Delhi", is a geographically small city and union territory located in the north of India. According to the 2011 census, Delhi had a population of almost 17 million—the 19th largest state or union territory in the country—with 97.5% of the population living in an urban setting.[5] By 2020, the estimated

population increased by 12% to almost 19 million.[4] In the recent National TB Prevalence survey in India conducted from 2019-2021, Delhi was estimated to have the highest prevalence per 100,000 population for adults at 534 (365–704) per 100,000 and the highest estimated tuberculosis prevalence for all ages at 747 (510–984) per 100,000.[12] In 2020, Delhi reported over 100,000 tuberculosis cases, with 35% of reported notifications seeking care in the private sector.

Gujarat

The state of Gujarat is located on the west coast of India. With an estimated 64 million people living in Gujarat in 2020, it is the 9th largest state by population.[4] Gujarat is increasingly becoming more urban, with around 50% of the population living in urban settings. In contrast to Delhi, Gujarat has one of the lowest estimated tuberculosis prevalence per 100,000 population for adults [141 (78–203) per 100,000], the lowest estimated tuberculosis prevalence per 100,000 population among all ages [137 (76–198) per 100,000], as well as the lowest estimate of the prevalence to notification ratio (0.91).[12] In 2020, Gujarat reported almost 145,000 tuberculosis cases, with 65% of reported notifications seeking care in the public sector. Gujarat was awarded Bronze in 2021 for reducing the incidence rate by 20% compared to 2015 estimates, and it has been reported that six districts out of 26 total have already made claims of disease free status under the Certification of Disease Free Status initiative.

2. Model structure and equations

We extended existing age-stratified compartmental differential equation models of tuberculosis, including dimensions for age, tuberculosis natural history and vaccination.[13,14] As in Clark et al., 2023, we modelled single age groups from age 0 through 79, one compartment for age 80–89 and one compartment for age 90–99. The natural history model structure (Section 2.1) and natural history model equations (Section 2.2) are identical to the supplementary material in Clark et al, 2023 and reproduced here without modification.

2.1 Natural history model structure

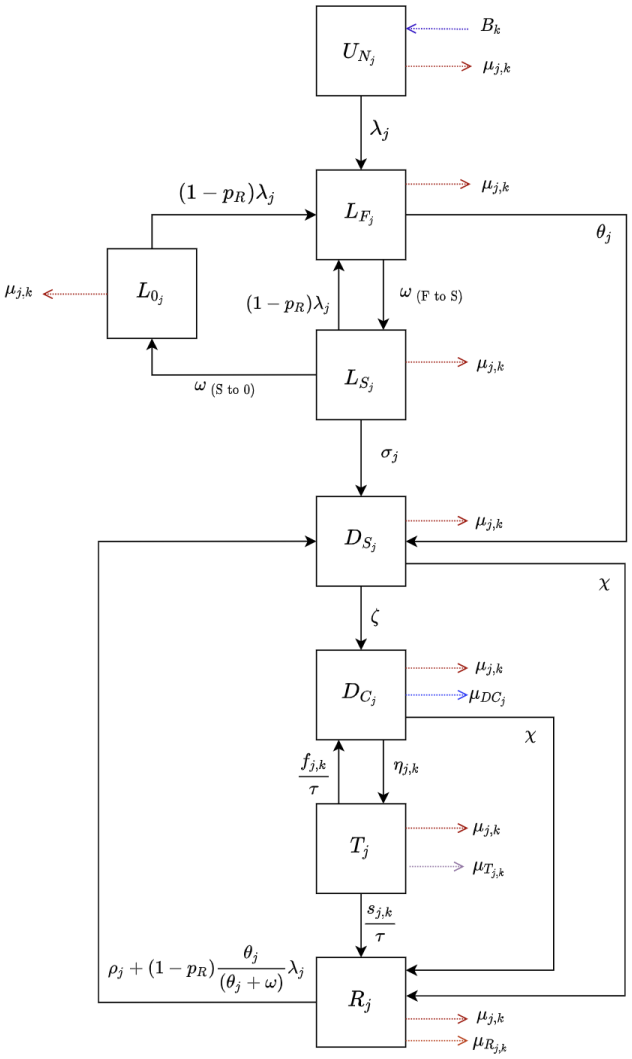


Figure S2.1 Tuberculosis natural history model structure

Subscript j represents parameters that vary by age, and subscript k represents parameters that vary over time.

Abbreviations: U_N = Uninfected-Naive; L_F = Latent-Fast; L_S = Latent-Slow; L_0 = Latent-Zero, D_S = Subclinical Disease; D_C = Clinical Disease; T = On-Treatment; R = Recovered.

A natural history structure with eight compartments in Figure S2.1 was created by adapting features of previous models, and has been described previously. The latency structure in this model demonstrates a progressive loss of ability to reactivate, with the reactivation rate in the Latent-Fast compartment greater than in Latent-Slow and greater still than in Latent-Zero, where we assume the rate of reactivation is 0. We do not explicitly have a self-clearance compartment. We assume that those in Latent-Fast can only fast progress to subclinical disease, or continue to remain latent and transition to Latent-Slow. There is no direct transition from Latent-Fast to Latent-Zero.

2.2 Natural history model equations

$Age\ j = 0$

$$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$$

$Age\ j \neq 0$

$$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_j}$$

$$\frac{dL_{F_j}}{dt} = \lambda_j U_{N_j} + (1-p_R)\lambda_j L_{0_j} + [(1-p_R)\lambda_j]L_{S_j} - (\omega_{FS} + \theta_j + \mu_{j,k})L_{F_j}$$

$$\frac{dL_{S_j}}{dt} = \omega_{FS} L_{F_j} - (\omega_{S0} + \sigma_j + (1-p_R)\lambda_j + \mu_{j,k})L_{S_j}$$

$$\frac{dL_{0_j}}{dt} = \omega_{S0} L_{S_j} - [(1-p_R)\lambda_j + \mu_{j,k}]L_{0_j}$$

$$\frac{dD_{S_j}}{dt} = \theta_j L_{F_j} + \sigma_j L_{S_j} + [\rho_j + (1-p_R)\frac{\theta_j}{\theta_j+\omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_j} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + \mu_{DC_j} + \mu_{j,k})D_{C_j}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k}+f_{j,k}}{\tau} + \mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [\rho_j + (1-p_R)\frac{\theta_j}{\theta_j+\omega}\lambda_j + \mu_{R_j} + \mu_{j,k}]R_j$$

3. Natural history

3.1 Natural history parameter values and data sources

Parameters used in the natural history model structure are provided in Table S3.1 below, along with their definitions, sources, and information on whether the parameter is fixed or varied (as well as whether they are varied by age or time) during calibration. Further details about how the age varying parameters are implemented are provided in section 3.2, and further details on parameters related to treatment are provided in section 3.3. The parameter ranges provided for the tuberculosis natural history parameters are priors fitted during calibration in a Bayesian analysis. We assume that all values within the prior range are equally likely. For certain natural history parameters that we believe will not vary within the country, we used the posterior distributions (95% uncertainty intervals) from the National India modelling study from Clark et al., 2023 as prior distributions for subnational modelling. The prior distributions for the National India model from Clark et al, 2023 were pre-specified based on literature review and reviewed as new data became available. Unless otherwise specified, we assume the same ranges for both Delhi and Gujarat.

Table S3.1 Description of natural history parameters used during calibration for Delhi and Gujarat

Description	Units	Symbol	Prior	Fixed or Varying During Calibration	Age Varying	Time Varying	Source
Births and deaths (excluding on-treatment mortality)							
Birth rate	Per year	B_k	Population estimates and projections as described in Section 4.3	Fixed	No	Yes	5,15
Background mortality rate	Per year	$\mu_{j,k}$	Calculated in the model from population estimates and projections	Fixed	Yes, age specific mortality rates from demographic dataset	Yes	5,15
Mortality rate for clinical tuberculosis disease	Per person per year	μ_{DC_j}	(0.124–0.177)	Varying	Yes, value for children is greater than value for adults	No	Posterior from the National India model[13]
Mortality rate post-tuberculosis disease	Per person per year	μ_{R_j}	0.22 × [(0.004–0.02)]	Fixed relationship	Yes because $\mu_{j,k}$ varies	Yes because $\mu_{j,k}$ varies	Posterior from the National India model[13]
Natural History							

Force of infection	Per year	λ_j	Fitted	Fixed Equation	Yes, age specific contact rates[16]	No	Calculated
Probability of transmission per infectious contact	-	p_T	(0–0.0068)	Varying	No	No	Assumed
Fraction of total tuberculosis that is extrapulmonary	-	ep	Delhi: 0.440 Gujarat: 0.179	Fixed	No	No	17–23
Infectiousness of subclinical relative to clinical tuberculosis	-	r	0.83	Fixed	No	No	24
Rate of fast progression to disease, by age	Per person per year	θ_j	(0.092–0.110)	Varying	Yes; Retain if value for children is less than value for adults.	No	Posterior from the National India model[13]
Rate from L_F to L_S	Per person per year	ω_{FS}	0.5	Fixed	No	No	Defined
Rate of reactivation from L_S, by age	Per person per year	σ	(0.00069–0.00112)	Varying	Yes; Retain if value for children is less than value for adults.	No	Posterior from the National India model[13]
Rate from L_S to L_0	Per person per year	ω_{S0}	(0.026–0.037)	Varying	No	No	Posterior from the National India model[13]
Rate of progression from D_S to D_C	Per person per year	ζ	(0.758–1.331)	Varying	No	No	Posterior from the National India model[13]
Rate of natural cure from D_C and D_S	Per person per year	χ	(0.109–0.188)	Varying	No	No	Posterior from the National India model[13]
Rate of relapse from R, by age	Per person per year	ρ_j	(0.015–0.023)	Varying	Yes; Retain if value for children is less than value for adults.	No	Posterior from the National India model[13]
Protection Parameters							
Protection from reinfection L_S, L_F, L_0, R	-	p_R	(0.616–0.779)	Varying	No	No	Posterior from the National India model[13]

3.2 Operationalising age varying parameters

We assume that aspects of tuberculosis natural history and mortality vary by age as in Clark et al., 2023.[13] This is implemented by stratifying certain natural history parameters by age and applying age-specific prior ranges and relative constraints during calibration.[25] The following table describes the method used to operationalise the age varying differences in parameters between adults, defined as all ages greater than and equal to 15, and children, defined as all ages less than 15. For the rate per year of reactivation, relapse, and fast progression to tuberculosis disease, we assume that the rate for children is less than that for adults. For mortality rates, we assume the opposite: the rate for children is higher than that for adults.

Table S3.2 How age varying parameters are operationalised

Parameter	Range	Age Varying Description	Age Scaling Parameter	Adults (θ_{A15})	Children (θ_{A0})
θ_j Rate per year of fast progression	(0.092–0.110)	Retain if value for children is **less** than value for adults	Sample j_1 from (0.073–0.66)	Sample θ_{A15} from (0.092–0.110)	$\max(0.092, \theta_{A15} \times j_1)$
σ_j Rate per year of reactivation	(0.00069–0.00112)	Retain if value for children is **less** than value for adults	Sample j_2 from (0.340–0.962)	Sample σ_{A15} from (0.00069–0.00112)	$\max(0.00069, \sigma_{A15} \times j_2)$
ρ_j Rate per year of relapse	(0.015–0.023)	Retain if value for children is **less** than value for adults	Sample j_3 from (0.371–0.969)	Sample ρ_{A15} from (0.015–0.023)	$\max(0.015, \rho_{A15} \times j_3)$
μ_{DC_j} Clinical TB mortality rate per year	(0.124–0.177)	Retain if value for children is **greater** than value for adults	Sample S_{Age} from (0.597–0.967)	$\mu_{DC_{A0}} \times S_{Age}$	Sample $\mu_{DC_{A0}}$ from (0.124–0.177)
$\mu_{T_j} = \frac{\kappa_j}{\tau}$ On-treatment mortality rate per year	DEL: (0–0.244) GUJ: (0–0.283)	Retain if value for children is **greater** than value for adults	Sample S_{Age} from (0.597–0.967)	$\frac{\kappa_{A0}}{\tau} \times S_{Age}$	Sample κ_{A0} from: Delhi: (0–0.122) Gujarat: (0–0.142)

3.3 Tuberculosis treatment

Steps for calculating treatment initiation, treatment completion, non-completion, and mortality rates are described in the Supplementary Material for Clark et. al, 2023, with Delhi and Gujarat specific adjustments described below.

Treatment initiation

We assumed that the steps for treatment initiation in Delhi were identical to Clark et al., 2023. We allowed the upper bound of the prior range for the treatment initiation rate in 2019 (eta) for Gujarat to be extended from 1 to 2 to allow for greater healthcare seeking (more than 100% of those with prevalent tuberculosis to be treated within one year).

Treatment outcomes

Region-specific treatment completion, non-completion, and mortality fractions were calculated as a weighted average of public and private sector reported estimates from the India TB Reports from 2018–2021.[21–23,26] We used the India TB Report 2022 to determine how many notifications were expected to be reported from the public and private sector for Delhi and Gujarat, and determined the proportion of treatment expected to occur in each sector (Delhi: 73% in the public sector, 27% in the private sector; Gujarat: 66% in the public sector, 34% in the private sector). We assumed that this proportion was constant over time. We then calculated the fraction of treatment completion, non-completion, and mortality for each region for the public and private sector separately, and then as a weighted average to obtain one estimate of each outcome for each region.

The weighted average of the treatment completion and non-completion estimates were used to calculate the SFR, which represented the ratio between treatment completions to the sum of treatment completions and non-completions. This was estimated to be 0.941 in Delhi and 0.949 in Gujarat. The weighted average of the on-treatment mortality was multiplied by 2 to give an upper bound of the range for kappa. This was estimated to be 0.122 in Delhi and 0.142 in Gujarat.

Table S3.3 Calculating treatment outcome parameter values for adults and children

Parameter	Adults	Children
κ_j On-treatment mortality fraction	$\kappa_{A0} \times S_{Age}$	Sample κ_{A0} from: Delhi: (0–0.122) Gujarat: (0–0.142)
s_j On-treatment completion fraction	$(1-\kappa_{A15})\mathrm{SFR}$	$(1-\kappa_{A0})\mathrm{SFR}$
f_j On-treatment non-completion fraction	$(1-\kappa_{A15})(1-\mathrm{SFR})$	$(1-\kappa_{A0})(1-\mathrm{SFR})$

4. Model simulation and calibration

4.1 Model simulation

Model simulation was as in both Clark et al., 2023 studies, reproduced here with some small modifications.[13,14] We specified a system of ordinary differential equations defining the derivatives with respect to time of a set of state variables, to simulate the tuberculosis epidemic between 1900 and 2050. We initialised the simulation by distributing the population between the eight tuberculosis natural history states using a fitted parameter representing the proportion of the population uninfected at the start of the simulation. For each year of the simulation (1900–2050), our models are designed to exactly match the age-specific population estimates and projections.

4.2 Model calibration

For this subnational modelling analysis of Delhi and Gujarat, we followed the same modelling approach as in both Clark et al., 2023 studies, reproduced here with some small modifications.[13,14]

Broadly, this was as follows:

1. Construct a mechanistic model
2. Calibrate the model by identifying areas of the input parameter space where the output of the mechanistic model was consistent with the historical epidemiologic data
3. Use the calibrated model to simulate and predict future tuberculosis epidemiology and model new vaccines

In the context of this analysis, step 1 was achieved by creating the compartment differential equation model as specified in Section 2. For step 2, we independently calibrated a model by identifying areas of the parameter space that made the output of the model match the corresponding calibration targets (Table S4.1). Further details on the sources for the calibration targets and any additional modifications are in the subsequent sections.

The model was fitted to the calibration targets using history matching with emulation, a method that allows us to explore high-dimensional parameter spaces efficiently and robustly.[27–30] History matching progresses as a series of iterations, called waves, where implausible areas of the parameter space, i.e., areas that are unable to give a match between the model output (e.g., the predicted disease prevalence by the model) and the empirical data (e.g., the disease prevalence calibration target from the National TB Prevalence Survey), are found and discarded. In order to identify implausible parameter sets, emulators, which are statistical approximations of model outputs that are built using a modest number of model runs, are used. Emulators provide an estimate of the value of the model at any parameter set of interest, with the advantage that they are orders of magnitude faster than the model.

History matching with emulation, implemented through the *hmer* package in R,[31,32] considerably reduced the size of the parameter space to investigate. Rejection sampling was then performed on the reduced space to identify at least

1000 parameter sets that matched all targets. Once we had obtained 1000 parameter sets that produced output consistent with the calibration targets, we used those parameter sets with the mechanistic model to simulate the future (step 3) for each region.

We calibrated Delhi to three calibration targets and, separately, Gujarat to four calibration targets based on the differences in regionally available data. Calibration targets are in Table S4.1 below.

Table S4.1 Calibration targets for Delhi and Gujarat

Calibration Target	Year	Delhi	Gujarat
Tuberculosis disease prevalence for all ages (per 100,000 population)[12]	2021	747 (510–984)	137 (76–198)
Tuberculosis disease prevalence for adults (per 100,000 population)	2011	*NA*	383 (315–451)
Tuberculosis case notification rate for all forms and all ages (per 100,000 population) with 20% bounds[33]	2021	536 (429–644)	137 (110–165)
Subclinical TB prevalence ratio[34]	2020	0.564 (0.428–0.685)	

Adjustments to calibration targets

The notification rate from the India TB Report 2022 for Gujarat was 204 per 100,000 population. When comparing this estimate to the disease prevalence estimate from the National Tuberculosis Prevalence survey, a higher rate of the population was treated for tuberculosis than currently had prevalent disease (204 per 100,000 notifications compared to 137 per 100,000 with prevalent disease). We know that when healthcare services are improved and the prevalence of tuberculosis decreased, more false positives are expected. Therefore, we adjusted the notification rate target in Gujarat down to account for the possibility of false positives. As only 35% of the reported notifications in Gujarat were bacteriologically confirmed, we adjusted the reported notification rate (204 per 100,000 population) relative to the proportion of reported notifications that were bacteriologically confirmed in Delhi (52%), to obtain a new case notification target of 137 per 100,000.

As described in Section 3, we also allowed healthcare seeking to increase in Gujarat, by increasing the "eta" parameter to allow more than 100% of those with prevalent disease to be treated within one year. We included both adjustments (adjusting the case notification rate target down and increasing the treatment seeking parameter) as it is unknown which is correct, and we allowed the model to determine the best fit. We do not believe these modifications would be representative of Delhi, and therefore are only included for Gujarat.

4.3 Subnational demography

United Nations Population Data and Projections were available for India overall for single ages and years from 1950–2100, but this level of detailed data was not available for Delhi and Gujarat. We combined all available data to ensure we represented the total population size and age distribution as accurately as possible, as these two aspects may play an important role in vaccine impact estimation.

Total Population Size

To obtain accurate representations of total population size, we first collated all available demographic data for Delhi, and Gujarat. From the Government of India Census data, we obtained single age numbers (1000s) in 1991, 2001 and 2011. From the most recent Government of India census (2011), we obtained single age projections (1000s) for ages 5 to 23 in years 2016, 2021, 2026, 2031, and 2036, 5 year age group projections (1000s) in years 2016, 2021, 2026, 2031, and 2036 and total population projections (1000s) in years 2011 to 2036.

The total population estimates and projections for Delhi and Gujarat used in the model simulation are shown in Figure S4.1. Total population estimates were available from census data in 1991, 2001, 2011, and total population projections were available for 2011–2036. We used a linear interpolation between the estimates in 1991 and 2001 for the years in between, and similarly, a linear interpolation between the estimates in 2001 and 2011 for the years in between. These data and projections are represented on Figure S4.1 with the red and blue lines for Delhi and Gujarat respectively. The dashed grey lines represent projecting backwards and forwards from the data by holding the ratio between the population in Delhi or Gujarat and the population in India constant. To explain the method in further detail, the earliest data point available was the total population size in 1991. Dividing the total population size in Delhi or Gujarat by the total population size in India overall gives us a ratio we call P_D and P_G respectively. We then multiplied the population size in India from 1950–1990 by these ratios to obtain an estimate of the total population size in Delhi and Gujarat. We used the same method with the latest available projection (2036) to project forward.

Age Distribution

To accurately represent the age distribution in Delhi and Gujarat, we compared the age distribution projections in 2011, 2026, and 2036 for India, Delhi, and Gujarat from the 2011 census (Figure S4.2). We assumed that the distribution was similar enough to use the same age composition for Gujarat as in India, but observed a higher proportion of adults in Delhi. Therefore, the age distribution in 2011 for Delhi was applied to the total estimated population for all years leading up to 2011, and similarly, the age distribution in 2036 was applied for all years projecting forward from 2036. For the years between 2011 and 2036, we applied a linear interpolation between the age compositions in 2011 and 2026, and the age compositions in 2026 and 2036.

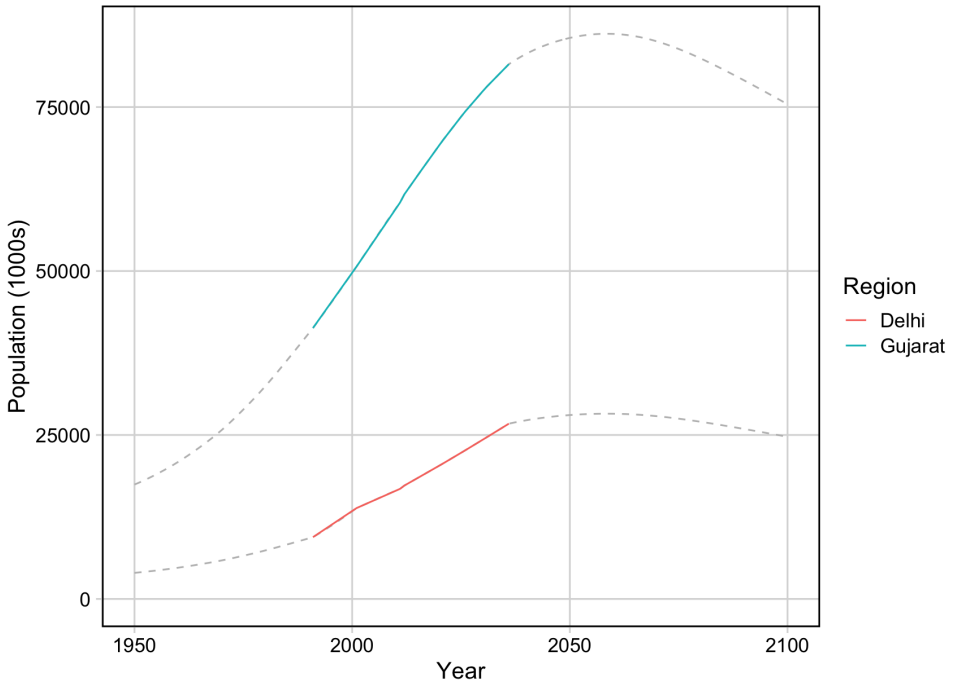


Figure S4.1 **Total population estimates and projections for Delhi and Gujarat used in model simulation**

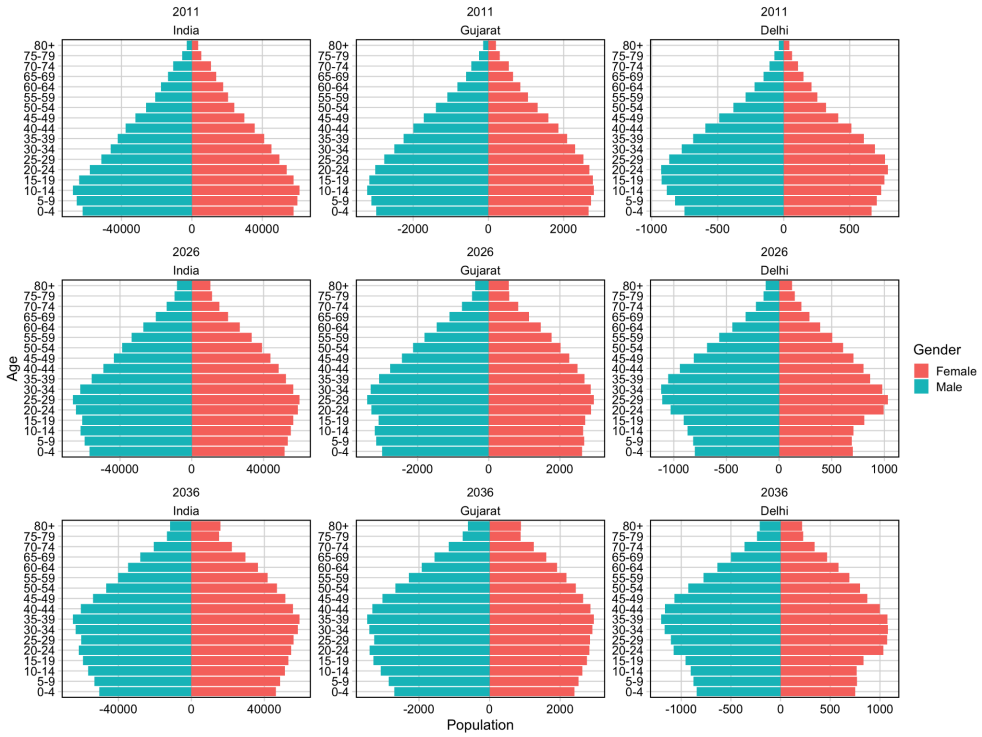


Figure S4.2 **Age structure in 2011, 2026, and 2036 for India, Gujarat, and Delhi**

5. Policy scenarios

Methods for introducing policy scenarios in Delhi and Gujarat are as in Clark et al., 2023, reproduced here with some small modifications.[13]

5.1 No-new-vaccine baseline

The primary no-new-vaccine simulated was the no-new-vaccine baseline, which assumed non-vaccine tuberculosis interventions continue at current levels into the future. As reported country-level data includes the high coverage levels of neonatal BCG vaccination, this was not explicitly modelled. We assumed that BCG vaccination would not be discontinued over the model time horizon.

5.2 Vaccine delivery

Two recently completed phase IIb trials have demonstrated encouraging efficacy results. The M72/AS01$_E$ candidate vaccine is a subunit vaccine for which results from a completed Phase IIb trial were published at the end of 2019.[35] After three years of follow-up, the efficacy of M72/AS01$_E$ at preventing disease in latently infected adults from South Africa, Zambia, and Kenya was estimated at 49.7% (95% confidence interval = 2.1–74.2).[35] To confirm this finding, a larger, Phase III follow-up study which includes participants who are uninfected, adolescents, as well as those living with HIV to assess safety and immunogenicity in these populations, is anticipated to begin in early 2024.

BCG-revaccination (administering a second dose of BCG to those who were vaccinated neonatally) was previously implemented in many countries, however evidence did not support the effectiveness of this practice. Interest in BCG-revaccination has recently been renewed following results from a trial for the vaccine candidate, H4:IC31. BCG-revaccination was assessed as a third parallel arm alongside H4:IC31 and a placebo in a pre-infection population in South Africa, and although neither vaccine appeared efficacious at preventing infection, BCG-revaccination appeared efficacious at preventing sustained infection (defined as three consecutive positive tests after day 84 of the trial) with an efficacy of 45.4% (6.4–68.1).[36] A larger trial of BCG-revaccination versus placebo in 1800 healthy adolescents from across South Africa is now underway to verify this finding.

We evaluated introducing vaccines with M72/AS01$_E$ and BCG-revaccination characteristics compared to the no-new-vaccine baseline as described in the subsequent sections.

5.2.1 Vaccine scenarios

For each vaccine product, we established one *Basecase* vaccine scenario based on clinical trial data and expert opinion. We then varied vaccine product and delivery scenarios as univariate scenario analyses from the *Basecase* scenario as described in Table S5.1. Vaccine delivery assumptions and model structure are identical to those described in Section 4.2 and 4.3 Clark et al., 2023.[13]

Table S5.1 M72/AS01$_E$ and BCG-revaccination *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios* for Delhi and Gujarat

Characteristic	M72/AS01$_E$		BCG-revaccination	
	Basecase	**Univariate scenario analyses**	**Basecase**	**Univariate scenario analyses**
Policy Scenarios				
Age targeting	Routine age 15, campaign for ages 16–34	*Older Ages:* Routine age 17, campaign for ages 18–55 *All Adults:* Routine age 18, campaign for ages 19+	Routine age 10, campaign for ages 11–18	*Older Ages:* Routine age 15, campaign for ages 16–34 *All Adults:* Routine age 18, campaign for ages 19+
Vaccine Characteristic and Coverage Scenarios				
Efficacy	50%	60%, 70%	45%	70%
Mechanism of effect	Prevents disease	Prevents infection and disease	Prevents infection	Prevents infection and disease
Infection status at time of vaccination required for efficacy	Any infection (current / no current infection)	Current infection only	No current infection only	Any infection (current / no current infection)
Duration of protection	10 years	5, 15, 20	10 years	5, 15, 20
Introduction year	2030	2036	2025	2031
Achieved coverage	Medium: 80% age 15, 70% campaign	Low: 70% routine, 50% campaign High: 90% routine, 90% campaign	Medium: 80% routine, 80% campaign	Low: 70% routine, 70% campaign High: 90% routine, 90% campaign

6. Economic analysis methods

We used the same economic analysis methods as in Clark et al., 2023, reproduced here with minor modifications.[13] Before undertaking this work, we established an economic analysis plan, involving stakeholders and government officials to ensure we had incorporated all necessary information and planned to report on all key outcomes, to outline the methods used in this work. This is summarised below.

6.1 Calculation of disability-adjusted life years

We calculated the difference in total disability-adjusted life years (DALYs) from vaccine introduction to 2050 for each scenario compared to the no-new-vaccine baseline. We used the disability weight for tuberculosis disease from the Global Burden of Disease 2019 study,[37] and age-specific life expectancy estimates for India overall from the United Nations Development Programme.[38] To incorporate parameter uncertainty in years lost due to disability weight estimates, we made 1000 draws from disability weight uncertainty ranges.

6.2 Tuberculosis-related cost model

We estimated health system unit costs, patient costs and productivity losses based on a scoping review of published literature. For the tuberculosis programme, we obtained unit costs for drug-susceptible and drug-resistant tuberculosis treatment and diagnostic costs, which are provided in Table S6.1. Uncertainty in cost estimates is characterised through gamma distributions around plausible unit cost estimates in a probabilistic sensitivity analysis.

6.3 Vaccine introduction costs

There was considerable uncertainty in the cost of delivering a vaccine, including the price of vaccine compounds and programmatic delivery among adolescents. Based on expert opinion from funders, for the M72/AS01E vaccine we assume a $2.50 per-dose vaccination price with two doses per course assumed in the Basecase. Based on the average estimated BCG price from 2020–2023 from UNICEF,[39] the vaccine price per dose for BCG-revaccination was set at $0.17, with one dose assumed per course.

Due to uncertainty in unit costs of vaccine supply and introduction among populations who may not typically receive large-scale mass vaccination, we make several assumptions around costs to supply and introduction of vaccines. One-time vaccine introduction costs are included in years where there is a campaign and represent non-recurring costs such as establishing infrastructure and providing training for healthcare professionals. The costs were assumed to be $2.40 (1.20–4.80) per total targeted age group population size (as opposed to the actual number of recipients) based on the vaccine introduction support policy of Gavi, the Vaccine Alliance.[40] Vaccine delivery was assumed to be $2.50 (1.00–5.00) per dose, with a further $0.11 (0.06–0.22) supply costs per dose.

In Clark et al., 2023, the cost of recipient vaccination time for India was $0.94 (0.13–1.52), which was calculated by multiplying a wage proxy of GDP per capita for India by an estimate of the time required for vaccination. To represent potential differences in the cost of recipient vaccination time between Delhi and Gujarat due to differences in urban and rural access to healthcare, we included a multiplier on the cost of recipient vaccination time estimate for Delhi

which was informed by the average distance to a health facility from the District Level Household and Facility Survey 2007-08.[41] The average distance to a health facility for Gujarat was similar to India overall, and therefore we used the same estimate. For Delhi, the average distance to a health facility was much lower, and therefore we included a multiplier equal to 0.308 on the sampled estimate. We assume a 5% wastage rate.

For each year in the five-year scale up, the vaccination cost is calculated as:
Vaccination cost = (one time introduction costs) × (targeted age group population size)× 0.2 + (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For each year where there is a repeat campaign, the vaccination cost is calculated as:
Vaccination cost = (one time introduction costs) × (targeted age group population size) + (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For each year where there is only routine delivery of the vaccine, the vaccination cost is calculated as:
Vaccination cost = (number of people vaccinated) × (number of doses) × (vaccine price + vaccine supply costs + cost of delivery) × (1 + wastage)

For the vaccination cost from the societal perspective, the patient time cost of vaccination is added as a multiplier to the number of doses, and therefore included in the equation along with vaccine price, vaccine supply costs, and the cost of delivery.

Table S6.1 Tuberculosis testing, diagnostic, and vaccination related cost inputs

Unit Cost	Estimate	Lower Bound	Upper Bound	Sources
Unit cost of testing/diagnosis for drug-susceptible cases per person	$22.45	$18.37	$26.53	42
Unit cost of testing/diagnosis for drug-resistant cases per person	$24.36	$5.04	$117.81	43
Unit cost of treatment for drug-susceptible cases per person	$317.00	$254.00	$374.00	44
Unit cost of treatment for drug-resistant cases per person	$3,891.00	$3,382.00	$4,401.00	45
Non-medical patient cost per drug-susceptible tuberculosis disease episode (including transportation) per person	$51.25	$22.12	$76.94	46,47
Indirect patient cost per drug-susceptible tuberculosis disease episode (time spent on treatment and transport × wage) per person	$117.01	$24.04	$460.24	47,48
Non-medical patient cost per drug-resistant tuberculosis disease episode (including transportation) per person	$143.49	$61.95	$215.42	46,47
Indirect patient cost per drug-resistant tuberculosis disease episode (time spent on treatment and transport × wage) per person	$327.63	$67.30	$1,288.66	47,48
Recurrent vaccine delivery cost per person per dose	$2.50	$1.00	$5.00	40
One-time vaccine introduction costs per targeted person	$2.40	$1.20	$4.80	40
Vaccine supply costs per person per dose	$0.11	$0.06	$0.22	49
Cost of vaccination time per person per dose	$0.94	$0.13	$1.52	50,51

6.4 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 2025 (when vaccination began) at 3% per year, per guidelines.[52] We measured cost-effectiveness by 2050 against three India specific cost thresholds: 1x gross domestic product (GDP) per-capita (US$1,928), and two country-level opportunity cost thresholds defined by Ochalek et al [the upper (US$443), and lower (US$328) bounds].[53]

6.5 Total costs from the health-system and societal perspectives

The following costs are included in the health-system perspective:

- Vaccine costs: One-time vaccine introduction costs, recurring vaccine delivery costs, vaccine price per dose, and supply costs
- Cost of testing and diagnosis for drug-susceptible and drug-resistant cases
- Cost of treatment for drug-susceptible and drug-resistant cases

In addition to the costs from the health-system perspective, costs from the societal perspective include:

- Vaccine costs: Patient time cost for vaccination
- Non-medical patient costs (including transportation) for drug-susceptible and drug-resistant cases
- Indirect patient costs for drug-susceptible and drug-resistant cases

7. Health impact outcomes

The following measures were calculated for each vaccine scenario as the median and 95% uncertainty range:

- Percent incidence rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Percent mortality rate reduction in 2050 for each vaccine scenario compared to the estimated value in 2050 by *No-New-Vaccine* baseline
- Cumulative cases averted for each vaccine scenario between 2025 and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative deaths averted for each vaccine scenario between 2025 and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years
- Cumulative treatments averted for each vaccine scenario between 2025 and 2050 compared to the cumulative number of cases estimated by the *No-New-Vaccine* baseline between the corresponding years

SUPPLEMENTARY RESULTS

8. No-new-vaccine baseline

8.1 No-new-vaccine baseline calibration

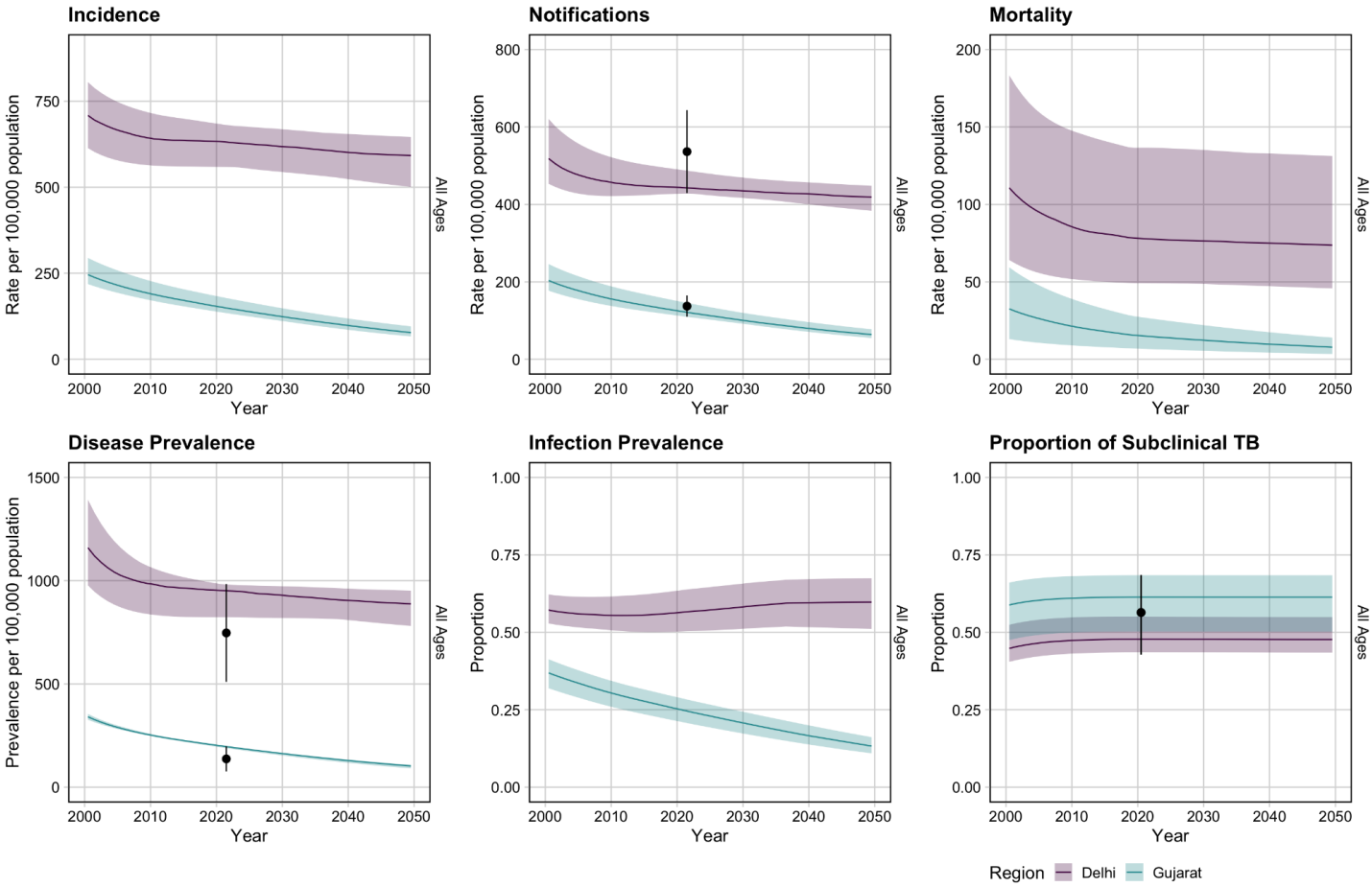


Figure S8.1 Baseline no-new-vaccine trends from 2000–2050 for all ages for Delhi and Gujarat

The trend line indicates the median modelled output with 95% uncertainty in shaded. The black dot and vertical line is the calibration target from Table S4.1.

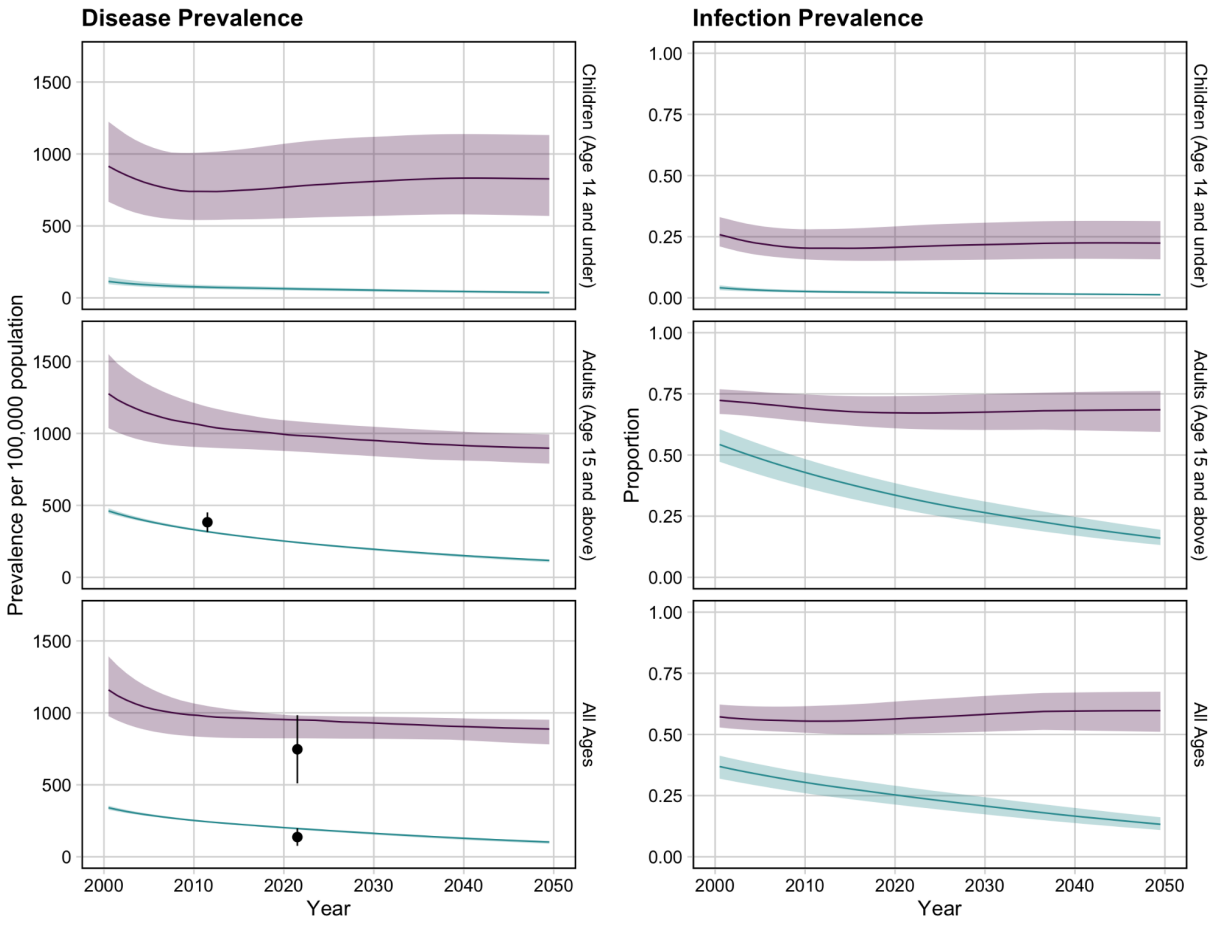


Figure S8.2 Age-specific trends of tuberculosis disease and infection prevalence in Delhi and Gujarat

8.2 Posterior distributions

Posterior distribution for the 1000 parameter sets used for vaccine impact estimation are in Figure S8.3 for Delhi and Figure S8.4 for Gujarat.

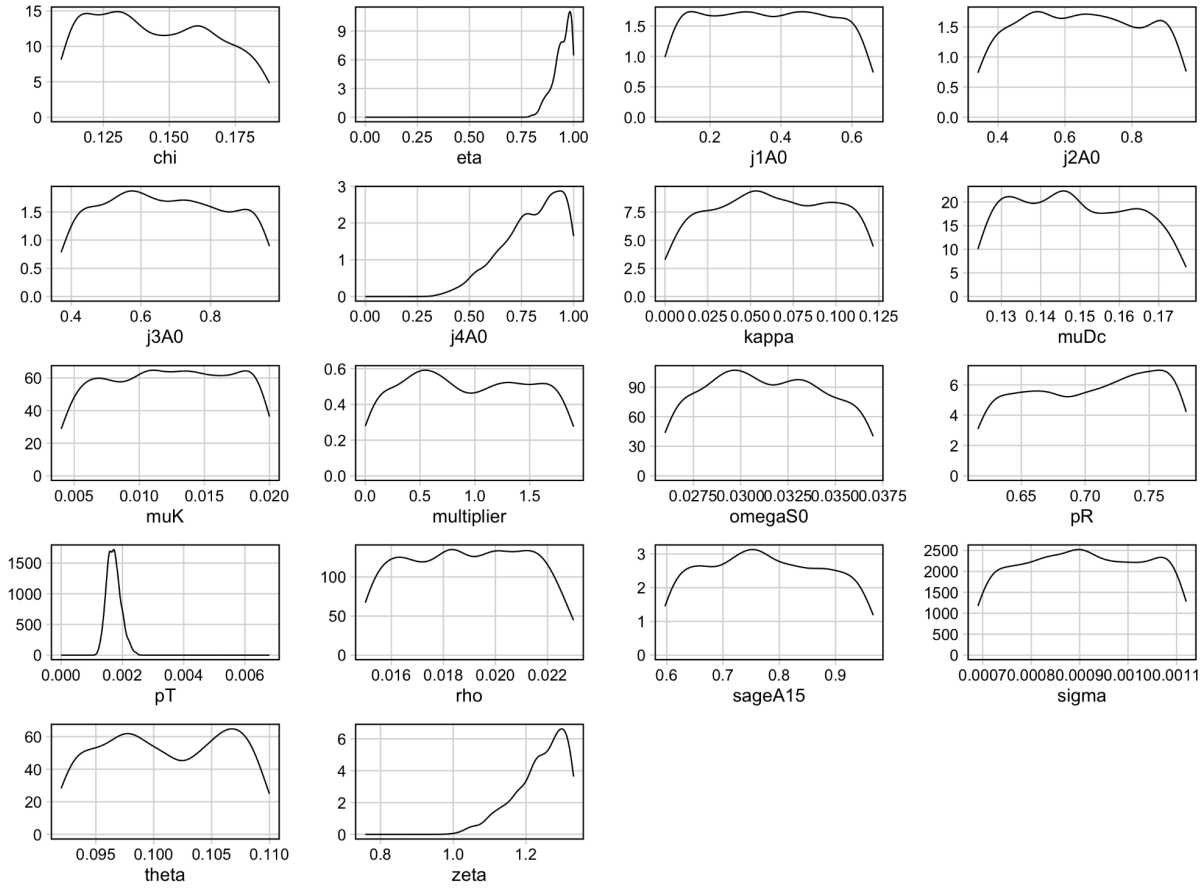


Figure S8.3 Posterior distributions for the 1000 parameter sets of the 18 parameters varied during calibration for Delhi

Parameters are plotted on their prior distributions. Definitions: chi = rate of natural cure, eta = rate of treatment initiation, j1A0 = age multiplier for rate of fast progression (theta), j2A0 = age multiplier for rate of reactivation (sigma), j3A0 = age multiplier for rate of relapse (rho), j4A0 = age multiplier for rate of treatment initiation, kappa = on-treatment mortality fraction, muDc = rate of clinical disease mortality, muK = rate of background mortality for increased mortality rate from the Recovered compartment, multiplier = the multiplier to see the initial distribution of the population into the natural history compartments, omegaS0 = rate of progression between Latent-Slow and Latent-Zero, pR = protection from reinfection for those in the Latency or Recovered compartments, pT = rate of transmission, rho = rate of relapse, sageA15 = age multiplier for mortality rates, sigma = rate of reactivation, theta = rate of fast progression following infection, zeta = rate of progression from subclinical to clinical disease compartments.

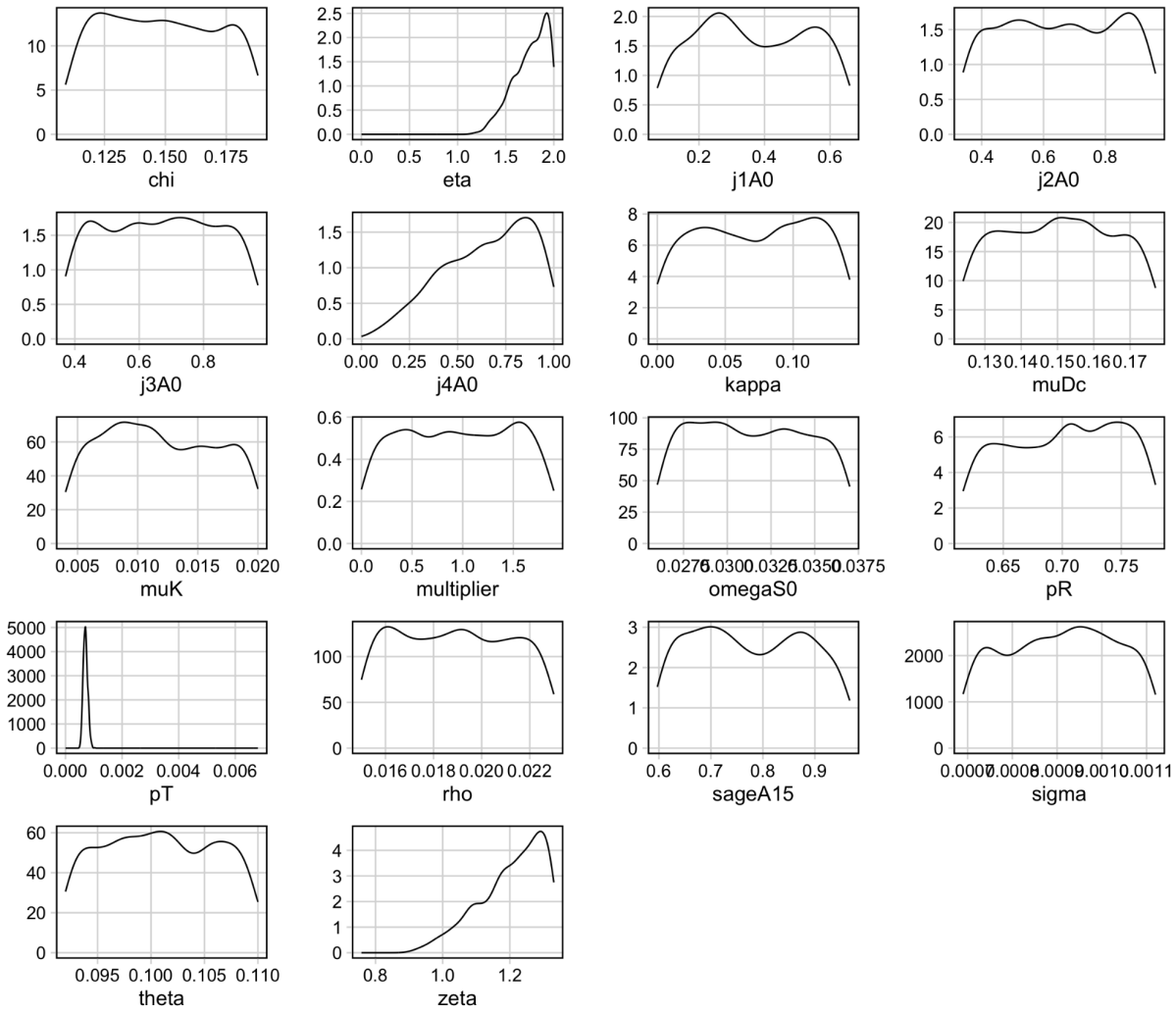


Figure S8.4 Posterior distributions for the 1000 parameter sets of the 18 parameters varied during calibration for Gujarat

Parameters are plotted on their prior distributions. Definitions: chi = rate of natural cure, eta = rate of treatment initiation, j1A0 = age multiplier for rate of fast progression (theta), j2A0 = age multiplier for rate of reactivation (sigma), j3A0 = age multiplier for rate of relapse (rho), j4A0 = age multiplier for rate of treatment initiation, kappa = on-treatment mortality fraction, muDc = rate of clinical disease mortality, muK = rate of background mortality for increased mortality rate from the Recovered compartment, multiplier = the multiplier to see the initial distribution of the population into the natural history compartments, omegaS0 = rate of progression between Latent-Slow and Latent-Zero, pR = protection from reinfection for those in the Latency or Recovered compartments, pT = rate of transmission, rho = rate of relapse, sageA15 = age multiplier for mortality rates, sigma = rate of reactivation, theta = rate of fast progression following infection, zeta = rate of progression from subclinical to clinical disease compartments.

9. Health impact results

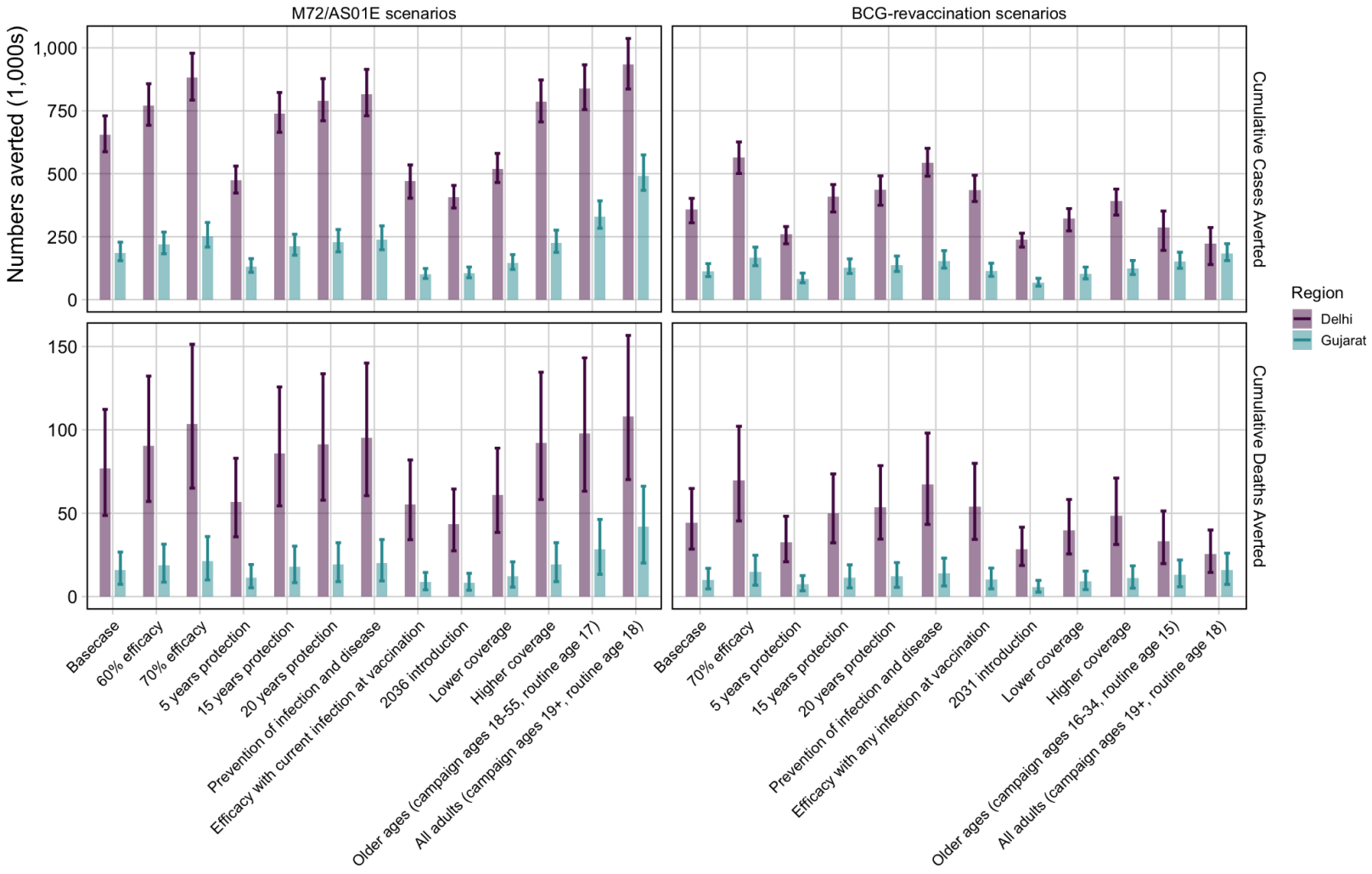


Figure S9.1 Cumulative cases and deaths averted by vaccine scenarios in Delhi (purple) and Gujarat (blue)

Table S9.1 Cumulative cases and deaths averted between 2025–2050 and rate reductions in 2050 for the vaccine scenarios compared to the no-new-vaccine baseline

Scenario	Cumulative cases averted between 2025–2050 (1000s)		Cumulative deaths averted between 2025–2050 (1000s)		Incidence rate reduction in 2050 (%)		Mortality rate reduction in 2050 (%)	
	Delhi	Gujarat	Delhi	Gujarat	Delhi	Gujarat	Delhi	Gujarat
M72/AS01$_E$ scenarios								
Basecase	655.2 (587.4–729.8)	186.1 (154.6–228.4)	76.9 (48.7–112.3)	15.9 (7.4–26.7)	26.1 (22.8–29.0)	16.4 (14.5–18.6)	26.7 (23.4–29.5)	16.8 (14.9–18.9)
60% efficacy	771.1 (692.2–857.2)	219 (182.2–268.3)	90.5 (57.1–132.2)	18.7 (8.7–31.5)	30.7 (27.0–33.8)	19.2 (16.9–21.6)	31.3 (27.5–34.4)	19.6 (17.4–21.9)
70% efficacy	881.3 (792.1–978.7)	250.6 (208.8–306.3)	103.6 (65.1–151.3)	21.4 (10.0–36)	35.0 (31.0–38.3)	21.7 (19.3–24.4)	35.6 (31.5–38.9)	22.2 (19.8–24.8)
5 years protection	474.4 (423.5–530.5)	131.6 (108.8–162.6)	56.8 (35.8–83.0)	11.4 (5.3–19.3)	16.3 (13.8–18.4)	9.8 (8.5–11.3)	17.3 (14.8–19.5)	10.4 (9.0–11.8)
15 years protection	740.0 (664.6–822.8)	212.3 (176.6–259.9)	86.0 (54.4–125.7)	18.0 (8.4–30.3)	31.3 (27.6–34.3)	20.0 (17.7–22.4)	31.4 (27.7–34.4)	20.1 (17.9–22.5)
20 years protection	790.1 (710.3–877.8)	227.9 (190–278.7)	91.4 (57.8–133.6)	19.2 (9–32.3)	34.4 (30.5–37.5)	22.2 (19.8–24.8)	34.1 (30.2–37.4)	22.1 (19.9–24.7)
Efficacy with current infection at vaccination	471.4 (402.9–534.9)	101 (84.2–123.6)	55.3 (34.1–82.0)	8.7 (4.1–14.5)	17.0 (15.7–18.8)	7.7 (6.9–8.5)	17.8 (16.4–19.6)	8.0 (7.2–8.8)
Prevention of infection and disease	816.5 (729.9–914.4)	238.4 (198.2–293.1)	95.4 (60.5–140.1)	20.3 (9.4–34.2)	33.3 (28.7–37.2)	21.7 (19.2–24.5)	33.8 (29.1–37.6)	22.0 (19.5–24.7)
2036 introduction	407.7 (363.7–453.5)	105 (86.8–129.6)	43.5 (27.4–64.5)	8.3 (3.9–13.9)	26.8 (24.4–29.2)	15.6 (13.8–17.6)	26.2 (23.6–28.4)	15.4 (13.8–17.3)
Lower coverage	519.9 (464.8–580.9)	145.1 (120.1–178.9)	60.9 (38.5–89.0)	12.3 (5.7–20.9)	21.1 (18.4–23.5)	13.1 (11.5–14.9)	21.5 (18.7–23.9)	13.3 (11.7–15.1)
Higher coverage	785.1 (705.6–872.7)	225.5 (187.7–275.7)	92.2 (58.2–134.6)	19.3 (9–32.4)	31.0 (27.2–34.1)	19.6 (17.4–22.1)	31.7 (27.9–34.8)	20.1 (17.9–22.4)

Older Ages (campaign ages 18–55, routine age 17)	839.0 (754.7–932.4)	330.8 (283.5–392.6)	97.9 (63.2–143.2)	28.4 (13.4–46.3)	29.3 (25.1–32.7)	24.7 (22.6–26.8)	30.8 (26.4–34.0)	26 (23.9–28.1)
All Adults (campaign ages 19+, routine age 18)	934.5 (836.3–1,037.4)	491.8 (433.9–574.9)	108.1 (70.2–156.6)	41.9 (20.2–66.2)	30.5 (25.8–34.4)	31.8 (30.2–33.7)	32.2 (27.4–36.1)	33.9 (32.3–35.8)
BCG-revaccination scenarios								
Basecase	358.7 (305.3–402.0)	112.9 (91.5–142.9)	44.3 (28.5–64.9)	10.1 (4.7–17)	13.3 (9.6–16.2)	10.1 (8.7–11.8)	13.7 (10.2–16.4)	10.1 (8.8–11.8)
70% efficacy	564.0 (501.0–626.4)	165.8 (134.8–208.6)	69.9 (45.3–102.2)	14.8 (6.8–24.8)	21.4 (16.6–25.0)	14.5 (12.6–16.8)	21.8 (17.3–25.2)	14.6 (12.8–16.9)
5 years protection	259.9 (222.0–290.2)	82.8 (66.7–105.2)	32.7 (20.9–48.1)	7.5 (3.4–12.6)	8.9 (6.3–11.1)	7.0 (6–8.2)	9.5 (6.9–11.5)	7.1 (6.2–8.3)
15 years protection	407.8 (348.3–457.1)	128 (103.9–161.7)	50.0 (32.3–73.6)	11.3 (5.2–19.1)	15.8 (11.5–19.0)	11.8 (10.2–13.8)	16.0 (12.1–19.0)	11.7 (10.2–13.7)
20 years protection	437.8 (374.8–491.2)	137.2 (111.7–173.2)	53.5 (34.5–78.5)	12.1 (5.6–20.4)	17.4 (12.8–20.8)	13 (11.2–15.1)	17.5 (13.2–20.7)	12.8 (11.2–14.9)
Efficacy with any infection at vaccination	434.3 (389.6–494.2)	114.1 (92.3–144.6)	54.0 (34.3–79.9)	10.2 (4.7–17.1)	16.3 (13.2–19.1)	10.1 (8.7–11.9)	16.7 (13.7–19.3)	10.2 (8.8–11.9)
Prevention of infection and disease	544.1 (490.0–601.2)	154.2 (125.2–194.5)	67.3 (43.3–98.1)	13.8 (6.4–23.1)	20.9 (16.9–24.1)	13.5 (11.7–15.6)	21.3 (17.5–24.2)	13.5 (11.8–15.7)
2031 introduction	237.1 (208.8–263.6)	66.5 (53.6–84.8)	28.5 (18.6–41.6)	5.8 (2.7–9.8)	11.5 (8.7–13.7)	7.7 (6.6–9.2)	12.0 (9.4–14.0)	7.8 (6.8–9.3)
Lower coverage	322.2 (273.2–361.7)	102 (82.6–129.3)	39.7 (25.6–58.3)	9.1 (4.2–15.3)	12.0 (8.6–14.7)	9.2 (7.9–10.8)	12.4 (9.2–14.8)	12.6 (10.9–14.4)
Higher coverage	392.3 (336.0–438.9)	122.9 (99.7–155.4)	48.5 (31.2–71.1)	11 (5.1–18.5)	14.4 (10.5–17.6)	10.8 (9.4–12.7)	14.9 (11.2–17.8)	15 (13.3–16.9)
Older Ages (campaign ages 16–34, routine age 15)	286.9 (195.7–351.7)	151.6 (124.5–188.2)	33.2 (19.8–51.4)	13 (5.9–22)	10.1 (6.0–13.9)	12.7 (11–14.6)	10.1 (6.0–13.9)	9.2 (8.0–10.8)
All Adults (campaign ages 19+, routine age 18)	223.7 (139.4–286.6)	184.3 (154.9–222.4)	25.4 (14.5–40.0)	15.8 (7.3–26)	7.9 (4.3–11.4)	15.1 (13.3–17.0)	7.9 (4.3–11.3)	10.9 (9.5–12.7)

Cumulative cases and deaths averted between 2025 and 2050 for each of the vaccine scenarios compared to the no-new-vaccine baseline and incidence and mortality rate reductions in 2050 for each of the vaccine scenarios compared to the rate predicted in 2050 with the no-new-vaccine baseline

10. Economic results

10.1 Delhi Economic Results - M72/AS01$_E$

Table S10.1 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for the M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline for Delhi

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	1.5 (1, 2.1)	5 (-37, 63)	4 (cost-saving, 47)	-31 (-109, 37)	cost-saving (cost-saving, 26)
Vaccine Characteristic and Coverage Scenarios					
60% efficacy	1.7 (1.2, 2.4)	-15 (-60, 44)	cost-saving (cost-saving, 27)	-59 (-149, 14)	cost-saving (cost-saving, 10)
70% efficacy	2 (1.3, 2.8)	-34 (-81, 25)	cost-saving (cost-saving, 12)	-85 (-187, -8)	cost-saving
5 years protection	1.1 (0.7, 1.5)	34 (-7, 91)	31 (cost-saving, 89)	9 (-55, 71)	8 (cost-saving, 68)
15 years protection	1.6 (1.1, 2.3)	-8 (-52, 50)	cost-saving (cost-saving, 33)	-49 (-136, 22)	cost-saving (cost-saving, 14)
20 years protection	1.7 (1.2, 2.4)	-16 (-60, 43)	cost-saving (cost-saving, 26)	-60 (-150, 13)	cost-saving (cost-saving, 9)
Prevention of infection and disease	1.8 (1.2, 2.6)	-22 (-67, 37)	cost-saving (cost-saving, 21)	-68 (-163, 7)	cost-saving (cost-saving, 4)
Efficacy with current infection at vaccination	1.1 (0.7, 1.5)	36 (-4, 91)	34 (cost-saving, 100)	12 (-50, 75)	11 (cost-saving, 75)
2036 introduction	0.8 (0.5, 1.1)	33 (2, 78)	43 (2, 109)	16 (-32, 65)	20 (cost-saving, 89)
Lower coverage	1.2 (0.8, 1.6)	1 (-32, 45)	1 (cost-saving, 42)	-28 (-89, 25)	cost-saving (cost-saving, 22)
Higher coverage	1.8 (1.2, 2.5)	10 (-42, 82)	6 (cost-saving, 51)	-33 (-128, 50)	cost-saving (cost-saving, 30)

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

Table S10.2 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the health-system perspective for Delhi

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	118 (80, 173)	-5 (-6, -4)	-0.2 (-0.8, -0.001)	-75 (-91, -60)	-32 (-37, -28)	5 (-37, 63)
Policy Scenarios						
Older ages (campaign for ages 18–55, routine age 17)	191 (129, 281)	-7 (-8, -6)	-0.3 (-1.1, -0.001)	-97 (-118, -78)	-42 (-49, -36)	45 (-21, 139)
All adults (campaign for ages 19+, routine age 18)	235 (159, 346)	-8 (-9, -6)	-0.3 (-1.2, -0.001)	-108 (-131, -87)	-46 (-54, -40)	73 (-7, 190)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	118 (80, 173)	-6 (-8, -5)	-0.2 (-1.0, -0.001)	-88 (-107, -71)	-38 (-44, -33)	-15 (-60, 44)
70% efficacy	118 (80, 173)	-7 (-9, -6)	-0.3 (-1.1, -0.001)	-101 (-123, -81)	-44 (-50, -37)	-34 (-81, 25)
5 years protection	118 (80, 173)	-4 (-5, -3)	-0.1 (-0.6, -0.001)	-56 (-68, -45)	-24 (-28, -21)	34 (-7, 91)
15 years protection	118 (80, 173)	-6 (-7, -5)	-0.2 (-0.9, -0.001)	-84 (-102, -67)	-36 (-42, -31)	-8 (-52, 50)
20 years protection	118 (80, 173)	-6 (-8, -5)	-0.2 (-1.0, -0.001)	-89 (-108, -71)	-38 (-44, -33)	-16 (-60, 43)
Prevention of infection and disease	118 (80, 173)	-7 (-8, -5)	-0.2 (-1.0, -0.001)	-93 (-113, -74)	-40 (-47, -34)	-22 (-67, 37)
Efficacy with current infection at vaccination	118 (80, 173)	-4 (-5, -3)	-0.1 (-0.6, -0.001)	-54 (-66, -44)	-23 (-27, -20)	36 (-4, 91)
2036 introduction	93 (63, 137)	-3 (-3, -2)	-0.1 (-0.4, -0.001)	-40 (-49, -32)	-17 (-20, -15)	33 (2, 78)
Lower coverage	90 (61, 132)	-4 (-5, -3)	-0.2 (-0.7, -0.001)	-59 (-72, -47)	-26 (-30, -22)	1 (-32, 45)
Higher coverage	146 (99, 214)	-6 (-8, -5)	-0.2 (-1.0, -0.001)	-90 (-110, -72)	-39 (-45, -33)	10 (-42, 82)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S10.3 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the societal perspective for Delhi

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	124 (84, 180)	-5 (-7, -4)	-107 (-128, -89)	-13 (-22, -7)	-29 (-99, -1)	-31 (-109, 37)
Policy Scenarios						
Older ages (campaign for ages 18–55, routine age 17)	202 (137, 292)	-7 (-9, -6)	-139 (-166, -114)	-17 (-28, -9)	-38 (-128, -2)	1 (-110, 106)
All adults (campaign for ages 19+, routine age 18)	248 (168, 359)	-8 (-10, -6)	-154 (-184, -127)	-19 (-32, -10)	-42 (-140, -2)	25 (-101, 153)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	124 (84, 180)	-6 (-8, -5)	-126 (-151, -104)	-16 (-26, -8)	-35 (-117, -2)	-59 (-149, 14)
70% efficacy	124 (84, 180)	-7 (-9, -6)	-144 (-172, -119)	-18 (-29, -10)	-40 (-134, -2)	-85 (-187, -8)
5 years protection	124 (84, 180)	-4 (-5, -3)	-80 (-95, -66)	-10 (-16, -5)	-22 (-74, -1)	9 (-55, 71)
15 years protection	124 (84, 180)	-6 (-7, -5)	-120 (-143, -99)	-15 (-24, -8)	-33 (-111, -1)	-49 (-136, 22)
20 years protection	124 (84, 180)	-7 (-8, -5)	-127 (-151, -105)	-16 (-26, -8)	-35 (-118, -2)	-60 (-150, 13)
Prevention of infection and disease	124 (84, 180)	-7 (-8, -6)	-133 (-159, -109)	-17 (-27, -9)	-36 (-123, -2)	-68 (-163, 7)
Efficacy with current infection at vaccination	124 (84, 179)	-4 (-5, -3)	-78 (-93, -64)	-10 (-16, -5)	-21 (-72, -1)	12 (-50, 75)
2036 introduction	98 (67, 142)	-3 (-4, -2)	-57 (-68, -47)	-7 (-12, -4)	-16 (-53, -1)	16 (-32, 65)
Lower coverage	95 (65, 137)	-4 (-5, -4)	-85 (-101, -70)	-11 (-17, -6)	-23 (-78, -1)	-28 (-89, 25)
Higher coverage	154 (104, 222)	-7 (-8, -5)	-129 (-154, -106)	-16 (-26, -9)	-35 (-119, -2)	-33 (-128, 50)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

10.2 Delhi Economic Results - BCG-revaccination

Table S10.4 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for the BCG-revaccination *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline for Delhi

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, thousands)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	0.9 (0.6, 1.3)	-38 (-58, -13)	cost-saving	-59 (-103, -26)	cost-saving
Vaccine Characteristic and Coverage Scenarios					
70% efficacy	1.5 (1.0, 2.0)	-74 (-100, -46)	cost-saving	-110 (-176, -67)	cost-saving
5 years protection	0.7 (0.5, 1.0)	-21 (-39, 3)	cost-saving (cost-saving, 5)	-36 (-69, -8)	cost-saving
15 years protection	1.1 (0.7, 1.5)	-46 (-68, -20)	cost-saving	-71 (-120, -35)	cost-saving
20 years protection	1.1 (0.8, 1.6)	-51 (-74, -25)	cost-saving	-78 (-129, -41)	cost-saving
Prevention of infection and disease	1.4 (1.0, 1.9)	-71 (-96, -43)	cost-saving	-105 (-168, -64)	cost-saving
Efficacy with any infection at vaccination	1.1 (0.8, 1.6)	-52 (-74, -25)	cost-saving	-79 (-130, -43)	cost-saving
2031 introduction	0.6 (0.4, 0.8)	-20 (-33, -4)	cost-saving	-33 (-59, -12)	cost-saving
Lower coverage	0.8 (0.6, 1.2)	-34 (-52, -12)	cost-saving	-54 (-93, -24)	cost-saving
Higher coverage	1.0 (0.7, 1.4)	-41 (-63, -13)	cost-saving	-65 (-112, -28)	cost-saving

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

Table 10.5 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the health-system perspective for Delhi

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	27 (12, 49)	-3 (-4, -2)	-0.1 (-0.5, -0.001)	-43 (-53, -34)	-18 (-22, -15)	-38 (-58, -13)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	48 (20, 88)	-2 (-3, -2)	-0.09 (-0.4, 0)	-35 (-46, -23)	-15 (-19, -10)	-4 (-36, 40)
All adults (campaign for ages 19+, routine age 18)	95 (40, 176)	-2 (-3, -1)	-0.07 (-0.3, 0)	-27 (-37, -16)	-12 (-16, -7)	55 (-3, 139)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	27 (12, 49)	-5 (-6, -4)	-0.2 (-0.7, -0.001)	-67 (-83, -54)	-29 (-34, -24)	-74 (-100, -46)
5 years protection	27 (12, 49)	-2 (-3, -2)	-0.08 (-0.3, 0)	-32 (-39, -25)	-14 (-16, -11)	-21 (-39, 3)
15 years protection	27 (12, 49)	-3 (-4, -3)	-0.1 (-0.5, -0.001)	-48 (-60, -38)	-21 (-25, -17)	-46 (-68, -20)
20 years protection	27 (12, 49)	-4 (-4, -3)	-0.1 (-0.6, -0.001)	-52 (-64, -41)	-22 (-26, -18)	-51 (-74, -25)
Prevention of infection and disease	27 (12, 49)	-5 (-6, -4)	-0.2 (-0.7, -0.001)	-65 (-80, -52)	-28 (-33, -24)	-71 (-96, -43)
Efficacy with any infection at vaccination	27 (12, 50)	-4 (-5, -3)	-0.1 (-0.6, -0.001)	-52 (-65, -42)	-23 (-27, -19)	-52 (-74, -25)
2031 introduction	18 (8, 33)	-2 (-2, -1)	-0.07 (-0.3, 0)	-25 (-31, -20)	-11 (-13, -9)	-20 (-33, -4)
Lower coverage	24 (10, 43)	-3 (-3, -2)	-0.1 (-0.4, 0)	-38 (-48, -30)	-17 (-20, -14)	-34 (-52, -12)
Higher coverage	30 (13, 55)	-3 (-4, -3)	-0.1 (-0.5, -0.001)	-47 (-58, -37)	-20 (-24, -17)	-41 (-63, -13)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S10.6 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the societal perspective for Delhi

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	30 (14, 51)	-3 (-4, -2)	-61 (-74, -49)	-8 (-13, -4)	-17 (-55, -1)	-59 (-103, -26)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	53 (24, 93)	-3 (-3, -2)	-50 (-65, -33)	-6 (-11, -3)	-14 (-44, -1)	-19 (-65, 29)
All adults (campaign for ages 19+, routine age 18)	105 (46, 185)	-2 (-3, -1)	-38 (-53, -24)	-5 (-9, -2)	-10 (-34, 0)	49 (-14, 136)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	30 (14, 51)	-5 (-6, -4)	-97 (-116, -79)	-12 (-20, -7)	-26 (-88, -1)	-110 (-176, -67)
5 years protection	30 (14, 51)	-2 (-3, -2)	-45 (-55, -36)	-6 (-9, -3)	-12 (-41, -1)	-36 (-69, -8)
15 years protection	29 (14, 51)	-4 (-4, -3)	-69 (-84, -55)	-9 (-14, -5)	-19 (-62, -1)	-71 (-120, -35)
20 years protection	29 (14, 51)	-4 (-5, -3)	-74 (-89, -59)	-9 (-15, -5)	-20 (-67, -1)	-78 (-129, -41)
Prevention of infection and disease	30 (14, 51)	-5 (-6, -4)	-93 (-111, -77)	-12 (-19, -6)	-26 (-85, -1)	-105 (-168, -64)
Efficacy with any infection at vaccination	30 (14, 52)	-4 (-5, -3)	-75 (-91, -61)	-9 (-15, -5)	-21 (-68, -1)	-79 (-130, -43)
2031 introduction	20 (9, 34)	-2 (-2, -1)	-36 (-44, -29)	-5 (-7, -2)	-10 (-33, 0)	-33 (-59, -12)
Lower coverage	26 (12, 45)	-3 (-3, -2)	-55 (-67, -44)	-7 (-11, -4)	-15 (-49, -1)	-54 (-93, -24)
Higher coverage	33 (15, 57)	-3 (-4, -3)	-67 (-81, -54)	-8 (-14, -5)	-18 (-60, -1)	-65 (-112, -28)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

10.3 Gujarat Economic Results - M72/AS01$_E$

Table S10.7 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for the M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline for Gujarat

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	0.3 (0.2, 0.5)	332 (213, 505)	1 078 (567, 2 402)	385 (251, 556)	1 250 (663, 2 649)
Vaccine Characteristic and Coverage Scenarios					
60% efficacy	0.4 (0.2, 0.6)	327 (208, 500)	898 (469, 2 007)	377 (242, 549)	1 037 (545, 2 212)
70% efficacy	0.4 (0.2, 0.7)	321 (203, 494)	770 (397, 1 725)	369 (234, 539)	884 (464, 1 901)
5 years protection	0.2 (0.1, 0.4)	341 (222, 513)	1 511 (805, 3 336)	398 (263, 569)	1 762 (960, 3 730)
15 years protection	0.3 (0.2, 0.5)	328 (210, 501)	947 (496, 2 106)	379 (245, 552)	1 094 (576, 2 325)
20 years protection	0.4 (0.2, 0.6)	326 (208, 499)	882 (459, 1 960)	376 (241, 547)	1 017 (538, 2 169)
Prevention of infection and disease	0.4 (0.2, 0.6)	323 (206, 496)	818 (425, 1 852)	372 (238, 543)	942 (491, 2 020)
Efficacy with current infection at vaccination	0.2 (0.1, 0.3)	347 (228, 518)	2052 (1 104, 4 466)	406 (271, 578)	2402 (1313, 4 994)
2036 introduction	0.1 (0.1, 0.2)	260 (170, 390)	1 737 (928, 3 808)	304 (201, 433)	2029 (1100, 4 349)
Lower coverage	0.2 (0.1, 0.4)	256 (164, 389)	1 067 (561, 2 395)	297 (194, 428)	1236 (651, 2 633)
Higher coverage	0.4 (0.2, 0.6)	409 (262, 621)	1 095 (576, 2 424)	475 (310, 685)	1269 (679, 2 688)

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

Table S10.8 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the health-system perspective for Gujarat

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	366 (248, 536)	-2 (-2, -1)	-0.036 (-0.157, 0)	-25 (-33, -19)	-6 (-8, -5)	332 (213, 505)
Policy Scenarios						
Older ages (campaign for ages 18–55, routine age 17)	573 (388, 841)	-3 (-4, -2)	-0.066 (-0.282, 0)	-46 (-59, -35)	-11 (-13, -9)	513 (327, 784)
All adults (campaign for ages 19+, routine age 18)	713 (482, 1049)	-5 (-6, -4)	-0.098 (-0.41, 0)	-68 (-86, -53)	-16 (-20, -13)	624 (393, 960)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	366 (248, 536)	-2 (-3, -2)	-0.043 (-0.185, 0)	-30 (-39, -22)	-7 (-9, -6)	327 (208, 500)
70% efficacy	366 (248, 536)	-2 (-3, -2)	-0.049 (-0.212, 0)	-34 (-45, -26)	-8 (-10, -6)	321 (203, 494)
5 years protection	365 (248, 536)	-1 (-2, -1)	-0.026 (-0.114, 0)	-18 (-24, -14)	-4 (-6, -3)	341 (222, 513)
15 years protection	366 (248, 536)	-2 (-3, -2)	-0.041 (-0.177, 0)	-28 (-37, -21)	-7 (-9, -5)	328 (210, 501)
20 years protection	366 (248, 536)	-2 (-3, -2)	-0.043 (-0.189, 0)	-30 (-40, -23)	-7 (-9, -6)	326 (208, 499)
Prevention of infection and disease	366 (248, 536)	-2 (-3, -2)	-0.046 (-0.198, 0)	-32 (-42, -24)	-8 (-10, -6)	323 (206, 496)
Efficacy with current infection at vaccination	365 (248, 536)	-1 (-1, -1)	-0.02 (-0.087, 0)	-14 (-18, -11)	-3 (-4, -3)	347 (228, 518)
2036 introduction	276 (187, 405)	-1 (-1, -1)	-0.018 (-0.076, 0)	-12 (-16, -9)	-3 (-4, -2)	260 (170, 390)
Lower coverage	282 (191, 413)	-1 (-2, -1)	-0.028 (-0.121, 0)	-20 (-26, -15)	-5 (-6, -4)	256 (164, 389)
Higher coverage	449 (304, 660)	-2 (-3, -2)	-0.044 (-0.191, 0)	-31 (-40, -23)	-7 (-9, -6)	409 (262, 621)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S10.9 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the M72/AS01$_E$ scenarios from the societal perspective for Gujarat

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	432 (298, 605)	-2 (-2, -1)	-31 (-41, -24)	-4 (-7, -2)	-10 (-33, 0)	385 (251, 556)
Policy Scenarios						
Older ages (campaign for ages 18–55, routine age 17)	678 (467, 949)	-3 (-4, -3)	-57 (-72, -44)	-8 (-13, -4)	-18 (-59, -1)	593 (382, 863)
All adults (campaign for ages 19+, routine age 18)	845 (582, 1183)	-5 (-6, -4)	-85 (-106, -67)	-12 (-20, -6)	-26 (-87, -1)	717 (452, 1055)
Vaccine Characteristic and Coverage Scenarios						
60% efficacy	432 (298, 605)	-2 (-3, -2)	-37 (-48, -28)	-5 (-9, -3)	-11 (-39, 0)	377 (242, 549)
70% efficacy	432 (298, 605)	-2 (-3, -2)	-42 (-55, -32)	-6 (-10, -3)	-13 (-44, -1)	369 (234, 539)
5 years protection	432 (298, 605)	-1 (-2, -1)	-23 (-30, -17)	-3 (-5, -2)	-7 (-24, 0)	398 (263, 569)
15 years protection	432 (298, 605)	-2 (-3, -2)	-35 (-46, -27)	-5 (-8, -3)	-11 (-37, 0)	379 (245, 552)
20 years protection	432 (298, 605)	-2 (-3, -2)	-38 (-49, -29)	-5 (-9, -3)	-12 (-39, 0)	376 (241, 547)
Prevention of infection and disease	432 (298, 605)	-2 (-3, -2)	-40 (-52, -30)	-6 (-9, -3)	-12 (-42, -1)	372 (238, 543)
Efficacy with current infection at vaccination	432 (298, 605)	-1 (-1, -1)	-17 (-23, -13)	-2 (-4, -1)	-5 (-18, 0)	406 (271, 578)
2036 introduction	327 (225, 457)	-1 (-1, -1)	-15 (-20, -12)	-2 (-4, -1)	-5 (-16, 0)	304 (201, 433)
Lower coverage	333 (229, 466)	-1 (-2, -1)	-24 (-32, -18)	-3 (-6, -2)	-8 (-26, 0)	297 (194, 428)
Higher coverage	532 (366, 744)	-2 (-3, -2)	-38 (-49, -29)	-5 (-9, -3)	-12 (-40, 0)	475 (310, 685)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

10.4 Gujarat Economic Results - BCG-revaccination

Table S10.10 Incremental DALYs averted, incremental costs averted, and ICERs from the health-system and societal perspectives for the BCG-revaccination *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline for Gujarat

Scenario	Incremental DALYs averted between 2025–2050 (millions)	Health-system perspective		Societal perspective	
		Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)	Incremental costs between 2025–2050 ($, millions)	ICERs ($/DALY averted)
Basecase	0.2 (0.1, 0.3)	77 (21, 158)	351 (91, 973)	99 (35, 177)	452 (143, 1 139)
Vaccine Characteristic and Coverage Scenarios					
70% efficacy	0.3 (0.2, 0.5)	67 (12, 148)	208 (33, 609)	85 (19, 164)	263 (58, 709)
5 years protection	0.2 (0.1, 0.3)	82 (26, 162)	497 (149, 1329)	106 (43, 186)	644 (235, 1 582)
15 years protection	0.2 (0.1, 0.4)	74 (19, 155)	303 (71, 853)	95 (31, 174)	389 (112, 995)
20 years protection	0.3 (0.1, 0.4)	72 (17, 153)	279 (61, 789)	93 (28, 172)	357 (98, 919)
Prevention of infection and disease	0.3 (0.2, 0.5)	69 (14, 150)	230 (40, 665)	88 (22, 167)	292 (72, 772)
Efficacy with any infection at vaccination	0.2 (0.1, 0.4)	76 (21, 157)	346 (89, 964)	99 (34, 177)	446 (140, 1 127)
2031 introduction	0.1 (0.1, 0.2)	52 (16, 105)	454 (132, 1255)	68 (26, 120)	589 (206, 1 466)
Lower coverage	0.2 (0.1, 0.3)	67 (19, 138)	343 (90, 950)	87 (30, 155)	440 (139, 1 115)
Higher coverage	0.2 (0.1, 0.4)	86 (24, 176)	360 (94, 994)	111 (40, 199)	465 (150, 1 162)

Abbreviations: DALYs = disability-adjusted life years, ICERs = incremental cost-effectiveness ratio, US$ = United States Dollar. Values in cells are the mean and 95% uncertainty ranges.

Table S10.11 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the health-system perspective for Gujarat

Scenario	Vaccination costs (US$, millions)	DS-TB diagnostic costs (US$, millions)	RR-TB diagnostic costs (US$, millions)	DS-TB treatment costs (US$, millions)	RR-TB treatment costs (US$, millions)	Incremental cost (US$, millions)
Basecase	97 (42, 178)	-1 (-2, -1)	-0.02 (-0.1, 0)	-16 (-21, -12)	-4 (-5, -3)	77 (21, 158)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	152 (64, 279)	-2 (-2, -1)	-0.03 (-0.1, 0)	-22 (-29, -16)	-5 (-7, -4)	124 (35, 252)
All adults (campaign for ages 19+, routine age 18)	294 (123, 543)	-2 (-2, -1)	-0.04 (-0.2, 0)	-26 (-34, -20)	-6 (-8, -5)	260 (86, 510)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	97 (42, 178)	-2 (-2, -1)	-0.03 (-0.1, 0)	-23 (-31, -17)	-6 (-7, -4)	67 (12, 148)
5 years protection	97 (42, 178)	-1 (-1, -1)	-0.02 (-0.07, 0)	-12 (-16, -9)	-3 (-4, -2)	82 (26, 162)
15 years protection	97 (42, 178)	-1 (-2, -1)	-0.03 (-0.1, 0)	-18 (-24, -13)	-4 (-6, -3)	74 (19, 155)
20 years protection	97 (42, 178)	-1 (-2, -1)	-0.03 (-0.1, 0)	-19 (-26, -14)	-5 (-6, -3)	72 (17, 153)
Prevention of infection and disease	97 (42, 178)	-2 (-2, -1)	-0.03 (-0.1, 0)	-22 (-29, -16)	-5 (-7, -4)	69 (14, 150)
Efficacy with any infection at vaccination	98 (42, 178)	-1 (-2, -1)	-0.02 (-0.1, 0)	-16 (-22, -12)	-4 (-5, -3)	76 (21, 157)
2031 introduction	63 (27, 116)	-1 (-1, 0)	-0.01 (-0.05, 0)	-8 (-11, -6)	-2 (-3, -2)	52 (16, 105)
Lower coverage	86 (37, 157)	-1 (-1, -1)	-0.02 (-0.09, 0)	-14 (-19, -11)	-3 (-4, -3)	67 (19, 138)
Higher coverage	109 (46, 198)	-1 (-2, -1)	-0.03 (-0.1, 0)	-17 (-23, -13)	-4 (-5, -3)	86 (24, 176)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

Table S10.12 Total vaccination costs, and incremental diagnostic, treatment, and net costs between 2025–2050 for the BCG-revaccination scenarios from the societal perspective for Gujarat

Scenario	Vaccination costs (US$, millions)	Diagnostic costs (DS + RR-TB) (US$, millions)	Treatment costs (DS + RR-TB) (US$, millions)	Non-medical costs (US$, millions)	Indirect costs (US$, millions)	Incremental cost (US$, millions)
Basecase	128 (64, 208)	-1 (-2, -1)	-20 (-26, -15)	-3 (-5, -1)	-6 (-21, 0)	99 (35, 177)
Policy Scenarios						
Older ages (campaign for ages 16-34, routine age 15)	202 (101, 328)	-2 (-2, -1)	-27 (-35, -20)	-4 (-6, -2)	-8 (-28, 0)	161 (61, 288)
All adults (campaign for ages 19+, routine age 18)	392 (195, 643)	-2 (-2, -1)	-33 (-42, -25)	-5 (-8, -2)	-10 (-34, 0)	342 (144, 591)
Vaccine Characteristic and Coverage Scenarios						
70% efficacy	128 (64, 208)	-2 (-2, -1)	-29 (-38, -22)	-4 (-7, -2)	-9 (-31, 0)	85 (19, 164)
5 years protection	128 (64, 208)	-1 (-1, -1)	-15 (-20, -11)	-2 (-3, -1)	-5 (-15, 0)	106 (43, 186)
15 years protection	128 (64, 208)	-1 (-2, -1)	-22 (-29, -17)	-3 (-5, -2)	-7 (-23, 0)	95 (31, 174)
20 years protection	128 (64, 208)	-1 (-2, -1)	-24 (-31, -18)	-3 (-6, -2)	-7 (-25, 0)	93 (28, 172)
Prevention of infection and disease	128 (64, 208)	-2 (-2, -1)	-27 (-36, -20)	-4 (-6, -2)	-8 (-29, 0)	88 (22, 167)
Efficacy with any infection at vaccination	128 (64, 208)	-1 (-2, -1)	-20 (-27, -15)	-3 (-5, -1)	-6 (-21, 0)	99 (34, 177)
2031 introduction	84 (42, 136)	-1 (-1, 0)	-10 (-14, -8)	-1 (-2, -1)	-3 (-11, 0)	68 (26, 120)
Lower coverage	113 (57, 183)	-1 (-1, -1)	-18 (-24, -13)	-2 (-4, -1)	-6 (-19, 0)	87 (30, 155)
Higher coverage	143 (72, 233)	-1 (-2, -1)	-21 (-29, -16)	-3 (-5, -2)	-7 (-23, 0)	111 (40, 199)

Abbreviations: DS-TB = drug-susceptible tuberculosis, RR-TB = rifampicin resistant tuberculosis, US$ = United States Dollars. Values in cells are the mean and 95% uncertainty ranges.

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5.4 Comparison with country-level modelling of India

The subnational models in Research Paper 3 are derived from the India country model in Chapter 4. Therefore, a number of the vaccine scenarios simulated in both studies were the same to facilitate comparison and investigate any relative differences in impact between national and region-specific subnational modelling.

I estimated that the *Basecase* M72/AS01$_E$ vaccine would avert 17.6% of cases (12.7 million out of 72.2 million) and 14.5% of deaths (2.0 million out of 13.8 million) in India overall between 2025–2050. Compared with the subnational modelling results, this was more similar to the *Basecase* vaccine scenario in Delhi, which averted 16.0% of cases (655 thousand out of 4.1 million) and 14.4% of deaths (77 thousand out of 533 thousand). A lower impact of the M72/AS01$_E$ *Basecase* scenario was estimated in Gujarat, which averted 8.5% of cases (186 thousand out of 2.2 million) and 7.8% of deaths (16 thousand out of 210 thousand). Comparing the *Basecase* BCG-revaccination results, I found a lower proportion of cases and deaths averted in Delhi and Gujarat than in India overall. The *Basecase* BCG-revaccination scenario averted 12.5% of cases and 10.9% of deaths in India overall, compared to 8.8% of cases and 8.3% of deaths in Delhi, and 5.1% of cases and 4.8% of deaths in Gujarat.

Assuming they were not misspecified, the differences between the impact of introducing M72/AS01$_E$ in Gujarat and introducing BCG-revaccination in both regions compared to India overall could have been due to differences in the modelled age-specific infection prevalence and disease incidence. There were no age-specific infection prevalence targets for India, Delhi, or Gujarat, or any age-specific incidence targets in Delhi or Gujarat. In India, the modelled infection prevalence was around 10–15% for ages <15, but increased to around 50% for ages ≥15. The majority of incident tuberculosis cases were in older adolescents (ages 16–19) during 2025–2040, and in older adults from 2045–2050. In Delhi, I modelled a high prevalence of infection for all ages, and the majority of cases in the no-new-vaccine baseline arose in younger ages (age 8–9) or older adolescents (ages 15–19). In Gujarat, I modelled a very low prevalence of infection for all ages, assuming that infection prevalence would correlate with disease prevalence and the largest number of incident cases were from the older age groups throughout the entire time period.

I found a lower estimated impact of the *Basecase* M72/AS01$_E$ scenario (assumed to prevent disease with any infection status at the time of vaccination, and delivered routinely to those aged 15 and as a campaign for ages 16–34) in Gujarat compared to India and Delhi. As I modelled a lower infection prevalence in Gujarat compared to India and Delhi, the majority of individuals who received the vaccine in Gujarat were uninfected. Therefore, the vaccine impact on disease was delayed by the time to infection followed by the time to disease. Additionally, the majority of cases in Gujarat arose in older age groups, and as the vaccine was targeted to ages 15–34 with a duration of protection of ten years on average, the vaccine was not protecting the group that was at the highest risk of developing tuberculosis disease. In India, as the majority of cases in the earlier time frame arose from older adolescents, the vaccine was protecting those at the highest risk of developing disease, and therefore the impact estimated from Gujarat was lower than India.

I estimated a lower impact of the *Basecase* BCG-revaccination scenario in both Delhi and Gujarat compared to India. I assumed that the vaccine would be efficacious with no current infection at the time of vaccination and would be delivered routinely to those aged 10 and as a campaign for ages 11–18. In Delhi, I modelled a higher infection prevalence for all ages compared to India. Therefore, a lower proportion of the population who received the vaccine would have received protection from it, resulting in the lower observed impact in Delhi than in India. In Gujarat, even though the vaccine would be efficacious in a higher proportion of the population given the lower modelled infection prevalence, it was not targeted to the age group where the largest number of cases arose, and therefore not protecting those at the highest risk of developing tuberculosis, resulting again in a lower impact compared to India.

The observed differences in infection prevalence and incidence could have resulted from differences in the national and subnational modelling approaches. As discussed in Research Paper 3, I was limited by the availability of subnational demographic data and calibration targets when modelling Delhi and Gujarat. While there were estimates and projections available for all years and ages for India overall, I extrapolated census data from 1991, 2001, and 2011, while incorporating estimates for India overall to represent the populations of Delhi and Gujarat, which may have resulted in the region-specific population age-distributions being misrepresented. The epidemic was also more fully characterised in India, as the model was fit to nineteen calibration

targets (including multiple incidence, mortality, and notification targets over time, and age-specific incidence and mortality targets). The models for Delhi and Gujarat were only fit to two or three region-specific calibration targets respectively. The lower number of calibration targets for the subnational modelling may have resulted in inaccurate representations of the epidemic in each region, which could have caused differences in impact. More region-specific data to characterise the epidemic would help to confirm or refute this hypothesis.

Additionally, the differences observed between India, Delhi, and Gujarat could imply that there are other states or union territories in India where these vaccines will have a greater impact. Due to demography, burden and other regional-level differences, the impact from the scenarios in Delhi and Gujarat could be lower than in other states, and the country-level results reflect the combined impact. However, the lower impact from vaccines found through subnational modelling could also mean that the predicted benefits from the country-level India modelling were overestimated when subnational differences in burden and demographics were not taken into account. Future work developing subnational modelling for additional states could help to determine whether these hypotheses are correct.

5.5 Summary

In Chapter 5, I addressed the final thesis **Aim 3** through **Objective 4**. I once again extended the developed model structures from **Objective 1** to address **Objective 4**, where I calibrated to regional-specific estimates of tuberculosis prevalence and case-notifications in Delhi and Gujarat to simulate the introduction of M72/AS01$_E$ and BCG-revaccination under varying delivery strategies. I estimated and compared how the health and economic impacts of M72/AS01$_E$ and BCG-revaccination would change in Delhi and Gujarat.

With the subnational modelling described in Research Paper 3, I found that more cases and deaths could be averted with M72/AS01$_E$ vaccines compared to BCG-revaccination in both regions, and in Delhi compared to Gujarat for both vaccine products. In Delhi, both vaccines could be cost-effective (or even cost-saving) compared to the most conservative country-level opportunity cost threshold. In Gujarat, M72/AS01$_E$ would be cost-effective at the 1×GDP per capita per DALY

averted threshold unless efficacy was restricted to those with current infection at vaccination, and BCG-revaccination could be cost-effective at 1×GDP per capita per DALY averted threshold regardless of the assumed product characteristics. In both regions, there were higher incremental cost-effectiveness ratios for M72/AS01$_E$ compared to BCG-revaccination scenarios, due to the higher assumed cost-per-dose for M72/AS01$_E$ (US$2.50 vs US$0.17) and doubled delivery and supply costs of requiring two doses per course.

Research Paper 3 demonstrated how important it is to account for subnational differences when modelling tuberculosis vaccines. Important differences in impact were only discovered when Delhi and Gujarat were modelled separately. The infection prevalence was a key determinant of vaccine impact, and therefore age- and region-specific estimates of infection prevalence are urgently needed to inform modelling estimates of delivery strategies. Future work to understand if M72/AS01$_E$ will be effective in all populations and to develop subnational models of other regions within India will help to appropriately inform decision makers on the predicted benefits of introducing vaccines by region.

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CHAPTER 6 Discussion

6.1 Summary of findings

The overall aim of the thesis was to use mathematical modelling to generate appropriate evidence to provide decision makers globally, and at various levels of government in India, with estimates of health and economic impact to support tuberculosis vaccine policy and introduction. I established three Aims which would be achieved by four Objectives.

Objective 1 was an overarching objective that would be used to address the three Aims and each of the remaining three Objectives.

Objective 1: Develop-

a. a new tuberculosis model structure which incorporates key aspects of the tuberculosis natural history and
b. a new vaccine model structure which allows for protection from multiple vaccines with varying product characteristics and is able to represent sophisticated and realistic vaccine delivery strategies.

The new tuberculosis model structure (**Objective 1a**) was developed and described in the supplementary material for each Research Paper and included in sections 3.3, 4.3, and 5.3. I searched the literature to investigate the novel aspects of tuberculosis natural history to include in the updated model structure, compared it with previous natural history models used in tuberculosis vaccine modelling, and consulted with tuberculosis natural history experts to verify my proposed structure. Additions to the structure included a compartment to represent self-clearance of *Mtb* infection, where progression to disease is not possible without reinfection,[1,2] and subclinical disease, where individuals display no symptoms of tuberculosis but in the model are considered to have active disease and are able to transmit.[3,4]

Based on the novel additions to the tuberculosis natural history structure used for vaccines, I revised the host infection status at time of vaccination required for vaccine efficacy classifications. In previous work, host infection status required for vaccine efficacy was classified as pre-infection

(PRI, meaning the vaccine was effective if the recipient was uninfected), post-infection (PSI, meaning the vaccine was effective if the recipient had ever had *Mtb* infection), and pre- and post-infection (PPI, meaning the vaccine was effective if the recipient was either infected or uninfected). However, with the evolving understanding that infection may not be lifelong, *post*-infection is not an accurate term, as individuals who have self-cleared may be considered "post" infection, but are no longer infected with viable bacteria so a vaccine that requires the individual to be infected may not be effective.

With the updated classification, host infection status *at the time of vaccination* required for vaccine efficacy can be divided into no-current-infection (NCI) vaccine, where the vaccine will only be efficacious if the recipient is uninfected at the time of vaccination, or a current-infection (CI) vaccine, meaning the vaccine will only be efficacious if it is delivered to populations with current infection with *Mtb* (infection or recovered populations) only, or an any-infection (AI) vaccine, where the vaccine will be efficacious in all populations. "*At the time of vaccination*" is a key addition to the terminology to represent the fact that it is the infection status when the individual is vaccinated that determines if the vaccine will be efficacious.

The new vaccine model structure (**Objective 1a**) was developed and described in the supplementary material for each Research Paper and included in sections 3.3, 4.3, and 5.3. The vaccine structure was constructed to model vaccination delivered routinely and as one mass vaccination campaign for Research Paper 1, and included three compartments: never vaccinated (for those who did not receive a vaccine), vaccinated–protected (for those who received a vaccine, it was efficacious, and they currently have protection) and vaccinated–not protected (for those who received a vaccine and it was not efficacious, or those who waned from the vaccinated–protected compartment). I extended the vaccine structure from Research Paper 1 to allow for modelling repeat vaccination campaigns in Research Paper 2 and 3. Building off of the three-vaccine compartment structure, I included additional compartments to track the number of vaccines received by each individual, to allow for boosting of vaccine protection if multiple vaccines were received.

6.1.1 Multi-country modelling

Aim 1 of the thesis was to estimate the health impact of introducing new tuberculosis vaccines in LMICs under alternative delivery strategies to support investment in vaccine manufacturing and development. Aim 1 was addressed through

Objective 2: Using the tuberculosis model structure developed in Objective 1a:

a. Independently calibrate the tuberculosis model to LMICs
b. Simulate the introduction of vaccines with characteristics aligned with WHO Preferred Product Characteristics for New Tuberculosis Vaccines under varying delivery strategies, and
c. Calculate and compare the health impact (cumulative cases, treatments and deaths averted) between vaccine delivery scenarios by WHO region, World Bank Income Group, WHO burden level.

Summary of Chapter 3

The burden of tuberculosis is highest in low- and middle-income countries.[5] New tuberculosis vaccines may have a positive impact on the epidemic, but there has historically been a lack of incentive from stakeholders to invest in a disease that primarily impacts those who are most disadvantaged. In 2018, WHO established the Preferred Product Characteristics (PPCs) for new tuberculosis vaccines, which outlined preferred characteristics for a novel adolescent/adult vaccine, and a novel infant vaccine to be used independently or as a booster for neonatal BCG.[6] While these characteristics had been established, no modelling studies had estimated the impact of vaccines meeting WHO PPCs.[7,8]

In Chapter 3, I used a mathematical model to estimate the health impact of introducing novel tuberculosis vaccines aligning with WHO PPCs in 105 LMICs, which was the first study to do so, in order to provide evidence of the health benefits possible from new tuberculosis vaccines for global stakeholders to support continued investment in their development.[9]

I used history matching with emulation to calibrate the updated tuberculosis natural history model structure from **Objective 1a** to country-specific data in 105 countries which accounted for 93% of

the global tuberculosis incidence in 2019 (**Objective 2a**). I used the calibrated models to simulate baseline epidemiology for each country assuming no-new-vaccine introduction and compared with simulations of introducing an infant and adolescent/adult vaccine with characteristics aligned with the WHO PPCs.

Using the updated vaccine model structure developed in **Objective 1b**, I investigated three vaccine delivery scenarios which varied vaccine introduction year, vaccine scale-up pace, and ages targeted (**Objective 2b**):

- *Basecase:* Routine neonatal delivery for the infant vaccine, routine delivery to those aged 10 and a campaign for ages 11+ for the adolescent/adult vaccine with introduction in realistic country-specific introduction years between 2028–2047 with five-year scale-up to target coverage
- *Accelerated Scale-up*: As *Basecase* except all countries introduce in 2025 with instantaneous scale-up to target coverage
- *Routine Only* (adolescent/adult vaccine only): As *Basecase* except only routine delivery to those aged 10 (no campaign delivery).

My multi-country modelling suggested that vaccines aligned with the WHO PPCs could have a substantial health impact in LMICs (**Objective 2c**). With the *Basecase* delivery scenario, the infant vaccine could avert 6.7 (5.8–7.7) million cases and 0.9 (0.8–1.0) million deaths by 2050, and the adolescent/adult vaccine could avert 44.0 (37.2–51.6) million cases and 5.0 (4.6–5.4) million deaths by 2050. The largest impact was estimated to be in the WHO South-East Asian Region, the WHO African Region, countries classified as lower-middle-income, and countries classified by WHO as having a high burden of tuberculosis.

Instantaneous introduction and scale-up of a vaccine as soon as it was available as well as delivery through campaigns to adolescents and adults showed the most rapid impact of the scenarios modelled. Comparing the *Basecase* with *Accelerated Scale-up* results highlighted the consequences of delayed introduction informed by historical LMIC vaccine introduction (infant vaccine: 9.6 million more cases and 1.4 million more deaths averted with *Accelerated Scale-up* vs *Basecase*; adolescent/adult vaccine: 21.5 million more cases and 2.9 million more deaths averted

with *Accelerated Scale-up* vs *Basecase*). Comparing *Basecase* with *Routine Only* results highlighted the consequences of only introducing the vaccine as routine delivery as opposed to introducing with both routine and a campaign (36 million more cases averted and 3.9 million more deaths averted with *Basecase* vs *Routine Only*).

Novel contributions to the literature from Chapter 3

This was the first tuberculosis vaccine modelling study to incorporate novel natural history aspects, such as self-clearance and subclinical disease, into vaccine impact estimates. It provided evidence for global decision makers based on the estimation of the health impact of novel tuberculosis vaccines with characteristics aligned with WHO PPCs in 105 LMICs introduced with realistic vaccine delivery such as varying country-specific introduction years and scale-up to target vaccine coverage over five years.

6.1.2 Country-level modelling

Aim 2 of the thesis was to estimate the health and economic impact of introducing M72/AS01$_E$ vaccines and BCG-revaccination in India to provide evidence for country-level decision makers. **Aim 2** was addressed through:

Objective 3: Extend the multi-country tuberculosis model from Objective 1a to develop a sophisticated country-level model for India, incorporating differences in public and private sector treatment outcomes

a. Calibrate the country-specific model for India to multiple calibration targets over time to constrain long-term dynamics
b. Simulate the introduction of M72/AS01$_E$ vaccines and BCG-revaccination under varying delivery strategies, and
c. Estimate the health and economic impacts of each vaccine scenario.

Summary of Chapter 4

India has the largest global burden of tuberculosis.[5] Elimination is a key focus for the Government of India, and the delivery of post-exposure tuberculosis vaccines is part of the National Strategic

Plan for Tuberculosis Elimination for 2020–2025.[10] The government of India is also planning to conduct a trial which will evaluate the impact of providing preventive treatment to adolescent household contacts of individuals with confirmed tuberculosis compared to providing BCG-revaccination.[11] Previous modelling of the introduction of new tuberculosis vaccines in India had predicted a positive health and economic benefit on the epidemic, but model structures used did not incorporate recent advances in the tuberculosis natural history which may affect vaccine impact estimates or evaluated specific scenarios of M72/AS01$_E$ and BCG-revaccination.[7,12–16]

To address **Aim 2**, I extended the mathematical model of tuberculosis natural history to create a detailed representation of India, incorporating differences in public and private sector treatment outcomes. I calibrated the model to nineteen India-specific tuberculosis calibration targets (**Objective 3a**), and projected baseline epidemiology forward to 2050 assuming no-new-vaccine introduction. I compared the cumulative cases, deaths, and DALYs averted as well as the costs and cost-effectiveness between the no-new-vaccine baseline and the introduction of thirteen M72/AS01$_E$ and twelve BCG-revaccination scenarios (**Objective 3b**).

For each vaccine product, I established a *Basecase* vaccine scenario with characteristics informed by trial data and expert opinion. The *Basecase* M72/AS01$_E$ scenario assumed a 50% prevention of disease vaccine which would be effective in both those infected and uninfected at the time of vaccination, delivered routinely to those aged 15 and as a campaign to ages 16–34 in 2030 and 2040. The *Basecase* BCG-revaccination scenario assumed a 45% efficacy prevention of infection vaccine which would only be effective in those uninfected at the time of vaccination, delivered routinely to those age 10 and as campaigns to ages 11–18 in 2025, 2035, and 2045. I created *Policy Scenarios* for each vaccine product which varied the ages targeted from the *Basecase*, and *Vaccine Characteristic and Coverage Scenarios* which varied vaccine profile characteristics to assess uncertainty.

Country-level modelling suggested that M72/AS01$_E$ and BCG-revaccination could have a large health impact in India and are likely to be highly cost-effective when measured against three country-specific opportunity cost thresholds (**Objective 3c**). I estimated that the most impactful M72/AS01$_E$ scenario (a 70% efficacy vaccine opposed to 50%) could avert up to 19.3

million cases and 3.1 million deaths, and the most impactful BCG-revaccination scenario (a 70% efficacy vaccine opposed to 45%) could avert up to 15.2 million cases and 2.6 million deaths in India by 2050.[17]

For M72/AS01$_E$, all scenarios were cost-effective at the most conservative country-level threshold compared to no-new-vaccine introduction except if vaccine efficacy was restricted to those with current infection at vaccination. The latter remained cost-effective at the intermediate opportunity cost threshold. For BCG-revaccination, all scenarios were highly cost-effective at all thresholds evaluated. The average annual cost of M72/AS01$_E$ vaccination was around four times greater than that of BCG-revaccination. Vaccination may lead to an annual incremental cost of US$190 million for the *Basecase* M72/AS01$_E$ scenario and US$23 million for the *Basecase* BCG-revaccination scenario. Cost-savings in tuberculosis diagnostics and treatment per year were approximately 1.4 times greater for the *Basecase* M72/AS01$_E$ scenario due to averting more treatments and deaths than the *Basecase* BCG-revaccination scenario.

Using the detailed country-level model, the evidence I have generated can directly support the Indian government with decisions regarding vaccine delivery. While uncertainty exists in the actual vaccine characteristics that will be realised when the vaccine is delivered (particularly whether M72/AS01$_E$ will be effective in people who are uninfected, and if BCG will prevent both infection and disease), my country-level modelling of India suggested that the positive health and economic impacts from new tuberculosis vaccines are likely to remain regardless.

Novel contributions to the literature from Chapter 4

This is the first model incorporating self-clearance and subclinical disease that investigated the impact of tuberculosis vaccines in India. I provided specific estimates of and compared the health and economic impacts of introducing either M72/AS01$_E$ or BCG-revaccination to adolescents and adults in India.

6.1.3 Subnational modelling

The final aim of the thesis, **Aim 3**, was to estimate the health and economic impact of introducing M72/AS01$_E$ and BCG-revaccination in Delhi and Gujarat to compare the effect of different population-level characteristics on vaccine impact to provide evidence for subnational decision makers. **Aim 3** was addressed through

Objective 4: Further extend the country-level India tuberculosis model to develop subnational models for Delhi and Gujarat

a. Calibrate to region-specific estimates of tuberculosis prevalence and case-notifications
b. Simulate the introduction of M72/AS01$_E$ vaccines and BCG-revaccination under varying delivery strategies, and
c. Estimate and compare the health and economic impacts of vaccine scenarios from each region

Summary of Chapter 5

The National Tuberculosis Prevalence Survey in India estimated wide variations in disease prevalence across the country.[18] The estimate in India overall was 316 per 100,000 population, but this ranged from 747 per 100,000 in Delhi to 137 per 100,000 in Gujarat.[18] Regional differences in burden and demography may influence the estimates of vaccine impact, but no previous modelling studies of tuberculosis vaccines had compared the health and economic impact of M72/AS01$_E$ and BCG-revaccination introduction for regions within India.

I further extended the mathematical model from Chapter 4 to create subnational models representing Delhi and Gujarat. I calibrated the models using region-specific estimates of tuberculosis disease prevalence from the national tuberculosis prevalence survey in India, and case-notification estimates from the Ni-kshay reporting system (**Objective 4a**). I simulated the introduction of vaccine scenarios similar to the scenarios from Chapter 4 to allow for comparison between country-level and subnational results.

M72/AS01$_E$ and BCG-revaccination could have a large health impact in Delhi and Gujarat. More cases and deaths could be averted by M72/AS01$_E$ vaccination compared to BCG-revaccination in

both regions under the assumed vaccine characteristics (M72/AS01$_E$ preventing disease with a vaccine effective with any infection status compared to BCG-revaccination preventing infection and only effective in those who were uninfected at the time of vaccination). Despite the larger population size of Gujarat, more cases and deaths were averted in Delhi for both vaccines due to the higher burden of disease in Delhi.

A number of the findings were related to the differences in modelled tuberculosis infection prevalence between Delhi and Gujarat. There were no region-specific estimates of infection prevalence available to constrain the modelled infection prevalence in each region, but I modelled a higher prevalence of infection in Delhi compared to Gujarat for all ages, assuming infection prevalence correlated with disease prevalence. I found a lower relative impact of vaccines effective if delivered to those that were uninfected (e.g., BCG-revaccination) in Delhi than in Gujarat particularly for vaccine delivery scenarios that targeted older adolescents and adults. I found a higher relative impact of BCG-revaccination in the *Older Ages* and *All Adults* scenarios compared to the *Basecase* scenario in Gujarat than in Delhi.

In Delhi, both M72/AS01$_E$ and BCG-revaccination would be cost-effective, or even cost-saving, at the most conservative opportunity cost threshold regardless of the assumed vaccine characteristics. In Gujarat, M72/AS01$_E$ would be cost-effective at 1×GDP per capita threshold of India assuming efficacy was not restricted to those with current infection at vaccination, and BCG-revaccination would be cost-effective at the intermediate opportunity cost-threshold.

The average annual cost of vaccination was 3.1–4.3 times lower in Delhi than in Gujarat, due to the lower population size, and I assumed there would be a reduced patient time cost for vaccination in Delhi than in Gujarat because of the proximity to health care services. Similar to results at the national level (Chapter 4), the cost of vaccination for M72/AS01$_E$ was 3.4–4.4 times larger than for BCG-revaccination in both regions, due to the differences in vaccine price ($2.50 per dose for M72/AS01$_E$ vs. $0.17 per dose for BCG-revaccination) and doubled delivery costs of providing two doses.

Chapter 5 has demonstrated how subnational modelling can reveal differences in impact within a large country when demography and epidemiology vary and has generated evidence to support obtaining age-specific regional estimates of the prevalence of infection to improve vaccine impact estimates. It would be beneficial to generate subnational models for all states and union territories in India to inform vaccine delivery strategies, but more region-specific data on the population composition and infection prevalence are needed.

Novel contributions to the literature from Chapter 5

This is the first study to generate and compare subnational estimates of the health and economic impacts of introducing M72/AS01$_E$ and BCG-revaccination in Delhi and Gujarat, and the first study to calibrate to subnational estimates of tuberculosis disease prevalence.

6.2 Limitations

In this section, I first highlight the common limitations that applied to all the modelling work presented in this thesis, and the implications for my findings overall. Key limitations for each Chapter were described in the discussion section of each research paper, but in the following specific subsections, I restate and further discuss selected limitations of the multi-country modelling, country-level modelling, and subnational modelling studies.

This thesis was a mathematical modelling exercise, where I developed a model structure to predict the impact likely with new tuberculosis vaccines. Therefore, limitations associated with mathematical models apply throughout. If I had made incorrect assumptions on the model structure, such as neglecting to incorporate key components of tuberculosis natural history or assuming an incorrect relationship between compartments, I may have misrepresented the tuberculosis epidemic in each setting. In the updated model structure, I incorporated self-clearance of *Mtb* infection and subclinical tuberculosis disease, but excluded more recent advances, such as minimal tuberculosis disease and regression from disease to infection.[19] If a current infection vaccine would not be efficacious for those with minimal tuberculosis disease, I may have overestimated the vaccine impact.

I made assumptions on how natural history compartments interacted with vaccine protection, such as assuming that vaccine protection instantly waned with progression to active disease, and that a vaccine was not efficacious if administered to an individual with subclinical disease. Given that estimates of vaccine impact are related to assumptions on how novel vaccine products interact with tuberculosis natural history, this limitation could mean that vaccine impact was over or underestimated. Future work (described in Section 6.3) could evaluate our assumptions around tuberculosis natural history and vaccine protection.

Another limitation of this work was how I accounted for extrapulmonary tuberculosis (EPTB). Research Paper 1 and Research Paper 2 used estimates of burden from WHO to calibrate the models, which included the contribution from both pulmonary tuberculosis and EPTB. However, in contrast to pulmonary tuberculosis, EPTB is not infectious. In order to not overestimate the amount of pulmonary tuberculosis in the population, I discounted the force of infection based on the assumed proportion of EPTB of total disease, and continued to fit the reported WHO targets during calibration.

For the multi-country modelling, I adjusted the force of infection by using the WHO reported country-specific average of the proportion of new incident EPTB cases from 2017–2019,[20] and for the country-level modelling of India, I adjusted the force of infection by using WHO reported average proportion of new incident EPTB cases from 2013–2020.[20] Research Paper 3 was not fit to any estimates from the WHO, but to keep consistent methodology and allow for comparison between Research Paper 2 and Research Paper 3, I adjusted by the region-specific average proportion of new incident EPTB cases from 2013–2019.[21–27]

However, this method has limitations due to differences between pulmonary tuberculosis and EPTB. I assumed that the age-specific distribution of EPTB would be equivalent to the age distribution of pulmonary tuberculosis, and therefore the average proportion of EPTB would apply for the entire population. Females or those at the extremes of age are at an increased risk of developing EPTB and therefore that assumption may have resulted in an increased or decreased adjustment to the force of infection, which could affect the number of new cases of tuberculosis predicted by the model each year.[28,29] Given the estimates for the average proportion of EPTB

were informed by reported new EPTB cases, if the duration of each case was longer than one year, the proportion of prevalent tuberculosis that was EPTB would be underestimated, similarly leading to an overestimation of the yearly incidence predicted by the model. That being said, the models were calibrated to incidence and/or prevalence targets, and therefore the main conclusions are likely to be robust to this potential limitation.

6.2.1 Multi-country modelling

Given resource and time constraints, it was not possible to develop a tailored model for each country. I assumed a consistent model structure with eight natural history compartments for each country and consistent prior distributions for parameters for all countries. I attempted calibration on 115 countries of the 135 countries classified as LMICs based on the 2019 World Bank classifications as data, such as contact matrices, or epidemiological data from WHO, was lacking for 20 countries. I calibrated the model for each country to nine targets, with an additional four targets included for countries classified as having a high burden of tuberculosis due to HIV. Given the number of countries included in the analysis, estimates for only one time point (the year 2019) were used for each calibration target, and therefore I was not able to fit a temporal trend in tuberculosis burden. While I verified that the trends in each country were qualitatively consistent with the data used, by not calibrating to multiple targets I may have over or underestimated the amount of tuberculosis in the population for a vaccine to avert.

I successfully calibrated 105 countries which form the basis for the estimates in Research Paper 1. In a paper describing the calibration process, Scarponi et al. performed a detailed analysis of the 10 countries that could not be calibrated. The authors found that in some countries the model structure and parameter constraints were not compatible with the epidemiological data reported by WHO.[30] While the model structure I used was appropriate for high-burden countries with established *Mtb* transmission for all ages, it was misspecified for countries with no or low childhood tuberculosis, as it required estimates of the tuberculosis incidence and case notification rates in children. As countries with low tuberculosis incidence in children are likely to have a lower tuberculosis burden overall, it is likely that excluding these countries would not significantly impact the number of averted cases and deaths overall.

The model structure did not incorporate drug-resistant tuberculosis. To estimate the number of drug-resistant cases, treatments, and deaths averted by vaccination, I multiplied the number of averted cases, treatments, and deaths for each country by a fixed factor, representing the country-specific proportion of tuberculosis that was drug-resistant, which did not capture any dynamic trends in drug-resistance. If future trends in drug-resistant tuberculosis differ substantially from this assumed factor, I may have over or underestimated the amount of averted drug-resistant tuberculosis cases and deaths.

Although country-specific introduction years were incorporated in two scenarios, I assumed that the scale-up trend of introducing vaccines would be equivalent for all countries. In the *Basecase* and *Routine Only* delivery scenarios, scale-up to target coverage would occur linearly over five years. In the *Accelerated Scale-up* delivery scenario, scale-up to target coverage was instant. However, the pace of vaccine scale-up will likely differ between countries. Smaller countries may be able to more rapidly scale-up to target coverage given the lower number of doses needed to deliver, or larger countries with more resources could be in a better place to operationalise and introduce the vaccine and achieve economies of scale. Therefore, I may have underestimated how rapidly the health benefits from vaccination would accrue. Given the model time horizon was only until 2050, I may have failed to capture some of the vaccine benefits as they would continue to accrue after this time point which was not accounted for.

6.2.2 Country-level modelling

There were a number of limitations associated with the country-level modelling in Chapter 4. In particular, while I incorporated the impact of COVID-19 in the India model, I did not dynamically model increases in tuberculosis mortality and incidence, or the reduction in treatment initiation. Given that the earliest vaccine introduction year was not until 2025, and the key impacts of the COVID-19 pandemic on tuberculosis occurred in 2020 and 2021, I assumed that the underlying epidemiological trends in tuberculosis would return to pre-COVID baselines by the time tuberculosis vaccines were introduced. If this assumption was incorrect, then I may have underestimated the amount of burden available for vaccines to address. However, as shifts in tuberculosis epidemiology are relatively slow, disruptions such as COVID-19 are unlikely to have

a long-lasting impact on tuberculosis trends, and therefore this limitation would likely have played a minor role in the impact estimation.

The Global Tuberculosis Report in 2021 used mathematical models to simulate the country-specific increase in tuberculosis incidence and mortality in 2025 due to COVID-19 compared to the scenario with no COVID-19 and estimated that the incidence and mortality rates in 2025 in India would be 10% higher than in 2020 due to COVID-19. Therefore, I ensured that the calibrated India model fit this target. However, the forward trajectory of tuberculosis incidence and mortality was relatively flat into the future. Therefore, I may have been overestimating the amount of burden available for vaccines to address.

I incorporated differences in public and private sector treatment in the country-level modelling. I assumed that a constant 60% of treatment was occurring in the public sector and 40% in the private sector. I varied treatment outcomes between sectors using a weighted average of treatment outcomes informed by yearly WHO estimates and assumed that treatment completion in the private sector remained at 40% without any future improvements in treatment outcomes. If I incorrectly represented the proportion of cases seeking treatment from each sector or the differences in treatment outcomes, I may have overestimated on-treatment mortality and non-completion.

In 2021, the WHO released updated lists of countries with a high tuberculosis burden, countries with high HIV/TB burden, and countries with a high burden of drug-resistant tuberculosis, classified as the top twenty countries by absolute number of cases in each category plus the next top ten countries in terms of incidence rate.[31] Combined, these countries account for 86–90% of the burden globally, and are likely to be key regions for introducing a new tuberculosis vaccine.[31] India is included on all three high burden lists, but I did not incorporate a separate HIV model structure or dynamically model drug-resistant tuberculosis in the country-level modelling work. While the absolute magnitude of cases occurring in PLHIV and that were drug-resistant was large, the proportion of total cases in India from each was low (e.g., 1.8% of the total tuberculosis cases in 2021 occurred in PLHIV,[32] and 2.8% of the total cases were drug-resistant in 2019).[33] However, if the effectiveness of a vaccine was reduced in PLHIV or did not prevent drug-resistant

tuberculosis with the same efficacy as drug-susceptible tuberculosis, then I may have overestimated the health and economic impacts.

6.2.3 Subnational modelling

A key limitation to the subnational modelling study was the availability of data to inform demography. United Nations population data and projections were available for single years and ages for India overall, but not for each individual region. I extrapolated using the population distribution for India overall and census data from 1991, 2001, and 2011 for Delhi and Gujarat as described in the supplementary material for Research Paper 3. *Mtb* infection is age dependent, with older ages more likely to have a higher prevalence of infection. The M72/AS01$_E$ and BCG-revaccination scenarios included in the modelling were targeted to specific age groups, with the *Basecase* M72/AS01$_E$ scenario targeted to an older age group than the *Basecase* BCG-revaccination scenario. I assumed in the *Basecase* scenario that BCG-revaccination would be effective in those uninfected at the time of vaccination. As the prevalence of infection increases with age, younger ages would benefit more from BCG-revaccination. Therefore, if the population distribution was incorrectly represented in either of the regions, this would result in larger or smaller population sizes in the vaccine targeted age groups. If more or less people were vaccinated, this could imply that vaccine protection was not distributed in the population appropriately.

I was also limited by the availability of region-specific data for model calibration. There was no regional data to inform constraints on tuberculosis mortality, and therefore the epidemiological trends simulated by the no-new-vaccine baseline for Delhi and Gujarat predicted wide uncertainty bounds on the mortality rate. The recent National Tuberculosis Prevalence Survey in India provided regional estimates of tuberculosis disease prevalence for Delhi and Gujarat, but there were no age- or region-specific estimates of infection prevalence, which may have resulted in the modelled infection prevalence for each region being over or underestimated.

One of the key results from Research Paper 3 was recognising how strongly infection prevalence determines impact from M72/AS01$_E$ or BCG-revaccination given the assumed vaccine characteristics. I assumed that infection prevalence would correlate with disease prevalence and modelled a higher infection prevalence in Delhi than in Gujarat. Consequently, BCG-revaccination

resulted in a higher relative impact in Gujarat due to the assumed efficacy in only uninfected populations. I also found that if M72/AS01$_E$ was only efficacious with current infection at vaccination, delivering the vaccine in Gujarat would have less of an impact and may not be cost-effective given the thresholds evaluated. If this was an incorrect assumption, or if the actual infection prevalence trends in Delhi and Gujarat are significantly different than those modelled in Research Paper 3, the conclusions from the impact modelling may be incorrect.

I assumed that vaccine delivery would be equally feasible between Delhi and Gujarat and that both regions could reach the target vaccine coverage. However, Delhi is almost entirely urban, compared to the urban-rural mix of Gujarat. Previous studies on various vaccine preventable diseases globally have reported disparities between rural and urban areas. Rural areas were more likely to have lower vaccine coverage,[34–36] delayed vaccine uptake,[35] and increased vaccine hesitancy. Therefore, by assuming that Delhi and Gujarat would be able to reach the same vaccine coverage with the same pace of introduction, I may have overestimated the possible vaccine coverage in Gujarat, leading to an overestimation of the health impact and health-system costs.

6.3 Areas for extending this research

While this thesis has addressed research gaps and generated vaccine impact estimates to inform decision makers, there are numerous ways that the model and research can be extended to address additional questions.

1. Extending vaccine modelling

Objective 1b was to develop a new vaccine model structure which allows for protection from multiple vaccines with varying product characteristics and is able to represent sophisticated and realistic vaccine delivery strategies. The new vaccine model structure was developed and described in Chapter 3, and used in Chapter 3–5 to introduce new vaccines in LMICs, India, Delhi, and Gujarat, but could be used in the future to address the following:

a. Vaccination of risk groups

Specific risk groups, such as healthcare workers, people completing anti-tuberculosis treatment, or household contacts of people with a confirmed diagnosis of tuberculosis disease, have been identified as high priority groups for vaccination by the Central TB division in the Government of India (Personal communication, Dr Sanjay Mattoo & Dr Dheeraj Tumu, April 2023). Previous modelling studies of vaccination in India have suggested that targeting populations at a high risk of developing tuberculosis, such as people with diabetes mellitus or those with undernutrition, could disproportionately reduce tuberculosis burden.[16,37] Given that these populations may already be integrated with healthcare services, they may be easier to reach with vaccination than the general population. Future work could extend the current modelling to estimate the impact of targeting high priority populations, assuming more realistic delivery and targeting strategies.

b. Vaccination by sex and/or gender

Tuberculosis burden is higher in males than in females.[38] In the modelling presented in this thesis, I disaggregated the population by age, access-to-care, and tuberculosis natural history compartments, but not by sex or gender, under the assumption that I would not expect the level of protection of a vaccine to vary between males and females, and because there were no indications that a sex or gender targeting strategy would be used for tuberculosis vaccine delivery.

However, it is possible that the initial assumption could be incorrect. There could be differences in vaccine efficacy and duration of protection between males and females, as demonstrated with other vaccines,[39–41] BCG vaccination in mice,[42] and shown non-significantly in a retrospective study of BCG in Native American populations.[43] It is also possible that other differences between males and females, such as healthcare access or willingness to be vaccinated, could result in different proportions of males and females receiving a new tuberculosis vaccine. Therefore, incorporating the sex distribution of the population into the modelling, evaluating differences in vaccine characteristics between males and females, or varying the likelihood of vaccination by sex could have an impact on the estimated vaccine impact overall. These questions could be evaluated in future work;

however, models could be difficult to parameterise due to limited sex- and gender-specific data availability and differences in contact structures.

c. Vaccination by access-to-care status

An access-to-care structure was incorporated into the models in Chapter 3 and 4 to accurately represent the negative association between access to healthcare services and tuberculosis burden, and was used by Portnoy et al., 2023 to evaluate the impact of tuberculosis vaccine on cases and catastrophic costs averted by wealth quintile.[9,44] Currently, I assumed that the likelihood of receiving a vaccine was equivalent between access-to-care compartments. However, it is likely that there may be differences. For example, those with higher access-to-care may be more likely to access a vaccine, and therefore there could be a higher likelihood of receiving protection from a vaccine in a population with a lower burden, and lower vaccine coverage in the population with a higher burden. Future work could investigate the impact of assuming differential vaccine delivery by access-to-care including targeting campaigns.

d. Vaccine supply constraints

Current studies have estimated the health and economic impact of new tuberculosis vaccines assuming that the supply of vaccines is aligned with the demand. While I investigated the impact of reaching different vaccine coverage levels, I did not model a situation where there was a specific constraint on the amount of vaccine doses available to deliver. In reality, the supply of new tuberculosis vaccines is likely to be limited immediately following licensure as manufacturing and logistical processes are brought up to scale. Future modelling work could investigate the health and economic impact possible with restrictions on the amount of vaccine product available each year, as well as comparing the impact from prioritising high-risk populations for vaccine delivery.

e. Tuberculosis natural history and vaccine protection

In Chapters 3–5, I assumed that the effect of a prevention of disease vaccine would be mediated by reducing the rate of progression to subclinical disease (i.e., reducing the rate of progression from “infection” to active disease). However, if the vaccine instead reduced the

rate of progression from subclinical to clinical disease without impacting the rate of progression to subclinical disease, the size of the subclinical compartment would be an underestimate across all modelled scenarios. Future research could investigate and compare the differences in overall impact between each of the proposed mechanisms of prevention of disease.

I also assumed that vaccine protection would instantly wane with progression to subclinical disease. Therefore, if an individual was vaccinated and protected by a vaccine while in a latency compartment, but subsequently progressed to subclinical disease while they were still protected, they would instantly lose the protective benefit of the vaccine. Upon transition to the resolved compartment, they would no longer have any vaccine protection. Future work could evaluate the impact if vaccine protection was retained with progression to subclinical disease, and the impact this would have on the proportion of incident cases resulting from relapse from the resolved compartment.

Given the above assumptions about how the prevention of disease mechanism is mediated and instantaneous waning of vaccine protection on transition to subclinical disease, I assumed that if an individual with subclinical tuberculosis received a vaccine that it would be ineffective, as the presence of active disease would overpower any protective effect from the vaccine (following expert advice from an immunologist). Therefore, if individuals were unaware they had subclinical tuberculosis and were vaccinated, they would receive no protective benefit. However, the updated vaccine structure continued to record the number of individuals with subclinical tuberculosis who received the vaccine for costing purposes. Future research could investigate the difference in estimated health and economic impact if this assumption was incorrect, and those individuals who received the vaccine while in the subclinical disease compartment did receive protection. As the understanding of subclinical tuberculosis, and other novelties in tuberculosis natural history such as self-clearance, improves, it is likely that mathematical models will be more appropriately parameterised and able to answer these questions.

f. Multiple vaccine products

In Chapter 2, I investigated the impact of a hypothetical infant vaccine or a hypothetical adolescent/adult vaccine in 105 LMICs. However, I did not investigate a situation where both an infant and an adolescent/adult vaccine were introduced in the same population simultaneously. Given that both adolescent/adult and infant vaccine candidates are currently in clinical trials, consultation with national policy makers about planned implementation strategies could suggest that both vaccines would be introduced. Future work could investigate the population level impact of such a situation.

Similarly, in Chapters 3 and 4, I investigated the impact of introducing M72/AS01$_E$ and BCG-revaccination separately in India, Delhi, and Gujarat. Therefore, the results are applicable for a situation where the government decides to introduce either M72/AS01$_E$ or BCG-revaccination. However, given the differences in anticipated introduction year and vaccine profile, it is likely that countries could decide to introduce both vaccines in the same population, but at different times.

While I assumed that the earliest introduction year for M72/AS01$_E$ was not until 2030, a policy change could lead to a substantially more rapid introduction of BCG-revaccination. One could imagine a situation where BCG-revaccination is introduced as soon as possible, followed by M72/AS01$_E$ when it becomes available. This would raise multiple questions, including: Which age groups would receive each vaccine? Are there any potential implications for vaccine protection if an individual receives both vaccines (e.g., would there be any boosting of vaccine protection)? Could it be feasible, safe, and cost-effective to administer both vaccines to everyone, or would testing with IGRA before vaccine delivery to estimate infection status be preferred?

These questions will likely remain unanswered until both vaccines are rolled out to the general population. However, mathematical modelling could present scenarios where multiple options are evaluated and provide a range of possible impact. Future work could model the health impacts possible with scenarios assuming delivery of more than one

vaccine in the same population and investigate the implications of interactions if multiple vaccines were administered to the same individual.

g. Optimal age for targeted vaccination

In each of Research Paper's 1–3, I evaluated the impact of specific vaccine delivery scenarios (*Basecase*, *Accelerated Scale-up,* and *Routine Only* scenarios in Research Paper 1, and *Basecase*, *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios* in Research Papers 2 and 3), which each had an associated age group targeted with vaccination based on consultation with country experts and clinical trial evidence. I did not investigate the separate question of determining the optimal age group to target to produce the largest vaccine impact for given product characteristic assumptions. While these were not questions I set out to answer in my thesis, they are important aspects for future research.[45]

2. Extending country-level and subnational modelling

The country-level modelling in Chapter 4 provided detailed estimates of the impact in India tailored to government needs for preparing for vaccine introduction. Moving forward, there is the opportunity to create similar detailed national models for other countries requiring this information. Modelling of additional countries on the WHO high tuberculosis burden lists, such as Indonesia, which is included on all three WHO lists and reported almost 1 million cases and 150 thousand deaths in 2021 (second only to India), could help support national decision makers with strategies for tuberculosis vaccine introduction.

Building off of the subnational modelling in Chapter 5, there is an opportunity for future research to extend to other states and union territories in India. I found that the impact of M72/AS01$_E$ and BCG-revaccination varied between Delhi and Gujarat based on the assumed underlying epidemiology. Modelling of other regions, such as Uttar Pradesh or those with differing population and epidemiological characteristics, would help to address further questions on how the impact of vaccines would vary across India, and support regional strategies for vaccine delivery.

3. Ability to compare the impact from different interventions

It is likely that no intervention alone will be enough to eliminate tuberculosis, and instead, countries will incorporate combinations of measures. The model developed for answering the questions posed in this thesis is very flexible, and in addition to future work investigating questions surrounding vaccine targeting, the structure can be extended to incorporate additional features. Strategies such as active case finding and tuberculosis preventive therapy are likely to play a role, and future work could estimate the impact of different combinations of interventions alongside vaccination.

6.4 Implications and conclusions

Decision makers globally, at the overall country-level, and for subnational regions within countries need tailored information on the likely health and economic impact following the introduction of new tuberculosis vaccines.

Multi-country modelling in Chapter 3 identified the importance of estimating the global health gains from new tuberculosis vaccines to provide evidence to support continued vaccine investment and development, and preparation for vaccine introduction. I highlighted that earlier vaccine introduction and rapid scale-up to target coverage, as well as delivery through mass vaccination campaigns to adolescents and adults is crucial to achieve maximum impact as quickly as possible.

Country-level modelling from Chapter 4 suggested that new vaccines such as M72/AS01$_E$, and policy revisions such as recommending BCG-revaccination for adolescents could reduce the burden of tuberculosis in India. Introducing M72/AS01$_E$ was predicted to have a larger health impact compared to BCG-revaccination by 2050 but resulted in higher cost-effectiveness ratios due to the higher assumed price per dose and requiring duplicated delivery costs. India is considering introducing a new vaccine or BCG-revaccination in the near future and this evidence will inform and support delivery strategies.

Modelling of Delhi and Gujarat in Chapter 5 suggested that the benefits of introducing M72/AS01$_E$ and BCG-revaccination are likely to persist at the subnational level. Differences in impact between

vaccines and regions were driven by differences in product characteristics and their interaction with epidemiology, particularly the modelled infection prevalence in each region. Further evidence on M72/AS01$_E$ product characteristics, which were important drivers of impact and cost-effectiveness in Gujarat, are key to improved estimates of population level impact.

For the tuberculosis vaccine community, having sixteen vaccine candidates in various trial phases is a positive development, but there remains room for improvement. Tuberculosis has caused disability and disease for millennia, but one of the most promising vaccine candidates, M72/AS01$_E$, has yet to start a Phase III trial despite almost five years since the completion of the first Phase IIb trial.[46,47] We need to continue to fill out the vaccine pipeline with candidates in early Phase trials, and invest in more development to increase the likelihood that we will receive a successful vaccine. There are only three candidates currently in Phase I trials, of which two have been in Phase I trials for the past five years.[47] There are candidates in late stage clinical trials, (such as M72/AS01$_E$, BCG-revaccination, MTBvac, and VPM1002), but sustained continued investment in candidates throughout the pipeline is needed, as it is unwise to solely focus on so few candidates as the vaccine solution to the epidemic.

Evidence provided in this thesis has and can help to inform and support future investment, policy recommendations and delivery strategies for global, national, and subnational tuberculosis vaccine introduction.

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