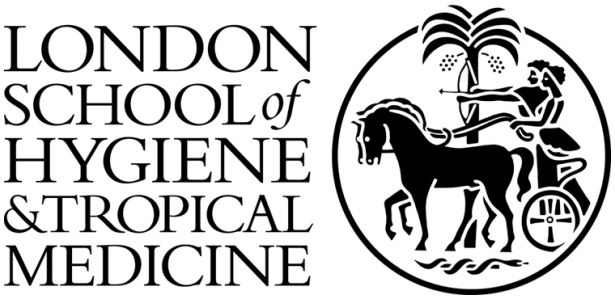

Estimating the burden of *Mycobacterium tuberculosis* infection and the impact of population-wide screening for tuberculosis

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Declaration of own work

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

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Abstract

An estimated quarter of the global population has been infected with *Mycobacterium tuberculosis* (*Mtb*), the causative agent of tuberculosis (TB). Despite ongoing efforts, TB reduction trends are only slightly declining. Mathematical modelling that recognises the spectrum of TB disease provides valuable insights into its policy implications. This thesis aims to generate accurate estimates of the burden of viable *Mtb* infection and evaluate the impact of population-wide screening interventions.

Firstly, I assessed the impact of immunoreactivity test reversion on the estimated annual risk of infection (ARI), a key metric in TB epidemiology that measures *Mtb* transmission risk. When accounting for reversion, the true ARI was determined to be 2–5 times higher than previously estimated. Secondly, I refined previous *Mtb* infection estimates using a mathematical model that incorporated reversion-adjusted ARI trends, age-specific mixing, and self-clearance of infection. This analysis estimated that 2%—equating to 156 million people—are recently infected with viable *Mtb* and at high risk of disease progression. Thirdly, I re-evaluated the effectiveness of mass screening interventions using chest radiography (CXR) as a strategy to significantly reduce TB prevalence. Finally, I calibrated a model to TB epidemiology in Vietnam and designed various population-wide screening algorithms to evaluate their impacts and costs. While a CXR-only algorithm rapidly reduced TB prevalence, they incurred high costs due to overtreatment. A combined approach of CXR followed by confirmatory bacteriological testing proved cost-effective and became cost-saving compared to a business-as-usual counterfactual after the intervention ended.

Overall, the findings of this thesis quantify the population eligible for TB preventive therapy and offer insights into cost-effective strategies for significantly reducing TB prevalence through population-wide screening in high-burden countries.

Acknowledgements

Although my brain still shrivels at the sight of maths, the past three years have been an incredible journey, and I am immensely proud of all that has been accomplished. None of this, however, would have been possible without the unwavering support of many.

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sad. To my sister: Thanks for nothing. To my parents: I know it is still shocking that I willingly work with maths but thank you for your constant encouragement. I've become a different kind of doctor than you once imagined, but I can still confidently say that you cannot get sick from feeling cold. Gracias, los quiero mucho.

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Tables appearing in the thesis, numbered by chapter and order of appearance. Tables included in research papers and supplementary material are not listed here.

List of abbreviations

For clarity and ease of reference, abbreviations are defined upon their first use in each chapter. Abbreviations appearing in research papers and supplementary material are not included in this list but are properly defined within their respective contexts. Below is a consolidated list of all abbreviations used throughout this thesis:

AFB	Acid-fast bacilli
ARI	Annual risk of infection
ATS	American Thoracic Society
BCG	Bacillus Calmette-Guérin
CAD	Computer-aided diagnosis
CXR	Chest radiography
DST	Drug susceptibility testing
HIV	Human immunodeficiency virus
ICE-TB	International Consensus for Early TB
IGRA	Interferon-gamma release assay
KPS	Karonga Prevention Study
LMIC	Low- and middle-income country
LTBI	Latent TB infection
Mtb	*Mycobacterium tuberculosis*
NAAT	Nucleic acid amplification tests
NTM	Non-tuberculous mycobacteria
TB	Tuberculosis
TPT	TB preventive therapy
TST	Tuberculin skin test
WHO	World Health Organization

Chapter 1: Introduction

In this chapter, the rationale for the thesis is presented, highlighting the research gaps that shaped its aims and objectives. The structure of the thesis is then outlined, along with an acknowledgment of the ethical considerations and funding sources that supported this research.

1.1 Rationale

This research focuses on refining tuberculosis (TB) disease modelling and public health interventions to better represent the complex natural history of TB along the disease spectrum. It re-evaluates assumptions about immunoreactivity and mycobacteria viability while exploring the impact of mass screening approaches. The thesis aims to enhance the precision of *Mycobacterium tuberculosis* (*Mtb*) infection burden estimates and identify cost-effective population-wide screening algorithms to reduce TB prevalence in high-burden countries. Ultimately, this work seeks to inform targeted, cost-effective interventions to accelerate progress towards TB elimination.

1.2 Thesis aims

The thesis has two main aims:

1. Estimate the global burden of viable *Mycobacterium tuberculosis* infection, and
2. Evaluate the potential impact, cost, and benefits of population-wide screening interventions for tuberculosis in a high-burden setting

1.3 Thesis objectives

To address Aim #1, there are two objectives:

1. Quantify the impact of immunoreactivity test reversion upon the estimated annual risk of infection (ARI).
2. Estimate the global burden of viable *Mtb* infection, accounting for reversion-adjusted and age-specific ARI trends in addition to self-clearance of infection.

To address Aim #2, there are two objectives:

3. Re-evaluate the impact of a historical mass chest radiography (CXR) screening intervention on the reduction of TB prevalence.
4. Assess the cost-effectiveness of various population-wide screening algorithms and durations using a natural history model of the spectrum of TB disease.

1.4 Thesis structure

This thesis is structured in a 'research paper style' format, as per the guidelines for doctoral students at the London School of Hygiene and Tropical Medicine. The seven chapters of this thesis are organised as follows:

- *Chapter 1:* The introductory chapter provides an overview of the thesis, presenting a concise rationale for the work. It outlines the aims, objectives, and structure of the thesis, as well as details on ethical considerations and funding.
- *Chapter 2:* This chapter presents a comprehensive literature review offering the necessary background knowledge for the research projects described in the subsequent chapters. It focuses on identifying the research gaps, as highlighted in *Section 1.1*.
- *Chapter 3:* Centred around the first research paper of the thesis, published in the *American Journal of Epidemiology*, this chapter quantifies the impact of immunoreactivity test reversion upon the estimated ARI [1]. It compares naïve ARI estimates (which do not account for reversion) against true ARI estimates derived from various reversion probabilities, up to 50%. This chapter addresses thesis *Objective #1*.
- *Chapter 4:* The second research paper, currently available as a preprint on *SSRN* pending peer review, is discussed in this chapter [2]. This study estimated the global burden of viable *Mtb* infection under different assumptions of long-term self-clearance rates by constructing country-specific ARI trends. These trends incorporated estimates of TB burden, age-specific contact mixing, and immunoreactivity reversion into a deterministic model tracking *Mtb* infection and self-clearance. This chapter addresses thesis *Objective #2*.
- *Chapter 5:* The third research paper, published in the *International Journal of Tuberculosis and Lung* Disease, re-evaluates the impact of a historical mass CXR screening programme [3]. The study examines whether there was a decline in TB incidence and to what extent was this due to the intervention. This chapter addresses thesis *Objective #3*.
- *Chapter 6:* The fourth and final research paper, also available as a preprint on *medRxiv*, is the focus of this chapter [4]. In this paper, an expanded a TB natural history model was calibrated to TB epidemiology in Viet Nam to simulate the impact of various population-wide screening strategies introduced in 2025. The study compares the incident TB and deaths averted under each intervention compared to the business-as-usual counterfactual. Additionally, the cost-effectiveness of each intervention is evaluated by

calculating the incremental cost-effectiveness ratio per disability-adjusted life years averted up to 2050. This chapter addresses thesis *Objective #4*.

- *Chapter 7:* The final chapter synthesises the findings from each of the research papers presented throughout the thesis, discussing their implications for TB prevention and care, as well as their limitations. It also outlines potential directions for future research to build upon this work.

1.5 Contributions of the author

For the research projects presented in this thesis (*Chapters 3–6*), I served as the lead author, taking primary responsibility for conceptualising the studies, conducting analyses, and drafting the manuscripts. I developed and calibrated mathematical models and designed screening algorithms in collaboration with co-authors. I performed data analysis, interpreted the results, and conducted sensitivity analyses to ensure robustness. Additionally, I drafted all manuscripts, incorporated feedback from co-authors, and prepared submissions to journals and preprint servers. Specific details of my contributions, as well as those of my co-authors, are detailed in Section D of the Research Paper Cover Sheet for each chapter. Although the use of first-person singular ('I' and 'my') throughout this thesis highlights my primary role, I wish to acknowledge that the successful completion of these research projects was the result of a collaborative effort.

1.6 Ethical considerations

In the discussion section of *Chapter 3*, an additional analysis is described that used participant data obtained from studies that had secured appropriate ethical approvals, including those from the Health Sciences Research Committee of the Malawi Ministry of Health, the Ethics Committee of the London School of Hygiene and Tropical Medicine, and the Standing Committee on Research in Human Subjects of the World Health Organization. For the remaining projects, all data were sourced from publicly available resources, such as peer-reviewed journals, books, and institutional reports.

1.7 Funding

No specific funding was received for the PhD. However, the research projects described in this thesis were partially supported by the European Research Council under the Horizon 2020 research and innovation program [grant number 757699] and the United States National Institutes of Health [grant number R-202309-71190].

1.8 References

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Chapter 2: Background

In this chapter, a comprehensive literature review is presented, offering the necessary background knowledge for the thesis. Furthermore, it identifies the research gaps that the subsequent chapters aim to address.

2.1 Tuberculosis

Tuberculosis (TB) is an airborne infectious disease and a leading cause of morbidity and mortality worldwide [1,2]. The World Health Organization (WHO) estimates that 10.8 million people fell ill and 1.3 million people died from TB in 2023, making it the deadliest infectious disease [2]. TB predominantly affects adults (aged 15 years and older), accounting for 88% of the global TB incidence, with men having a notably higher prevalence than women [2,3]. Moreover, while TB is present in all countries, its burden is disproportionally concentrated in low- and middle-income countries (LMICs) [2].

It is estimated that approximately a quarter of the global population has been infected with *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB [4]. *Mtb* is an aerobic, slow-replicating bacterium that, whilst primarily a pulmonary pathogen, can affect every organ in the body [5]. Exposure to *Mtb* occurs via the respiratory tract through inhalation and inoculation of the bacterium in the alveoli [5,6]. Then, a complex interplay between the innate and adaptive immune response of the host takes place, resulting in either the elimination of infection or the persistence of bacteria in the lung parenchyma [1,6]. Approximately 5-10% of individuals infected with *Mtb* will develop symptomatic TB disease during their lifetime, with a higher risk within the first two years after infection [7–10]. Thereafter, progression to disease without reinfection is relatively infrequent [9].

Pulmonary TB is the primary manifestation of the disease, with only around 16% of incident TB episodes attributed to extra-pulmonary TB [2]. The classic clinical manifestations of individuals with pulmonary disease include persistent, productive cough which might worsen into haemoptysis; additionally, non-specific, constitutional symptoms such as fever, chills, weight loss, fatigue, anorexia, and night sweats are often present [1,5]. Nevertheless, several TB prevalence surveys have highlighted that pulmonary TB may be asymptomatic, with up to 80% of those diagnosed with TB not reporting any symptoms [11]. Fortunately, TB is a treatable and curable disease [2]. The current first-line treatment regimen for drug-susceptible pulmonary TB consists of four drugs administered over a six-month period, though shorter regimens with

different drugs are now being introduced [1,12,13]. The standard regimen has a high success rate, with treatment failure generally linked to antibiotic resistance, toxicity and side effects, as well as challenges in maintaining therapy adherence stemming from health system issues, economic constraints, or personal circumstances [1,5]. In the case of drug resistance, treatment duration is extended and second or third-line agents are used, which tend to be more toxic, further compromising success rates [1,5].

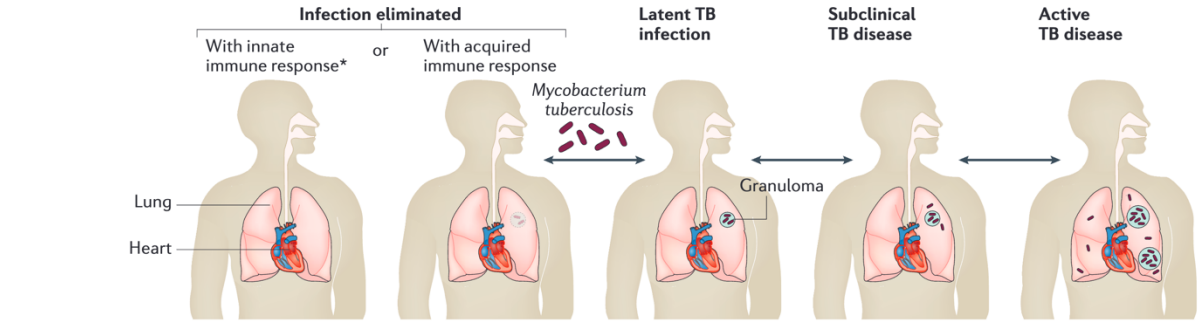
Over 30 years ago, in 1993, the WHO declared TB a global public health emergency, aiming to drive momentum to reduce TB burden [14]. More recently, in 2014, ambitious targets were established in the *End TB Strategy*, which envisions a world free of TB deaths, disease, and suffering by 2035 [15]. Unfortunately, with only a modest decline in TB incidence and mortality over the last decade, we are not on track to meet these milestones [2].

2.2 Natural history

TB is a complex disease with an intricate natural history. Nonetheless, a binary approach has traditionally been applied to TB, divided by a single threshold: latent TB infection (LTBI) and symptomatic TB disease (commonly referred to as clinical or active TB) [5,16]. The former is defined as having a positive immunoreactive test for *Mtb*, no symptoms, and no microbiologic or pathologic findings of symptomatic disease [17]. In this state, bacteria are assumed to persist dormant in a non-infectious state, with a lifelong risk of progression to disease [6,18,19]. On the other hand, as the name suggests, symptomatic TB disease is characterised by the presence of symptoms, along with microbiologic and/or pathologic findings; importantly, *Mtb* transmission also occurs in this state [1,18]. Although not always clear-cut in clinical settings, this classical paradigm has been widely adopted in public health settings due to its simplicity, forming the basis for numerous interventions and mathematical model structures [1].

Recent research increasingly recognises that TB is better understood as a spectrum rather than being confined to two distinct states [1,18,20–24]. This perspective is not entirely new; attempts to conceptualise and define TB states date back to observations made during the pre-chemotherapy era [25]. More recent efforts to unravel TB's complexity have led to the development of various conceptual frameworks, each with distinct terminology dependent on their focus (e.g., TB pathogenesis, immunology, clinical relevance, or epidemiology) [26]. **Figure 2.1** presents a proposed conceptual framework illustrating the spectrum of TB and the defining characteristics of each state [1]. A shared feature of these frameworks is the recognition that TB

exists along a dynamic continuum of infection and disease, with progression that is not strictly unidirectional and may instead follow undulating trajectories [1,18,20–24]. This stands in contrast to the classical binary approach, which acknowledges only the extremes of the spectrum [27]. Consequently, these frameworks highlight how the binary approach could hinder efforts towards achieving the *End TB Strategy* goals [15], as clinical management and research remains largely based on a binary understanding of the disease [23,24].



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

Figure 2.1 The spectrum of TB from *Mtb* infection to active TB disease. The spectrum of TB comprises of several states, from initial *Mtb* infection to active TB disease. Exposure to *Mtb* can lead to pathogen elimination, which may or may not leave immunological evidence of exposure. Individuals then harbour viable mycobacteria in a state where preventive therapy is recommended. Subclinical and active TB disease are infectious disease states, primarily distinguished by the presence and severity of symptoms. IGRA: Interferon-gamma release assay; *Mtb*: *Mycobacterium tuberculosis*; TB: Tuberculosis; TST: Tuberculin skin test. From Pai et al. *Nat Rev Dis Primers* 2016 [1].

Recognising the need for an updated and standardised classification of TB that accommodates key disease states, the International Consensus for Early TB (ICE-TB) group developed a framework outlining four conceptual states of TB disease (**Figure 2.2**) [23]. These states were defined based on three dimensions: macroscopic pathology, infectiousness, and symptoms and signs, all under the assumption of the presence of a viable *Mtb* infection [23]. This framework is intended to provide clarity and consistency in the terminology used for states across the spectrum of disease to enable progress in research [23].

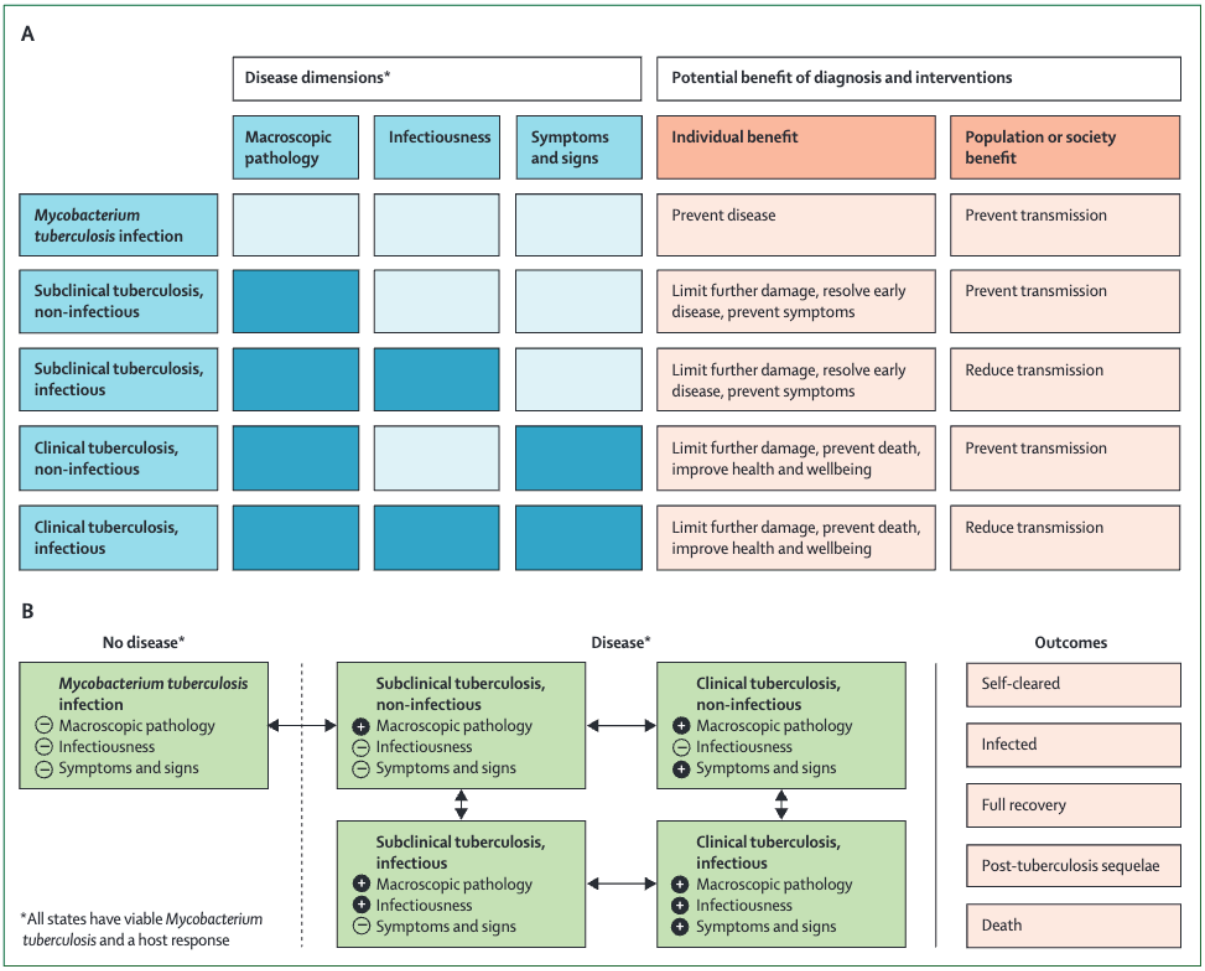


Figure 2.2 Conceptual states of *Mtb* infection and TB disease. Conceptual states of across the spectrum of *Mtb* infection and TB disease identified with consideration of potential benefits of diagnosis and treatment (A) and pathways across states (B). The four conceptual states are defined based on three dimensions: macroscopic pathology, infectiousness, and symptoms and signs. From Coussens et al. *Lancet Respir Med* 2024 [23].

Recently, the WHO convened experts to define subdivisions of early TB, with a particular focus on asymptomatic TB (widely known as subclinical TB) [28]. These discussions were guided by the proposed framework developed by the ICE-TB group but introduced a different naming convention [23,28]. The proposed conceptual states are as follows: bacteriologically confirmed symptomatic TB; bacteriologically confirmed asymptomatic TB; bacteriologically unconfirmed symptomatic TB; and bacteriologically unconfirmed asymptomatic TB [28]. It is expected that future editions of WHO guidelines, operational handbooks, reports, and other publications will use these definitions, facilitating further approaches to be made for early detection and treatment of early TB states [28].

Significant advancements in understanding the spectrum of TB disease have emerged in recent years. This thesis draws on key publications to inform the parameters and reporting relevant to the spectrum of TB disease. The overall model structure, as well as progression and regression rates across the spectrum, will primarily be based on the work of Horton et al. [22]. While definitions are closely aligned with the ICE-TB framework [23], naming conventions will adhere to the recent WHO terminology [28]. The following subsections will provide a detailed discussion of each relevant conceptual state.

2.2.1 *Mycobacterium tuberculosis* infection

Following exposure to *Mtb*, an individual's immune response can promptly eliminate the bacteria [1,6]. However, the pathway—whether through innate or acquired immunity—may or may not leave immunological evidence of exposure, despite achieving the same outcome [6]. Through innate immunity, bacteria are eliminated without the development of a specific immune response and thus markers of infection remain negative; whilst, with the acquired immune response, antigen-specific effector memory persists [6]. In established *Mtb* infection, immunoreactivity is often present without signs and symptoms of TB disease. Traditionally, it is assumed that *Mtb* infection carries a lifelong risk of reactivation, usually dependent on comorbidities or acquired immunosuppression [5]. Moreover, individuals with *Mtb* infection would stand to benefit from TB preventive therapy (TPT), commonly in the form of mono-drug regimens using first-line anti-TB drugs [1,5,27,29].

The assumption that *Mtb* infection is lifelong has been grounded by equating immunoreactivity to current infection; however, immunoreactivity is not a reliable proxy for infection but rather reflects immunological memory of exposure to *Mtb* [30]. Firstly, immunoreactivity is not stable and is dependent upon established thresholds to determine whether an individual is sufficiently immunoreactive (suggestive of *Mtb* infection) or not [17]. Secondly, several studies have shown that immunoreactivity is maintained for many years despite the provision of TPT and the observed benefit of lowered TB incidence [31–33]. Cohort studies following immunoreactive individuals who later acquired immunosuppression (through organ transplantation, immunosuppressive drugs, or human immunodeficiency virus (HIV) infection) revealed a much lower-than-expected rate of disease progression, suggesting that immunoreactivity does not indicate viable infection [30]. Analysis from these cohorts estimates that only 1% to 11% of immunoreactive individuals have viable *Mtb* infection, indicating that the proportion at risk of progressing to

disease is much lower than previously thought [30]. This underscores the importance of understanding self-clearance rates, which recent modelling efforts have sought to estimate for incorporation into TB transmission models [22,34]. If *Mtb* infection is not cleared, progression along the spectrum of disease may occur, albeit at variable speeds [18,22,35].

2.2.2 Bacteriologically unconfirmed tuberculosis

After *Mtb* infection, individuals may progress to a state of TB disease characterised by pathological changes detectable through imaging techniques, while remaining non-infectious and often asymptomatic [21,36,37]. This state, referred to as minimal TB in recent literature [21,22], represents the earliest state in the spectrum following progression from viable infection [21]. As previously mentioned, the disease trajectory is variable, with some individuals experiencing accelerated progression, others following an undulating course, and some even regressing and naturally recovering from the disease [27]. Symptoms are often absent but may also be present, as symptom thresholds can vary widely at the individual level due to differences in pathology [27]. Most extrapulmonary TB in adults (particularly symptomatic) and the majority of TB in children fall within this disease category [23]. Under the ICE-TB framework, two states are characterised by the presence of macroscopic pathology and non-infectiousness [23]. However, as previous studies on progression and regression rates across the spectrum were conducted using a natural history model that grouped these states into a single non-infectious category [21,22], this thesis will adopt this umbrella state for non-infectious TB, following the WHO naming convention [28].

2.2.3 Bacteriologically confirmed, asymptomatic tuberculosis

One widely recognised intermediate state between *Mtb* infection and classical symptomatic disease is asymptomatic TB—referred to as subclinical TB in recent literature— where individuals do not exhibit symptoms, are not aware of them, or do not report them [11,23]. A review of TB prevalence surveys has found that approximately half of prevalent bacteriologically confirmed TB was asymptomatic [11]. Furthermore, an individual participant meta-analysis of TB prevalence surveys, showed varying proportions according to the chosen definition of the phenotype, as no persistent (less than 2 weeks), no cough, and no TB symptoms [38]. Regardless of the definition, the proportion asymptomatic was substantial [38], highlighting how thinking of TB as binary states would lead to a underrepresentation of a sizeable population with TB who are also contributing to transmission [39–41]. Under this state, individuals are capable of transmitting *Mtb*, although

intensity may vary relative to overt symptomatic disease [41,42]. Modelling estimates also suggest that half of all transmission is attributable to individuals with asymptomatic TB, even when assuming a lower relative infectiousness compared to symptomatic TB [43].

2.2.4 Bacteriologically confirmed, symptomatic tuberculosis

The most advanced and widely recognised state of the spectrum is symptomatic TB, with its key characteristics outlined in *Section 2.1*. Symptoms are overtly evident and individuals are generally more infectious than earlier TB states [1,41]. This is the target state of national TB programmes to diagnose and treat individuals as most individuals would seek care [1]. Symptomatic disease is associated with a long duration of infectiousness, which can last over a year in some cases [1]. If untreated, the mortality rate from symptomatic TB is high, approximately 70% [44].

2.3 Diagnosis of *Mycobacterium tuberculosis* infection

In the absence of TB disease, no test can directly detect the presence of *Mtb* in an individual; however, *Mtb* exposure or infection has traditionally been inferred through assessments of immune response to *Mtb*-related antigens [17,29]. Currently, the two primary immunoreactivity tests used are the tuberculin skin test (TST) and interferon-gamma release assay (IGRA) [5,17]. These tests are primarily intended to identify individuals with *Mtb* infection who may benefit from effective prophylactic treatment to prevent progression to active disease [17,45]. However, both tests have limitations: a positive result cannot distinguish between present or past infection and, although some high IGRA values or larger TST indurations are associated with a greater disease risk, they have low accuracy in predicting progression [17,46,47].

The TST is a low-cost, in vivo test in which antigenic purified protein derivative of *Mtb* is injected intradermally on the forearm to elicit a delayed hypersensitivity reaction, typically occurring 2 to 12 weeks after infection [5,17,48]. The injection site is examined 48 hours after inoculation, and the reaction is measured by the skin induration diameter in millimetres [17,49]. A reaction is considered positive if the induration diameter meets specific cut-off values, which vary based on factors such as exposure risk, setting, and comorbidities [17,49]. Generally, an induration of ≥10mm or an increase of ≥6mm is considered TST-positive; nevertheless, false-positive results can occur due to exposure to environmental non-tuberculous mycobacteria (NTM) or prior Bacillus Calmette-Guérin (BCG) vaccination [5,17,50]. False-negative results may arise in immunocompromised individuals with a weakened adaptive immune response, such as those

infected with HIV or organ transplant recipients [5]. Additionally, TST is prone to inter and intra-reader variability and digit bias [17,51]. Despite its limitations, TSTs have been widely used since their introduction in the late 1800s, mainly for universal screening of the general population or targeted screening of at-risk populations, and to derive *Mtb* transmission risk trends in the community [48,52,53].

A century later, IGRAs were introduced to address some limitations of TSTs [54]. This in vitro assay is based on the principle that T-cells of individuals infected with *Mtb* release interferon-gamma when exposed to mycobacterial antigens [54,55]. IGRAs offer several advantages over TST: they require only one visit and, unlike induration measurements, the results are less subjective [54]. Additionally, the antigens used in IGRAs are specific to *Mtb,* so the test does not produce positive results in individuals exposed to most NTM or with prior BCG vaccination [54,55]. However, higher materials costs and the need for laboratory capabilities limit their widespread use, particularly in LMICs [17]. Similar to TSTs, IGRAs are less accurate in individuals with compromised immune systems [1,17].

Recently, newer diagnostic methods have been developed [56]. Novel skin tests now elicit a more specific immune response to *Mtb* than conventional TSTs by using the *Mtb*-specific antigens ESAT6 and CFP10, similar to those in IGRAs, while retaining the simplicity of traditional skin tests [57]. Additionally, new semi-automated lateral flow IGRAs require less blood and laboratory infrastructure, reducing financial and logistical barriers compared to its older counterparts [58]. The WHO has noted that these novel skin tests are cost-effective, acceptable, and feasible for diagnosing *Mtb* infection, and has recommended their use [59].

While immunoreactivity tests have limitations at the individual level, they can provide valuable insights into *Mtb* exposure at the population level [60,61]. Historically, cross-sectional surveys measuring TST positivity, primarily in children, have been used to estimate the risk of *Mtb* infection and track transmission trends [52,62]. One advantage of monitoring immunoreactivity is that ongoing recent transmission accounts for most incident TB episodes, making it useful for tracking trends over time [63,64]. Additionally, these surveys are generally less costly than TB disease prevalence surveys, as they require a significantly smaller sample size—only 3 to 20% of that needed for prevalence studies [61]. Immunoreactivity surveys are currently recommended in high-burden settings or among individuals at high risk of developing TB who may benefit from preventive measures [61,65]. As such, quantifying transmission through

infection surveillance offers a practical and cost-effective way to estimate *Mtb* infection and draw inferences on the TB disease burden, particularly in resource-limited settings with high TB prevalence.

Immunoreactivity prevalence is commonly used to derive the annual risk of infection (ARI), a critical metric quantifying the current magnitude of the *Mtb* transmission burden [53]. Changes in ARI serve as early indicators of trends in *Mtb* transmission: a decline suggests improvements in TB prevention and care, whereas an increase signals that interventions may be inadequate [53]. The ARI is typically calculated using tuberculous immunoreactivity test prevalence and the mean age of surveyed individuals [53]. However, its calculation relies on two key assumptions: first, that tuberculous immunoreactivity persists throughout an individual's lifetime, meaning a positive test result remains positive indefinitely [30]; and second, that immunoreactivity conveys a continuous risk of TB disease progression [66]. Emerging evidence challenges these assumptions. Immunoreactivity can wane over time, and positive TST/IGRA results may revert to negative [67]. Studies have even observed distinct, age-specific reversion probabilities in population-based surveys [66,68,69]. Given the ARI's importance in policy and TB models, its precision is crucial. Yet, without considering immunoreactivity test reversion, current estimates risk being unreliable, limiting their impact on interventions.

> ***Research gap:*** The impact of *Mtb* immunoreactivity test reversion on the estimated ARI and its interpretation has not been thoroughly explored.

2.4 Diagnosis of tuberculosis

There are several tools used to diagnose TB disease, which may present from asymptomatic, tuberculous pathology found incidentally in imaging, to overtly symptomatic disease with *Mtb* transmission (**Figure 2.3**) [1,70,71]. A timely and effective diagnosis is a key component of TB elimination ensuring integrated, patient-centred care and prevention [15,72]. However, it is known that millions that fall ill with TB are lost in the care cascade, in which diagnosis plays a pivotal role [73,74]. Additionally, some of these tools are often used for screening TB disease where, unlike diagnosis, there is no focus on the clinical characteristics of an individual seeking healthcare but it is rather initiated by a provider and targets apparently healthy individuals with or without risk factors [75]. While screening and diagnosis are part of the same cascade for some individuals, the key distinction lies in the focus: screening prioritises methods with high sensitivity to identify potential cases, whereas diagnosis requires high specificity for

confirmatory testing [71,75]. Four main techniques are used for the diagnosis (and sometimes screening) of TB disease: microscopy, culture-based methods, molecular tests, and imaging techniques; all often complemented by clinical appraisal [1].

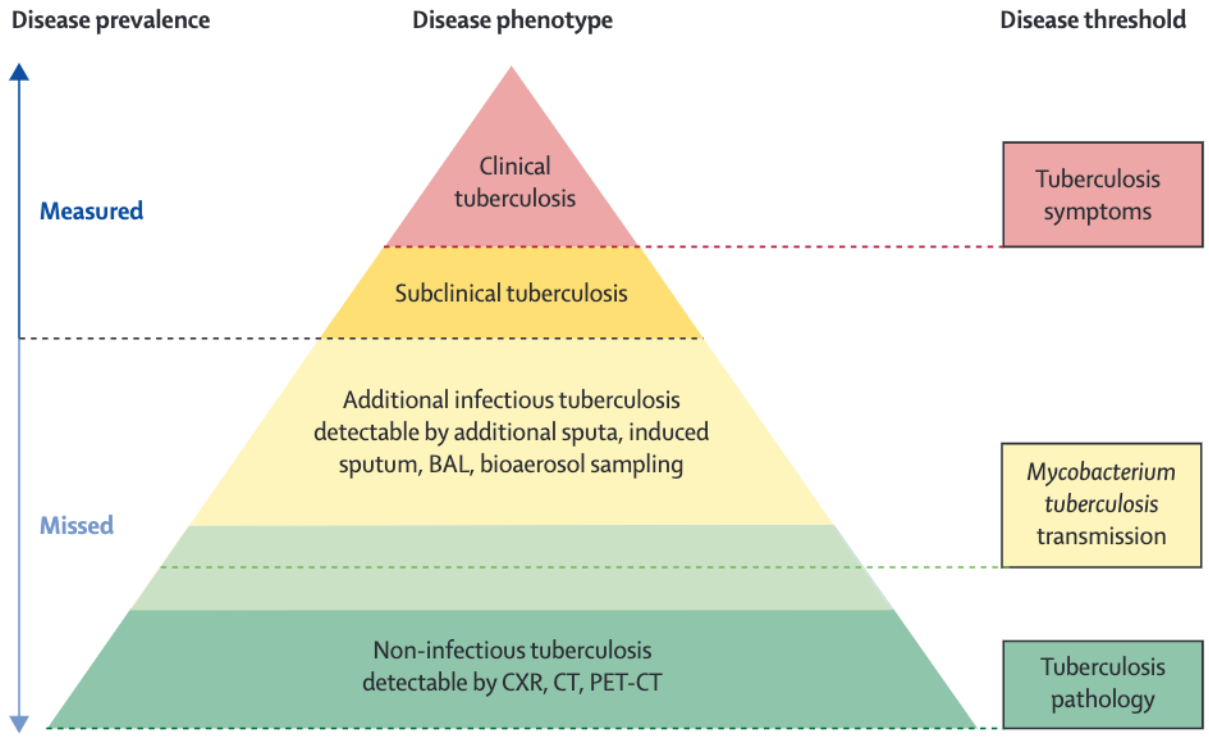


Figure 2.3 The iceberg of prevalent TB disease. The iceberg model illustrates the distinction between disease prevalence currently measured and all prevalence that is missed. Conceptual thresholds of TB disease are shown, with rough estimates representing individuals contributing to transmission or displaying TB pathology, though actual proportions vary by diagnostic methods and tools used. BAL: Bronchoalveolar lavage; CT: Computed tomography; CXR: Chest radiography; PET: Positron emission tomography; TB: Tuberculosis. From Houben et al. *Lancet Respir Med* 2022 [70].

2.4.1 Sputum smear microscopy

The most widely used method to diagnose TB disease, particularly in LMICs, is sputum smear microscopy, a fast and inexpensive method to directly observe mycobacterial acid-fast bacilli (AFB) [76]. By directly identifying bacilli, this method can diagnose individuals with infectious TB regardless of symptoms, although sputum yield is typically higher in individuals with symptoms [39]. Smear microscopy is a highly specific test but has low sensitivity which is slightly increased with at least two repeated samples [77]. The detection of AFB is used to classify sputum samples as smear-negative or positive, with the latter subclassified according to the number of bacilli per microscopy field [78]. Ziehl-Neelsen staining has been traditionally used in microscopy, although newer alternatives such as fluorescence

microscopy have greatly improved sensitivity [79]. Furthermore, its efficacy is operator-dependent, thus training is required for an adequate diagnostic yield [80].

2.4.2 Culture

Culture-based methods, in solid or liquid media, remain the gold standard diagnostic test for TB disease and are paramount for drug susceptibility testing (DST) [1]. Due to the slow turnaround of results (up to 8 weeks), it is often used in tandem with microscopy [72,76]. Additionally, the need for specialised infrastructure and highly-skilled laboratory technicians further limits its large-scale use [76]. Both microscopy and culture are often used in TB treatment monitoring, but cannot predict treatment failure or relapse [76,81]. As with sputum smear microscopy, these methods can be used to diagnose individuals with infectious TB.

2.4.3 Molecular tests

Currently, there is a shift toward the use of molecular methods, referred to as nucleic acid amplification tests (NAATs) [78]. These assays, often performed by real-time polymerase chain reaction amplification of an *Mtb* gene, can detect TB from usual samples and perform DST for the most important first-line and some second-line drugs, providing rapid results while being a good proxy for the detection of multidrug-resistant strains [76,82,83]. This leads to significant reductions in delays in TB diagnosis and treatment initiation [84,85]. One of the most widely known NAATs is Xpert MTB/RIF (Cepheid, USA), which was endorsed by the WHO in 2010 for the diagnosis of TB and resistance to rifampicin, a first-line drug [82,86]. A next generation NAAT, Xpert MTB/RIF Ultra (Cepheid, USA), included modifications that increased their sensitivity compared with the previous generation, albeit at a slightly worse specificity [82]. In 2017, Xpert MTB/RIF Ultra was also endorsed by the WHO as the initial TB diagnostic test for adults and children, regardless of HIV status, over smear microscopy and culture [87]. Regardless of their diagnostic accuracy, these tests have not been fully implemented in countries with the highest TB burdens [82]; however, some are cartridge-based tests, facilitating their spread in resource-limited settings [78]. The advances in molecular testing show great promise for the future of TB diagnostics and screening.

2.4.4 Imaging

Imaging techniques have also improved and while the range of imaging modalities extends to positron emission tomography/computed tomography, conventional chest radiography (CXR)

remains the initial image-based screening tool for suspected pulmonary TB [88]. It is a valuable aid in diagnosis when pulmonary TB cannot be confirmed bacteriologically [89]. Computed tomography and magnetic resonance imaging have proven valuable in distinguishing TB lesions from cancerous lesions and in diagnosing lesions outside the lungs; they also identify non-infectious TB disease, i.e., small pulmonary lesions that are not actively transmitting *Mtb* bacilli [90]. While pulmonary TB may be diagnosed with CXR alone, tuberculous pulmonary lesions can easily mimic other conditions and vice versa, therefore, abnormal findings should be followed up with the other methods mentioned above [1,91]. Like microscopy, radiography is operator-dependent, limited by the reader's ability to detect abnormal opacities which has been shown to have notable inter/intra-observer variation [92]. To address these limitations, computer-aided diagnosis (CAD) has emerged as a prominent method [93]. Additionally, artificial intelligence is beginning to play a role in imaging diagnostics, with some studies suggesting high accuracy using this technology [94]. The main advantage of imaging techniques is that patients with non-infectious or extrapulmonary TB may be missed via the usual diagnostic algorithm using any of the bacteriological methods mentioned before [95].

2.5 Burden of *Mycobacterium tuberculosis* infection

Due to limitations in current tools and resource constraints for identifying *Mtb* infection, global prevalence estimates have relied heavily on mathematical modelling [4,96,97]. In 1997, an expert panel, chosen by the WHO, estimated that 32% (1.86 billion people) of the global population had LTBI [96]. This consensus was reached with the estimation of ARIs derived directly from TST-surveys or indirectly by using TB incidence rates as a proxy, the so-called Stýblo rule (smear-positive pulmonary TB incidence of 50 per 100,000 inhabitants equates to an ARI of 1%) [96,98]. The panel agreed that this was at best a plausible estimate, given the poor quality of the underlying data [96]. After two decades, a re-estimation was generated accounting for population growth and demographic shifts, availability of new surveys, and disassociation from reliance on the Stýblo rule [4]. The re-estimation placed the global burden of LTBI to be 23% (95%CI: 20.4-26.4%), amounting to 1.7 billion people in 2014 [4]. Additionally, it was estimated that 0.8% of the global population (55.5 million individuals) had recently (within two years) been infected with *Mtb* and were at a higher risk of developing TB disease [4]. Another re-estimation by the Global Burden of Disease study used similar data and methods to examine trends from 1990 to the present and also approximated the current burden of LTBI to be near one-quarter of the global population (23.5%; 95%CI: 21.4-25.8%) [97].

Both recent estimations agree that it is unlikely that we will reach the 2035 *End TB Strategy* goals since ongoing TB transmission will be greatly driven by the large reservoir of *Mtb* infections [4,97]. All these re-estimations linger on the assumption of permanent positive immunoreactivity, which also expands to permanent viable infection and continuous risk of disease development. However, both assumptions are challenged by reversion and self-clearance, respectively. These phenomena are often not considered when interpreting immunoreactivity prevalence, which leads to an overestimation of the population at risk of TB disease [34,99,100]. A more accurate global *Mtb* infection burden estimate would consider the viability of the microorganism of progressing to disease and would be a valuable insight for TB prevention and care practices, particularly TPT.

> ***Research gap:*** Current global estimates of *Mtb* infection burden do not accurately identify individuals with viable infections who are at risk of disease progression.

2.6 Tuberculosis screening

Worldwide, national TB strategies are often based on passive detection, where diagnosis and care are restricted to individuals experiencing symptoms who then access and receive healthcare [75,101]. However, in order to achieve *End TB Strategy* targets, relying solely on passive detection is insufficient [102]. This approach results in a significant gap, leaving approximately 40% of individuals undiagnosed, and fails to reduce *Mtb* transmission by focusing solely on the measured outcomes at the symptomatic extreme of the spectrum [2,43]. In contrast, population-wide screening aims to find and treat individuals with TB disease that would otherwise not have been diagnosed through the usual patient-initiated pathway, not only reaching more but treating individuals earlier in the disease pathway to halt onward transmission [101,102]. Additionally, population-wide screening could extend access to care for vulnerable populations and help mitigate patient costs associated with diagnosis, both of which are significant barriers to current healthcare access [103].

While mass CXR screening programmes were once common, they were abandoned in the past half-century following recommendations that focused on a perceived impracticality—namely, the low yield and high cost of identifying individuals with smear-positive TB [89]. However, a large body of evidence suggests the opposite. Screening campaigns using mobile CXR units were conducted as early as the 1930s [104,105]. Remarkable results were found with its

implementation: TB prevalence rate halved in a Welsh mining community (1950-1953) [106], TB mortality rate among Alaskan Eskimos and Indians experienced a five-fold drop (1950-1957) [107], detected over 50,000 individuals with TB in the Netherlands (1951-1967) [108], and contributed greatly to decreasing TB burden in the Kolín district, Czechoslovakia (1960-1972) [109–111]. Additionally, there was an observable temporary decrease in TB notification rates in South Africa (1950-1970) during a period of population-wide screening with miniature CXR, alongside reductions in the ARI in 1950s Japan, where annual CXR screenings covered a substantial portion of the population [112–114]. Data from the mass CXR screening campaign in Glasgow, which occurred in the span of 5 weeks in 1957, has been estimated to avert over 4,500 pulmonary TB notifications [115]. Recently, CAD has been implemented for CXR films, providing computer-driven, standardised assessment and scoring, which interprets the likelihood that the individual has TB [78,89]. Despite its success as a TB detection strategy, it was not deemed a cost-effective tool to interrupt TB transmission and was mostly abandoned as healthcare systems shifted towards a more symptom- and health facility-centric approach [104,111,116].

> ***Research gap:*** Symptom-agnostic mass screening interventions using CXR have been perceived as impractical, yet clear benefits could be seen when considering the spectrum of TB disease.

In the search for more effective strategies, recent cluster-randomised trials have assessed the impact of community-wide screening on TB epidemiology, yielding mixed results [117,118]. The ZAMSTAR trial in Zambia and South Africa, which employed symptom-based screening with sputum smear microscopy, did not demonstrate a reduction in TB prevalence [117]. In contrast, the ACT3 trial utilised a symptom-agnostic approach, similar to historic mass screening efforts, implementing annual community-wide screenings over three years with the Xpert MTB/RIF assay [118]. Notably, the results demonstrated a significant reduction in the prevalence of pulmonary TB within communities where community-wide screening was employed, compared to those utilising standard passive-detection methods alone [118]. The findings from the ACT3 trial represent contemporary evidence of the impact of community-wide screening that goes beyond mere theory and thus, underscore the importance of introducing proactive healthcare measures in our current approaches to TB prevention and care. As suggested from historical studies, its application should extend beyond high-risk groups to encompass broader community outreach, and that the initiative requires sustained, multiple rounds for

effectiveness [119]. However, its implementation as a central component of TB elimination strategies remains under debate. The challenge lies in identifying the optimal implementation of population-wide screening, including the ideal duration and algorithm, to determine the most effective approach to reducing the TB burden. Additionally, careful evaluation of the interventions' cost-effectiveness, along with the required front-loaded investment and overall budget impact, is essential.

> ***Research gap:*** While population-wide screening interventions may reduce TB prevalence, the optimal algorithm and duration—balancing resource considerations—have not been fully examined, especially in the context of the spectrum of TB disease.

2.7 Mathematical modelling

Mathematical modelling is a valuable tool used in infectious disease epidemiology, allowing the testing of hypotheses about disease natural history, understanding underlying mechanisms through empirical data, and exploring effective, impactful, and cost-efficient care strategies [120,121]. When focused on transmission, models enhance our ability to understand and predict outbreaks, supporting informed decision-making [122]. This is especially useful, as disease outcomes are often rare or delayed which makes observational studies impractical and costly. Additionally, modelling facilitates analyses based on various parameters to enable estimates in changing conditions that might not be present during the conduction of real-world studies. Moreover, models can evaluate scenarios that would be unethical to test in practice, offering insights into the consequences of inaction or the impact of specific interventions [121].

Mathematical modelling is widely used in TB research to gain insights into the complexities of TB epidemiology. The first TB model, developed by Hans Waaler and colleagues in 1962, acted as a proof of concept that modelling could be used to study TB epidemiology [123]. Model definitions and structures have since evolved and are tailored to address specific research question, though many share some similarities. TB models often use a deterministic SEIR framework, broadly dividing the population into categories of susceptible (S), exposed (E), infected (I), and recovered (R) individuals [124,125]. These models often add further granularity by incorporating population-level strata based on risk factors, such as HIV, age, and drug-resistant [124,125].

Today, TB mathematical models serve various purposes. Coupled with empirical data, models generate burden estimates, including the annual WHO Global TB Report figures [2,126], as well as estimates of paediatric and drug-resistant TB [127–129]. Modelling has also been used to estimate the burden of *Mtb* infection [4,97], and to determine the number of TB survivors and individuals with post-TB sequelae [130,131]. Additionally, models have assessed the impact and cost-effectiveness of interventions [132–137], and have explored the natural history of TB in greater depth [21,22,34,43,138]. For example, work on self-clearance of *Mtb* infection arrived at the conclusion that the population with viable *Mtb* is likely much lower than previously thought [34]. Other models have proposed TB disease states along the spectrum, and estimated progression and regression rates between these states [22,35]. Further studies have examined the relative infectiousness of asymptomatic TB and its role in overall transmission [41,43]. The findings from these models can inform policy changes, enabling the implementation of cost-effective interventions, such as vaccines, screening interventions, and preventive therapies [139–141].

2.8 Research gaps

This chapter provides an overview of tuberculosis, covering its epidemiology, natural history, diagnostic methods, and the resources available to combat it. It also introduces the research gaps that this thesis aims to address, with a summary of these gaps and the corresponding chapters where they are explored listed below:

- The impact of *Mtb* immunoreactivity test reversion on the estimated ARI and its interpretation has not been thoroughly explored (*Chapter 3*).
- Current global estimates of *Mtb* infection burden do not accurately identify individuals with viable infections who are at risk of disease progression (*Chapter 4*).
- Symptom-agnostic mass screening interventions using CXR have been perceived as impractical, yet clear benefits could be seen when considering the spectrum of TB disease (*Chapter 5*).
- While population-wide screening interventions may reduce TB prevalence, the optimal algorithm and duration—balancing resource considerations—have not been fully examined, especially in the context of the spectrum of TB disease (*Chapter 6*).

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Chapter 3: Immunoreactivity reversion and the annual risk of infection

In this chapter, the first research paper of the thesis is presented to address *Objective #1*: to quantify the impact of immunoreactivity test reversion on the estimated annual risk of infection (ARI). The chapter opens with a concise overview of the research gap, followed by the published paper, additional analyses using a longitudinal dataset of tuberculin skin test (TST) measurements, and concludes with a brief summary.

3.1 Introduction

The ARI is a key metric in tuberculosis (TB) epidemiology, reflecting the intensity of *Mycobacterium tuberculosis* (*Mtb*) transmission [1]. Its calculation is crucial for guiding public health interventions, and often serves as an input for TB mathematical models [1]. Conceptualised in the mid-20th century, Muench introduced a method to estimate annual infection rates from immunoreactivity prevalence data [2], and later refined into a standard formula by Nyboe [3]. This approach was further developed by Styblo, Meier, and Sutherland, who applied it to Dutch data, demonstrating the utility of converting TST prevalence into a continuous series of infection risks [4,5]. By incorporating the mean age and immunoreactivity prevalence, the ARI became a valuable tool for tracking TB trends and evaluating the success of national TB programmes, independently of notification performance [5,6].

The calculation of the ARI traditionally assumes that once an individual tests positive, using a TST or an interferon-gamma release assay (IGRA), the result remains positive throughout their lifetime [7]. However, reversion, defined as the change from a positive to a negative immunoreactivity test result upon repeat testing, has been recognised since the earliest use of TST [8]. Thus, questions about the accuracy of the assumption of long-lasting immunoreactivity arose early on [4]. In the 1970s, Sutherland conducted a theoretical study examining the impact of waning immunoreactivity over time on ARI estimates, showing that reversion rates as low as 1% per year could significantly underestimate the ARI, with higher rates leading to even greater underestimation [9]. Empirical studies have shown that immunoreactivity reversion does regularly occur and is not negligible, with probabilities varying depending on the tool, threshold, and definition used to measure reversion [10]. Additionally, the ARI is often calculated from immunoreactivity surveys conducted among school-age children (8–12 years old) to capture recent infection [1]. However, reversion remains a relevant factor even in this age group, with its impact being cumulative over time [9]. Notwithstanding, the phenomenon of reversion was largely overlooked in subsequent population-based surveys and policy decisions [10].

The implications of not considering reversion are substantial: underestimating ARI distorts the understanding of *Mtb* transmission intensity, misguides public health interventions, and introduces biases into TB mathematical models that rely on ARI as a key input [11,12]. These challenges underscore the urgent need to fully quantify ARI underestimation by incorporating empirical reversion estimates, ensuring a more accurate representation of transmission intensity and disease burden.

3.2 Research paper

The following pages contain the Research Paper Cover Sheet, the copyright license, the published research paper, and the supplementary material for: *Schwalb A, Emery JC, Dale KD, Horton KC, Ugarte-Gil CA, Houben RMGJ. Impact of Reversion of Mycobacterium tuberculosis Immunoreactivity Tests on the Estimated Annual Risk of Infection. Am J Epidemiol. 2023. DOI:10.1093/aje/kwad028* [11].

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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	2004111	**Title**	Dr
First Name(s)	Alvaro		
Surname/Family Name	Schwalb		
Thesis Title	Estimating the burden of Mycobacterium tuberculosis infection and the impact of population-wide screening for tuberculosis		
Primary Supervisor	Prof Rein Houben		

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?	American Journal of Epidemiology		
When was the work published?	7 February 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	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 reviewed and discussed the relevant epidemiological data from the literature with Rein Houben. I recreated Sutherland's formula with help from Jon Emery. I co-developed the model with Jon Emery and Katherine Horton. 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	Alvaro Schwalb
Date	7 January 2025

Supervisor Signature	Rein Houben
Date	7 January 2025

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Original Contribution

Impact of Reversion of *Mycobacterium tuberculosis* Immunoreactivity Tests on the Estimated Annual Risk of Tuberculosis Infection

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A key metric in tuberculosis epidemiology is the annual risk of infection (ARI), which is usually derived from tuberculin skin test (TST) and interferon-γ release assay (IGRA) prevalence surveys carried out in children. Derivation of the ARI assumes that immunoreactivity is persistent over time; however, reversion of immunoreactivity has long been documented. We used a deterministic, compartmental model of *Mycobacterium tuberculosis* (Mtb) infection to explore the impact of reversion on ARI estimation using age-specific reversion probabilities for the TST and IGRA. Using empirical data on TST reversion (22.2%/year for persons aged ≤19 years), the true ARI was 2–5 times higher than that estimated from immunoreactivity studies in children aged 8–12 years. Applying empirical reversion probabilities for the IGRA (9.9%/year for youths aged 12–18 years) showed a 1.5- to 2-fold underestimation. ARIs are increasingly underestimated in older populations, due to the cumulative impact of reversion on population reactivity over time. Declines in annual risk did not largely affect the results. Ignoring reversion leads to a stark underestimation of the true ARI in populations and our interpretation of Mtb transmission intensity. In future surveys, researchers should adjust for the reversion probability and its cumulative effect with increasing age to obtain a more accurate reflection of the burden and dynamics of Mtb infection.

interferon-γ release assay; *Mycobacterium tuberculosis* transmission; TST/IGRA surveys; tuberculin skin test; tuberculosis

Abbreviations: ARI, annual risk of infection; CI, confidence interval; IGRA, interferon-γ release assay; Mtb, *Mycobacterium tuberculosis*; TB, tuberculosis; TST, tuberculin skin test.

Editor's note: *An invited commentary on this article appears on page 1944, and the authors' response appears on page 1947.*

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide, and it is estimated that one-quarter of the global population is latently infected with *Mycobacterium tuberculosis* (Mtb) (1–3). Mtb infection is inferred from the presence of a host immune response to Mtb protein components with the use of the tuberculin skin test (TST) or interferon-γ release assay (IGRA) (4, 5). While it is known that Mtb immunoreactivity does not equate to Mtb infection, population surveys of TST positivity have historically been used to derive estimates of Mtb infection risk and transmission trends, most conducted among school-age children (ages 8–12 years) (6). A key metric in TB epidemiology is the annual risk of infection (ARI), which aims to provide a more insightful picture of the risk of Mtb transmission (7). It is calculated using Mtb immunoreactivity test prevalence data and the mean age of the individuals surveyed (8). In a public health setting, a decrease in the ARI is interpreted as an early indicator of a decline in Mtb transmission in a population; on the other hand, an increase could indicate that TB prevention and care measures are insufficient (8).

When calculating ARIs, there is a conventional, usually implicit, assumption that positive Mtb immunoreactivity is persistent throughout an individual's lifetime (9). Nevertheless, this assumption does not hold. TB immunoreactivity

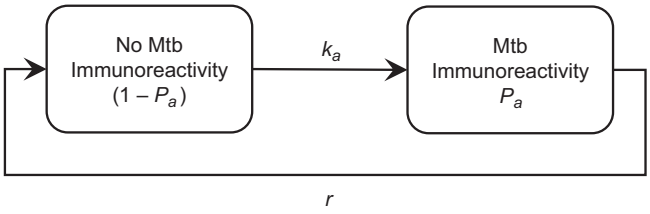

Figure 1. Model of *Mycobacterium tuberculosis* (Mtb) immunoreactivity accounting for reversion. k_a represents real infection risk, which is a function of the annual risk of infection (ARI) at birth (ARI_0), with a subsequent annual decrease in risk; P_a represents the proportion of the population found to be Mtb-immunoreactive at age *a* years; and *r* represents the annual constant proportion of individuals with positive immunoreactivity who will revert.

can wane over time, and positive TSTs and IGRAs can revert to negative (reversion) (10–12). Therefore, a major caveat in the ARI is that the phenomenon of reversion is not accounted for in its calculation, thus resulting in a naive ARI which might differ from the true value. In previous studies, investigators have considered the limitations of the current formula in arriving at an accurate estimate and interpretation of the ARI (10, 13). In a theoretical study by Sutherland (13), the effects of TST reversion on the ARI were explored, suggesting a considerable underestimation when annual reversion probabilities exceed 1% (nearly 50% and 67% when facing annual reversion probabilities of 5% and 10%, respectively). However, the Sutherland study considered only low reversion probabilities (≤10%); it did not consider age-specific effects, nor did it link to observed reversion data. While empirically observed reversion probabilities were documented over a century ago (14), their importance has been largely dismissed. With a few notable exceptions, immunoreactivity surveys do not usually consider reversion when estimating the ARI (10, 12). This is an issue, because ARI estimates without consideration of reversion are likely to underestimate the proportion of individuals once infected with Mtb (8).

In contemporary policy, the ARI remains important and is estimated in TST/IGRA surveys in populations or high-risk settings (15–17). The ARI is also a common parameter in the mathematical modeling of TB—for example, to estimate the global burden of latent Mtb infection or to set the intensity of transmission in a population (3, 18). Moreover, as novel diagnostic tools that measure Mtb immunoreactivity become available and immunoreactivity surveys may be reconsidered in global policy, it is important to consider the reversion level of specific tests so ARI underestimation can be appropriately quantified through current methods. In this paper, we aimed to use empirical estimates of reversion for TST and IGRA to quantify the extent of ARI underestimation due to reversion.

METHODS

Model overview

We developed a deterministic, compartmental model of Mtb infection (Figure 1). It builds on the theoretical study on the effect of constant TST reversion probabilities upon the ARI estimation proposed by Sutherland (13). The proportion of the population found to be immunoreactive at age *a* years is expressed by P_a. The parameter k_a represents the real infection risk, a function of the ARI at birth (ARI_0), with subsequent annual decrease *d* in risk: $k_a = (1-d)^a \times ARI_0$. Additionally, the model includes an annual constant proportion *r* of individuals with positive immunoreactivity who will revert. In order to estimate the proportion infected in the next year, the following formula is used:

$$P_{(a+1)} = P_a + (1 - P_a) \times k_a - P_a \times r.$$

The formula has 3 components: 1) the proportion of the population infected with Mtb in the current year, 2) plus the proportion of noninfected individuals who convert to positive immunoreactivity over the following year, 3) minus the proportion of immunoreactive individuals who revert over the following year. For a fixed initial ARI of 1.5%, Mtb immunoreactivity prevalence was calculated in daily time steps using increasing reversion probabilities from 0% to 50% with 1% increments from birth to age 80 years. For all ages and Mtb immunoreactivity prevalence, the ARI was calculated using the classic formula $ARI_a = 1-(1-P_a)^{1/a}$. Then, the base ARI (not accounting for reversion) was compared against each reversion ARI (up to 50% reversion) as a ratio. Since we are considering that reversion is occurring but not accounted for in the calculation of the ARI, this ratio reflects how much the naive ARI must increase to match the measured prevalence, resulting in the true ARI. The model was constructed and the analysis run using R, version 4.1.0 (May 18, 2021) for statistical computing and graphics (19). Plots were created using the *ggplot2* package (20).

Model assumptions

The key assumption of our model is that Mtb infection always leads to Mtb immunoreactivity, regardless of different cutoff values and incremental changes considered in conversion criteria (21). Furthermore, the model does not account for reinfection, assuming that reinfections occur at a similar rate as primary infections; this was done for simplicity. Finally, it assumes that no child is immunoreactive at birth; therefore, $P_0 = 0$.

Table 1. Age-Specific Annual *Mycobacterium tuberculosis* Immunoreactivity Test Reversion Probabilities in 3 Different Studies

First Author, Year (Reference No.) and Age Group, years	Setting (Date Range)	Annual Reversion Probability, %	95% CI
	TST Surveys		
Grzybowski, 1964 (11)	Victoria County, Ontario, Canada (1958–1962)		
≤19		22.2	15.2, 31.4
20–39		8.0	4.9, 12.6
40–59		4.8	3.2, 6.9
≥60		9.0	6.5, 12.3
Fine, 1999 (10)	Karonga District, Malawi (1980–1989)		
≤4		17.9	
5–9		10.2	
10–14		7.5	
15–19		6.1	
20–24		5.3	
25–29		4.8	
30–39		4.1	
≥40		3.7	
	IGRA Survey		
Andrews, 2015 (12)	Worcester, South Africa (2005–2007)		
12–18		9.9	8.8, 11.1

Abbreviations: CI, confidence interval; TST, tuberculin skin test; IGRA, interferon-γ release assay.

Data sources for ARI estimates

A global ARI estimate was calculated from TST surveys used to reestimate the global burden of latent TB infection by Houben and Dodd (3). This value was a simple average of ARI estimates from 141 TST surveys collected from Cauthen et al. (8) and a systematic review of the literature (3). The resulting global average ARI of 1.5% (95% confidence interval (CI): 1.3, 1.7) was used for the primary analysis. For the primary results, k_a was only dependent on ARI_0. The annual decline (2.3%) component of k_a was evaluated further in the sensitivity analyses.

Data sources for Mtb immunoreactivity test reversion

Reversion probabilities—classified per age group—were used to illustrate the degree of ARI underestimation obtained from the model. These were collected from 2 population-wide TST surveys and 1 adolescent IGRA survey. The first TST survey, by Grzybowski and Allen (11), was conducted in 1959 among 29,000 individuals of all ages in Victoria County, Ontario, Canada; it consisted of 5 consecutive annual TST surveys, in which an area of induration greater than or equal to 5 mm was considered a positive result. At the time, Bacillus Calmette-Guérin vaccination was not considered in newborns or infants and was only recommended for contacts of patients with active TB. The study provided numerators (number of reversions) and denominators (positive reactors retested in 1 year) used for age-group–specific reversion probabilities; we calculated 95% CIs for the given proportions to account for uncertainty in the probabilities. In the second TST survey, Fine et al. (10) described a set of over 64,000 TSTs performed in 2 total population surveys in the Karonga District, northern Malawi, from 1980 to 1989; TST reversion data were available from paired results from 6,991 individuals who participated in both surveys. An area of induration greater than or equal to 10 mm was considered a positive result. Reversion probabilities in females without a Bacillus Calmette-Guérin scar were presented in a plot and were extracted using a Web-based plot digitizer (22). Confidence intervals were not available, since the absolute numerator and denominator were not provided. On the other hand, in the IGRA survey, which was conducted by Andrews et al. (12) from 2005 to 2007, students aged 12–18 years were recruited from local schools in Worcester, South Africa. The age-specific annual Mtb immunoreactivity test reversion probabilities from all studies are displayed in Table 1.

To test the application of the model, we used ARI estimates from 2 population-wide TST surveys as illustrative examples to calculate the difference between the observed ARIs of the studies and the true ARIs of the model. Firstly, the study by Hoa et al. (16) was a nationwide TST survey

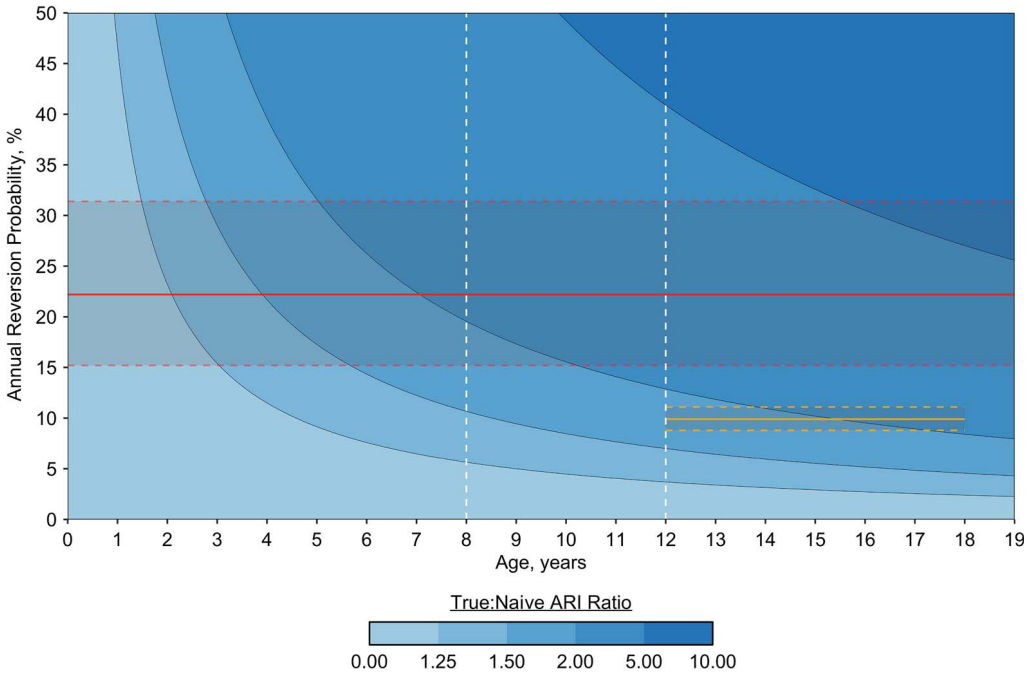

Figure 2. Underestimation of the annual risk of infection (ARI) with *Mycobacterium tuberculosis* according to varying annual reversion probabilities. The ratio between the true ARI (varying reversion levels) and the naive ARI (no reversion) represents the true increase in the ARI. Baseline parameters were a 1.5% ARI at birth and no decline in annual risk. Tuberculin skin test (TST) reversion probabilities (red line; dashed red lines represent 95% confidence intervals) were derived from the paper by Grzybowski and Allen (11), and interferon-γ release assay reversion probabilities (yellow line; dashed yellow lines represent 95% confidence intervals) were derived from the paper by Andrews et al. (12). White dashed lines represent the age range of populations in which most TST surveys are conducted. The study by Grzybowski and Allen (11) was conducted in Ontario, Canada (1958–1962), and the study by Andrew et al. (12) was conducted in Worcester, South Africa (2005–2007).

carried out in Vietnam among children aged 6–14 years from 2006 to 2007; the study produced an ARI estimate of 1.7% (95% CI: 1.5, 1.8), calculated from a TST-positive prevalence of 16.7% in a population with a mean age of 10.8 years. Secondly, the study by Wood et al. (17) was conducted among human immunodeficiency virus–negative individuals aged 5–40 years in Cape Town, South Africa. The study derived an ARI of 3.9% (95% CI: 2.2, 5.7) from an estimated TST-positive prevalence of 18.1% among 5-year-olds, an ARI of 3.9% (95% CI: 3.3, 4.5%) from an estimated prevalence of 32.7% among 10-year-olds, and an ARI of 4.8% (95% CI: 4.1, 5.5) from an estimated prevalence of 52.0% among 15-year-olds.

Sensitivity analyses

We performed sensitivity analyses to assess the impact of the parameters on the ARI underestimation output. First, model outputs using the lower and upper bounds of the 95% CIs of the baseline ARI (1.3–1.7) were explored. Additionally, considering the heterogeneity in the global TB burden, we also used an initial ARI of 5%, accounting for high-burden settings. Moreover, the component of annual risk decrease was incorporated into parameter k_a. The global annual rate of decline for TB incidence was estimated to be 2.3%, with some regions presenting more notable decreases (2).

RESULTS

Figure 2 shows the degree of ARI underestimation due to ignoring reversion. In the age range 8–12 years, where most TST surveys are conducted, we found that for the TST (and in the range of reversion probabilities from Grzybowski and Allen (11) and Andrews et al. (12)), the true ARI was 2–5 times higher than that estimated under the naive scenario (i.e., assuming no reversion). With the following age-group reversion probabilities, the ARI underestimation was maintained in the older populations, rising to at least a 5-fold increase of the true ARI after age 60 years (see Web Figure 1, available at https://doi.org/10.1093/aje/kwad028). The lower observed TST reversion probabilities from Fine et al. (10) gave a 1.25- to 1.50-fold increase of the true ARI from age 3 years onwards and a more than 2-fold increase from age 12 years onwards (Web Figure 2). In the case of IGRA, the narrow reversion probabilities led to a 1.50- to 2-fold increase of the true ARI for ages 12–18 years, within the reversion probabilities from Andrews et al. (12).

Outside of the empirical reversion probabilities, Figure 2 shows how ARI underestimation grew with increasing levels of annual reversion probabilities, as well as with increasing age at which immunoreactivity was tested. Annual reversion probabilities up to 2.5% increased the true ARI by less than 1.25 times. After the first life year, changes in reversion

probabilities for a particular age could reach diverse levels of underestimation (Web Figure 1).

The impact of reversion on the observed ARIs was evaluated in 2 population-wide surveys. For the study by Hoa et al. (16), the observed ARI of 1.7% at the mean age of 11 years, adjusting for reversion (using empirical reversion probabilities from Grzybowski and Allen (11)), showed the true ARI to be twice that originally observed. Likewise, in the survey by Wood et al. (17), the observed ARI of 3.9% would be increased by a factor of 1.5 at age 5 years and by a factor of 2 or more at ages 10 and 15 years (considering the empirical reversion probabilities from Grzybowski and Allen (11)).

Sensitivity analyses

There was no notable difference between the contour maps produced by the lower and upper bounds of the 95% CI of the 1.5% baseline ARI, within the reversion probability ranges from the TST and IGRA surveys (Web Figures 3 and 4). When using a 5% baseline ARI, more discernible true ARI increases were evident at higher reversion probabilities (Web Figure 5). Incorporating the global decline in TB incidence (2.3%) into the model increased the true ARI underestimation, albeit slightly (Web Figure 6).

DISCUSSION

We estimated that the true ARI for Mtb immunoreactivity surveys conducted in school-age children and using empirical data on TST reversion was 2–5 times higher than the baseline value that did not account for reversion. Failing to account for Mtb immunoreactivity test reversion in estimating the ARI significantly underestimates the true value, and the cumulative effect of reversion can be seen in time. In recent work, Dowdy and Behr (23) explored ARI underestimation due to increasing infection risks in adolescence and early adulthood, resistance to infection, and immunoreactivity test reversion, concluding that the latter could underestimate the risk of infection by one-third or more. In our study, we used empirical data for reversion and explored the impact across age groups in detail, highlighting how reversion is important on its own but probably differs by age and immunoreactivity test. More recent data on reversion, especially of new tools (24), are urgently needed; this is an important concept to explore and consider when interpreting future ARI estimates of recent surveys.

In the original work, Sutherland concluded that reversion probabilities above 1% would significantly impact ARI estimates (13). However, as we have seen, empirical data for TST/IGRA reversions in populations have shown that the probabilities strongly exceed 1% per year and vary by age (10–12), although the reversion probabilities are still poorly quantified and understood for new tests. Reversions may result from a myriad of different factors, including self-clearance of Mtb infection, cross-reactivity with Bacillus Calmette-Guérin vaccination or nontuberculous mycobacteria (in the case of the TST), and false-negative reactions due to impaired immune response. Note that the difference in ARI underestimation depending on the tool used might not be related to the actual tool but probably depends on the TB incidence in those settings at the time of the surveys, since the likelihood of reversion might be influenced by reinfection. Thus, lower reversion probabilities could be seen in settings with a higher risk of reinfection (25, 26). While data on reversion from novel diagnostic methods are nonexistent at present, our work highlights why it is crucial to acquire such data and how they may affect ARI estimates. Nonetheless, regardless of how—and to what extent—reversions occur, our findings focus more on the implications of the underestimation and interpretation of the resulting ARI.

Another essential issue with regard to interpretation of the ARI is its reliance on the host immune response to Mtb, which is an indirect ascertainment of Mtb infection. Because of the limitations of Mtb immunoreactivity tests, the interpretation of a positive test result as a marker of true infection—that is, harboring viable Mtb bacilli and being at risk of TB disease—is unclear. While our findings call for conscientious interpretations of the ARI given the reversion phenomenon, TB prevention and care may benefit from an improved biomarker for detecting Mtb infection that will enable more direct estimation of the true ARI. Luckily, some biomarkers are already being explored (27, 28), some providing the additional benefit of identifying individuals at higher risk of progression to active TB disease (28).

ARI estimates are key to understanding time trends in TB burden and dynamics and are important to inform subsequent policy. Given the substantial impact of reversion on ARI estimates, this naturally occurring phenomenon should be recognized in ARI calculations or, at minimum, its interpretations (29). Our exploratory analysis of the TST prevalence surveys by Hoa et al. (16) and Wood et al. (17) illustrates how the true ARI can be at least 2 times higher than the naive ARI. We may apply our understanding of the impact of ARI estimation to other existing surveys, such as India's recent nationally representative survey, as reversion would mean a true transmission risk 2–5 times as high (30). Caution in interpretation of the majority of published ARIs to date is essential, including global estimates of individuals recently or remotely infected with Mtb (3).

Limitations

The reversion probabilities used to highlight the degree of underestimation may differ by TB incidence in the setting, the immunoreactivity test, and the cutoff used. For the latter, issues arise from the use of reversion probabilities from the report of Grzybowski and Allen (11) because of the instability of the test, mainly the variability around the 5-mm single cutoff point. This issue is exacerbated by interreader variability and digit bias often encountered when using TSTs (31). In turn, the reversion probabilities from Fine et al. (10) are more convincing, as they adhere to the American Thoracic Society/Centers for Disease Control and Prevention definitions, which address this variability. Despite this, we opted to base our TST results on the reversion probabilities of Grzybowski and Allen (11), since they provide a range of uncertainty in their estimates (32). Similarly, IGRA reversions are also overemphasized in the so-called uncertainty zone (0.2–0.7 IU/ml) around the

default cutoff value, where they are as high as 52%, declining as the value increases (12, 32). By presenting a wide range of reversion probabilities (up to 50%), we provide a contour map that serves as a guide that could be used to explore ARI underestimation as seen by other empirical probabilities. While our simple model with 2 binary outcomes enabled a clear analysis of the impact of reversion, it excluded other phenomena which could also play a role in Mtb immunoreactivity and, subsequently, the ARI.

The model assumed that the risks of Mtb immunoreactivity were the same for primary infections and reinfections, and while it is not possible to determine whether there would also be a reduced risk of immunoreactivity conversion (33), studies have shown a risk reduction in the progression of TB disease in previously "infected" individuals—that is, persons with positive Mtb immunoreactivity (34). Hypothetically, if we assumed that a risk reduction would be observed among individuals who had converted before, then, for the estimates accounting for reversion, the Mtb immunoreactivity prevalences—and their corresponding ARIs—would have been lower than those obtained in the primary analysis, thus resulting in a higher ratio and a greater degree of underestimation. Another phenomenon that could affect the estimated ARI is resistance to Mtb infection in some individuals (i.e., repeatedly negative Mtb immunoreactivity tests in persons who have had close contact with pulmonary TB patients, such as household contacts, miners, etc.) (35–37). Including an Mtb resistance parameter would affect the naive and true ARIs in similar ways; therefore, it would not be expected to alter the true ARI:naive ARI ratios observed in our primary results. Finally, Bacillus Calmette-Guérin vaccination and nontuberculous mycobacteria exposure are known to cause false-positive TST results (4, 5), which may contribute to a degree of overestimation when using reactivity to assess ARI. However, their contribution to reactivity and whether and how they may modify infection risks and reversion probability is unknown, so we did not include them in the model.

Conclusions

Not accounting for reversion leads to a stark underestimation of the true ARI in populations, which changes our understanding and interpretation of Mtb transmission intensity. Considering our findings, interpretations of ARI estimates should be handled prudently. Categorization by ARI levels and mathematical models of TB disease relying on ARI as a parameter would need to be amended. Reversion probabilities specific to a region, test, and even age group are needed to increase the interpretation of ARIs from future cross-sectional surveys. Adjustment for the reversion probability and its cumulative effect with increasing age will provide a more accurate reflection of the burden and dynamics of Mtb infection.

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Data and analysis software code are available on GitHub (https://github.com/aschwalbc/ARI-Rev).

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Conflict of interest: none declared.

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WEB MATERIAL

Impact of Reversion of *Mycobacterium tuberculosis* Immunoreactivity Tests on the Estimated Annual Risk of Tuberculosis Infection

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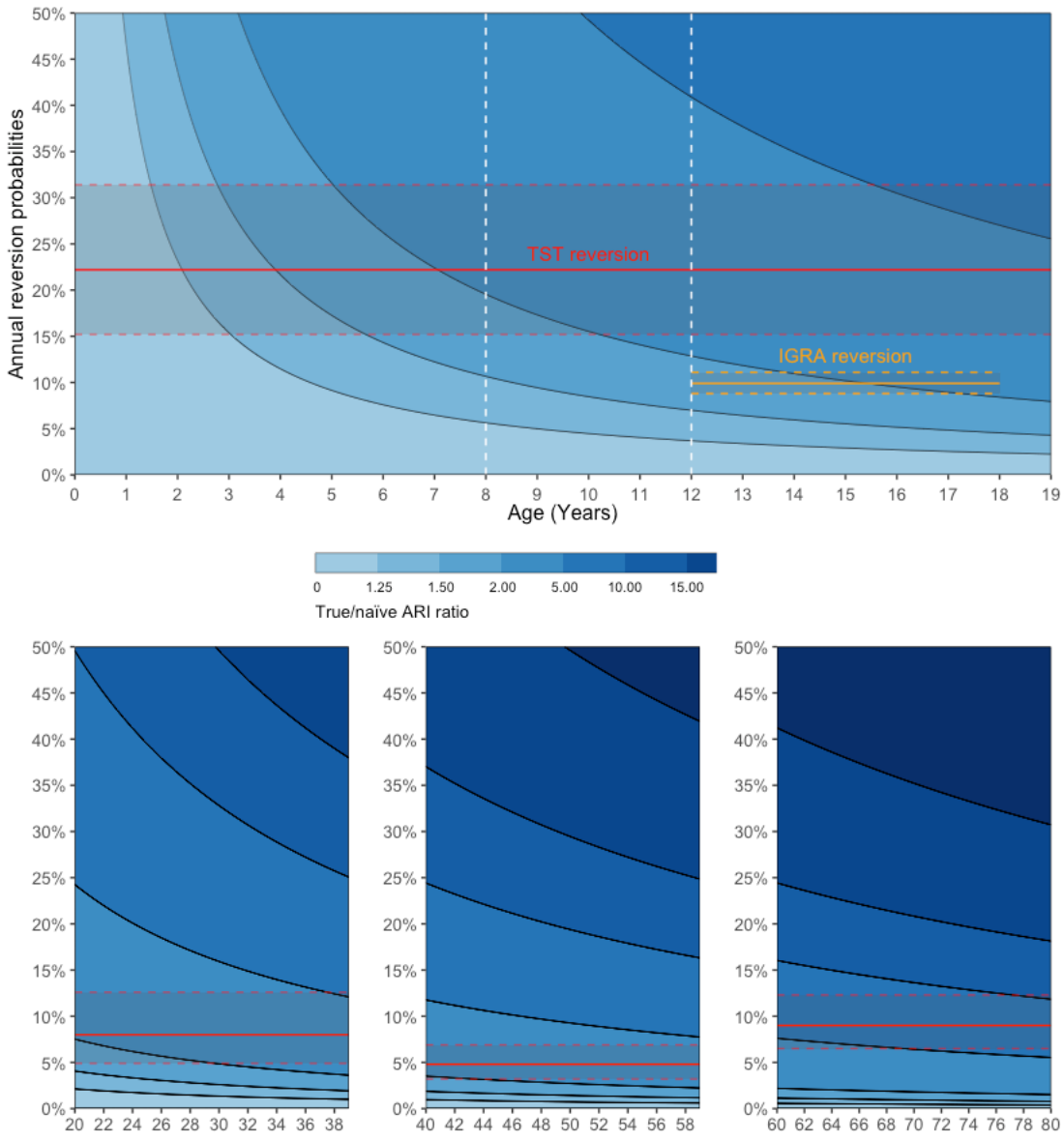
Web Figure 1

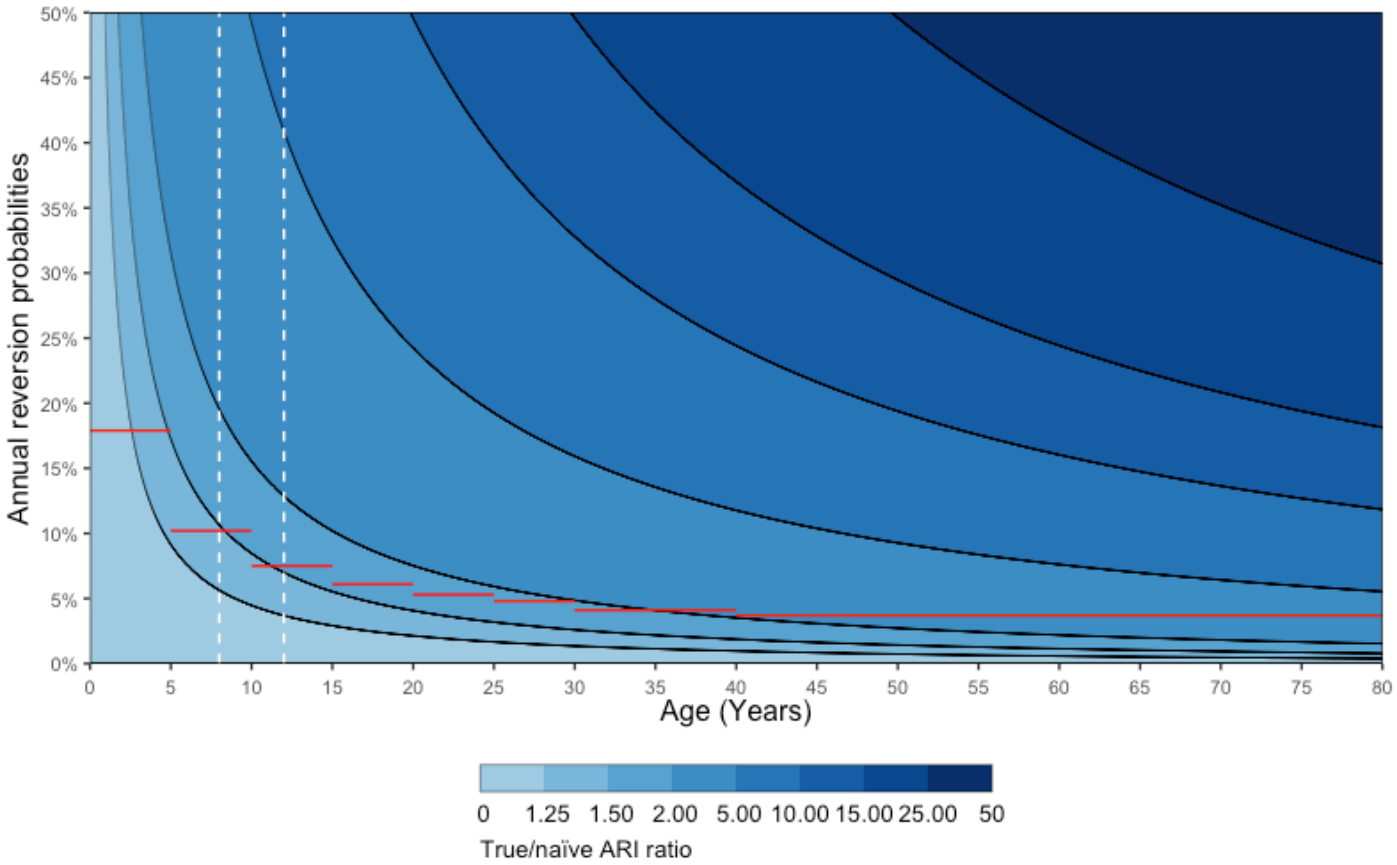
Contour maps of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: 1.5% ARI at birth and no decline in annual risk. TST reversion probabilities from Grzybowski and Allen (represented by the red line; dotted red lines represent 95%CI) and IGRA reversion probabilities from Andrews et al. (represented by the yellow line; dotted yellow lines represent 95%CI)(1,2). White dotted lines represent the age range of populations where most TST surveys are conducted. TST, Tuberculin skin test; IGRA, Interferon-gamma release assay.

Web Figure 2

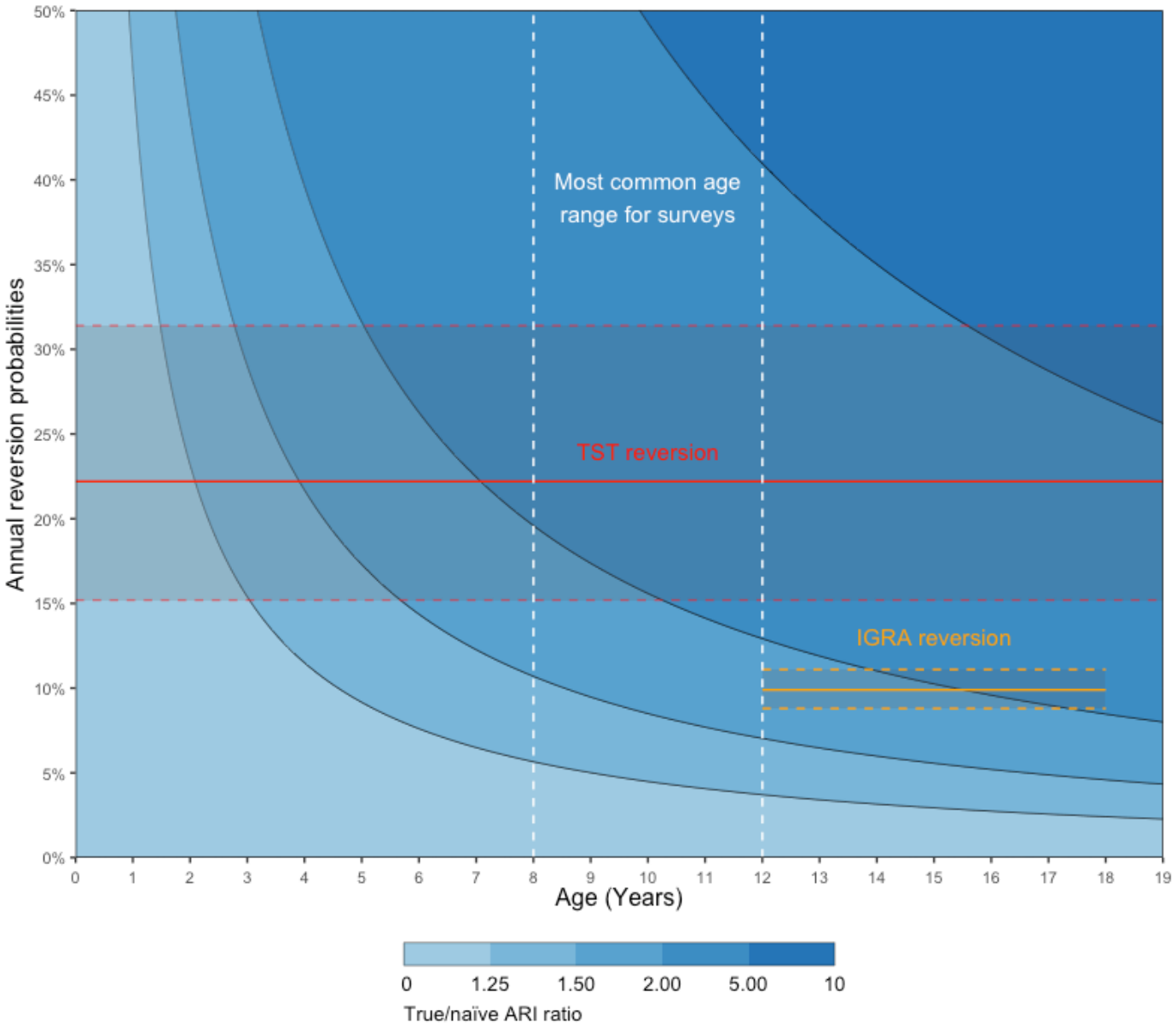
Contour map of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: 1.5% ARI at birth and no decline in annual risk. Age-specific TST reversion probabilities from Fine et al. (represented by the red lines)(3). White dotted lines represent age range of populations where most TST surveys are conducted. TST, Tuberculin skin test.

Web Figure 3

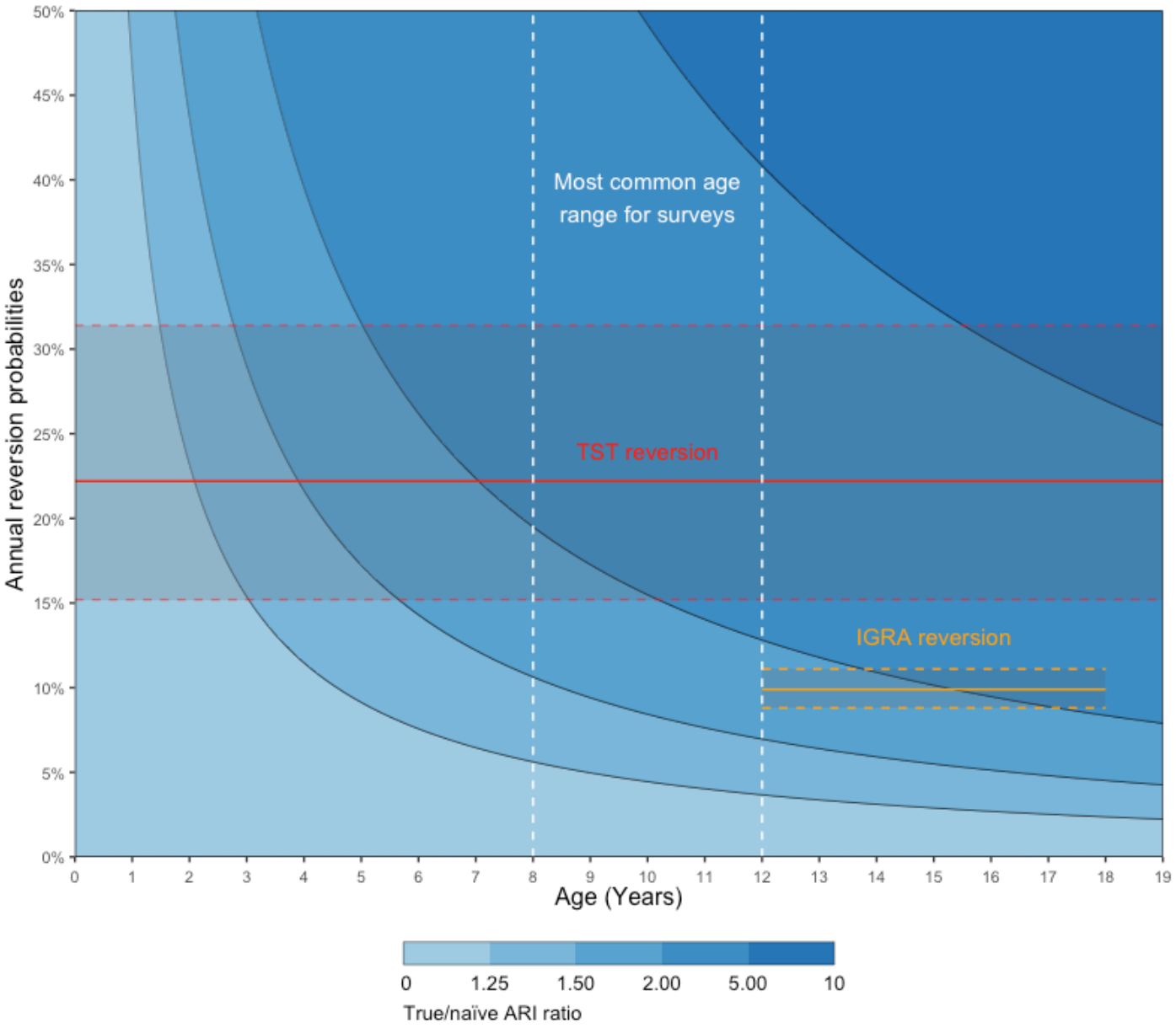
Contour map of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: ***1.3% ARI at birth and no decline in annual risk.*** *TST reversion probabilities from Grzybowski and Allen (represented by the red line; dotted red lines represent 95%CI) and IGRA reversion probabilities from Andrews et al. (represented by the yellow line; dotted yellow lines represent 95%CI)(1,2). White dotted lines represent age range of populations where most TST surveys are conducted. TST, Tuberculin skin test; IGRA, Interferon-gamma release assay.*

Web Figure 4

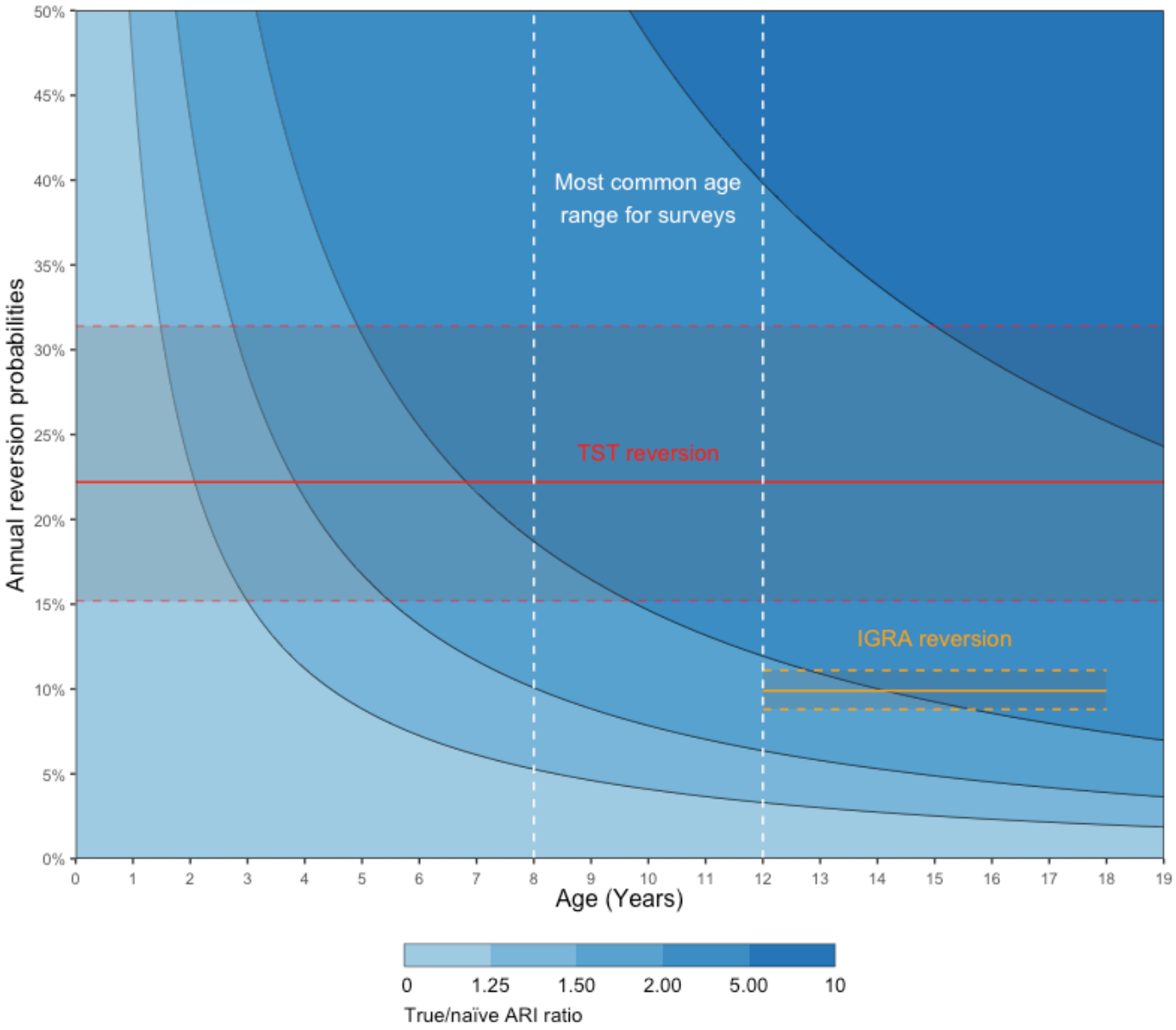
Contour map of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: ***1.7% ARI at birth and no decline in annual risk.*** *TST reversion probabilities from Grzybowski and Allen (represented by the red line; dotted red lines represent 95%CI) and IGRA reversion probabilities from Andrews et al. (represented by the yellow line; dotted yellow lines represent 95%CI)(1,2). White dotted lines represent age range of populations where most TST surveys are conducted. TST, Tuberculin skin test; IGRA, Interferon-gamma release assay.*

Web Figure 5

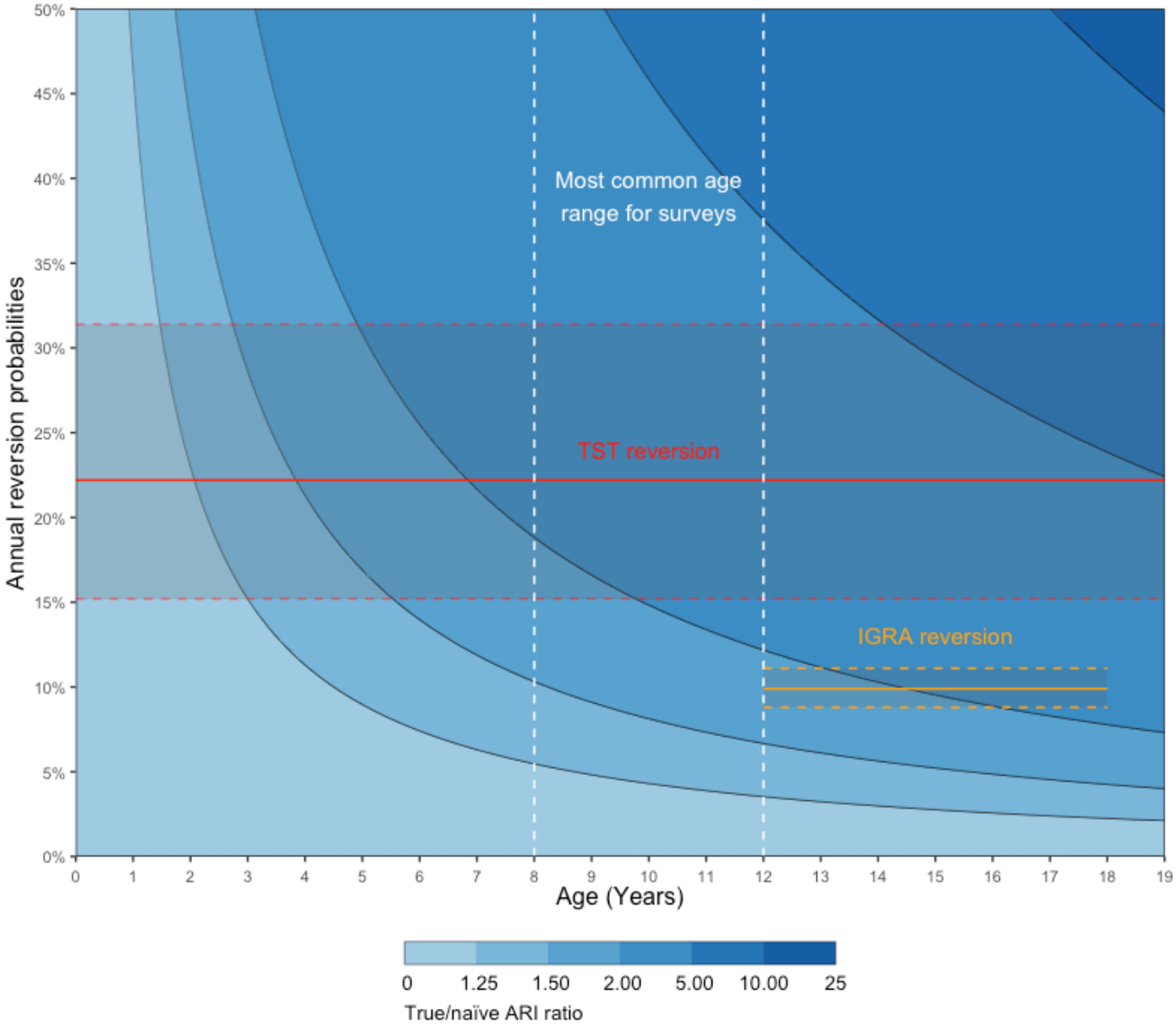
Contour map of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: ***5.0% ARI at birth and no decline in annual risk.*** *TST reversion probabilities from Grzybowski and Allen (represented by the red line; dotted red lines represent 95%CI) and IGRA reversion probabilities from Andrews et al. (represented by the yellow line; dotted yellow lines represent 95%CI)(1,2). White dotted lines represent age range of populations where most TST surveys are conducted. TST, Tuberculin skin test; IGRA, Interferon-gamma release assay.*

Web Figure 6

Contour map of ARI underestimation by varying annual reversion probabilities.



The ratio between true (varying reversion levels) and naïve ARI (no reversion) represents true ARI increase. Baseline parameters: ***1.5% ARI at birth and 2.3% decline in annual risk.*** *TST reversion probabilities from Grzybowski and Allen (represented by the red line; dotted red lines represent 95%CI) and IGRA reversion probabilities from Andrews et al. (represented by the yellow line; dotted yellow lines represent 95%CI)(1,2). White dotted lines represent age range of populations where most TST surveys are conducted. TST, Tuberculin skin test; IGRA, Interferon-gamma release assay.*

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3.3 Additional analyses

As noted by the research project, a pivotal study in calculating conversion and reversion rates was the research by Fine et al. in Malawi, which analysed an extensive longitudinal dataset of TST measurements [13]. This study was instrumental in providing age and sex-specific rates and accounted for Bacillus Calmette–Guérin (BCG) vaccine exposure, yet it notably omitted uncertainty estimates [13]. This absence hindered the precision of ARI calculations and limited their application, confining it to providing only the median estimates rather than a comprehensive range of probable outcomes. As the research project above showed the ARI may be significantly underestimated, primarily due to the neglect of immunoreactivity reversion in its calculation [11], it becomes imperative to explore the full range of estimates for more accurate and novel applications. Therefore, we re-evaluated longitudinal data from the Karonga Prevention Study (KPS) in Malawi, to estimate reversion rates from a cohort with repeated instances of TSTs.

The KPS was a large-scale research programme on the epidemiology of mycobacterial infection and disease, conducted in the Karonga district of northern Malawi [14]. Participant records were reviewed from two population surveys carried out as part of the KPS, spanning from 1980-1984 and 1986-1989 [15,16]. The latter survey also served as the recruitment phase for a subsequent leprosy and TB vaccine trial [16]. This essentially encompassed the same population as investigated in the study by Fine et al. [13]. Available data included sex, date of birth, TST induration size, BCG scar status, trial vaccine administration, and TB incidence. We included participants of all ages, with an initial positive TST result that had undergone a minimum of two TSTs, with a gap exceeding two years between tests. Additionally, we excluded individuals with uncertain BCG scar results, indicating different scar statuses between readings, and those who had received BCG vaccination as part of trial procedures before the administration of the second TST. We defined a positive TST (i.e., conversion) as an induration of ≥10mm following the 1981 American Thoracic Society (ATS) guidelines threshold [17]. As an opposite phenomenon to conversion, we defined TST reversion as an induration decrease from above 10mm, with an absolute reduction of at least 6mm [17]. We calculated TST reversion risks and rates per sex, age, and BCG scar status, providing confidence intervals for all estimates. Additionally, we evaluated the association between TB incidence and TST reversion. We used the chi-squared test to compare proportion and the Mann-Whitney U test to compare medians between groups.

Participant data were obtained from studies with appropriate ethical approval in place, including the Health Sciences Research Committee of the Malawi Ministry of Health, the ethics committee of the London School of Hygiene and Tropical Medicine, and the Standing Committee on Research in Human Subjects of the World Health Organization. All participants provided informed consent (either verbal or written) to be part of the studies.

From a total of 87,446 individuals with recorded TST induration measurements, 2,918 (3.3%) met our inclusion criteria and were selected for analysis (**Figure 3.1**). These participants contributed a cumulative follow-up time of 15,328 person-years. Most participants (54.6%) were female, and the median age at the first TST measurement was 32 years (IQR: 15-47). Among this population, 1,810 (62.0%) individuals were without a BCG scar, and 39 (1.3%) experienced a TB episode, resulting in a disease incident rate of 254 (95%CI: 181-348) per 100,000 inhabitants.

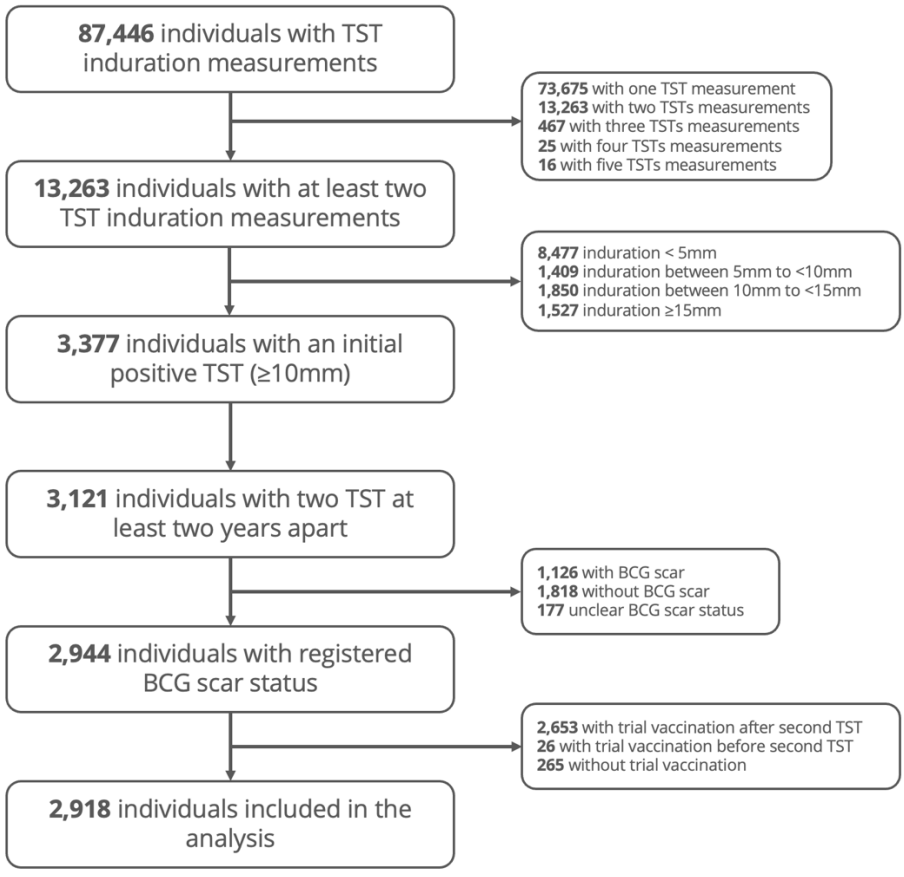

Figure 3.1 Inclusion flowchart for TST reversion analysis. Data collected from two population surveys in the Karonga district, northern Malawi, spanning from 1980-1984 and 1986-1989 [15,16]. TST: Tuberculin skin test.

There were 717 instances of reversion, with a median induration decrease of 11mm (IQR: 10-14). This corresponded to an overall risk of 24.6% (95%CI: 23.0-26.2) and an annualised rate of 4.7 reversions (95%CI: 4.3-5.0) per 100 person-years. Reversion rates appeared higher in children than in adults (**Figure 3.2** and **Table 3.1**).

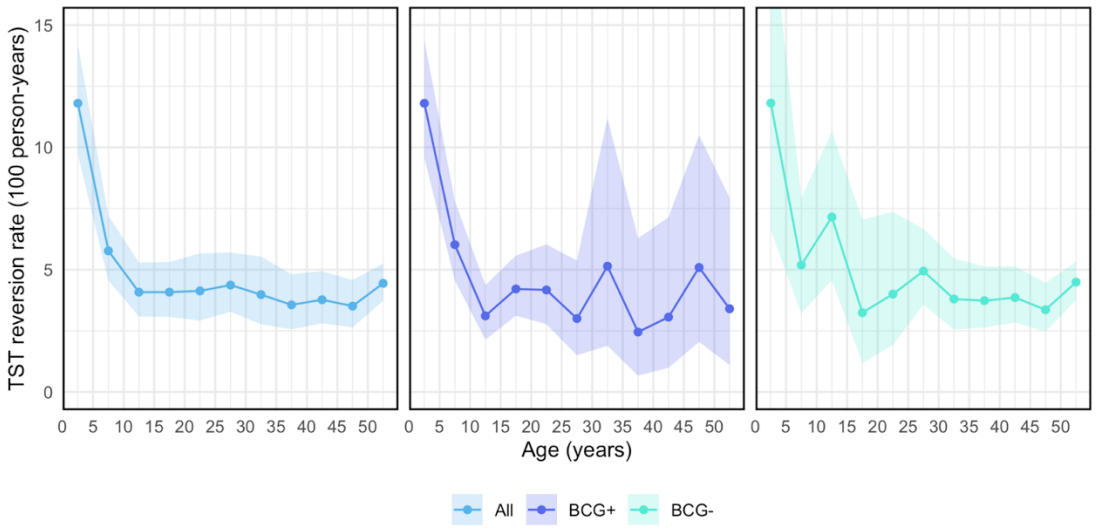

Figure 3.2 Age-specific TST reversion rates by BCG scar status. TST reversion rates by BCG scar status from population surveys in the Karonga district, northern Malawi. Lines and points represent annualised reversion rate at age group mid-point, and the shaded area shows 95% confidence interval. BCG: Bacillus Calmette-Guérin; TST: Tuberculin skin test.

Table 3.1 Age-specific TST reversion rates per BCG scar status

	All		BCG+		BCG-	
Age group	**Reversion**	**Rate per 100py (95%CI)**	**Reversion**	**Rate per 100py (95%CI)**	**Reversion**	**Rate per 100py (95%CI)**
0-5	113/180	11.8 (9.7-14.2)	98/156	11.8 (9.6-14.4)	15/24	11.8 (6.6-19.5)
5-10	78/250	5.8 (4.6-7.2)	57/176	6.0 (4.6-7.8)	21/74	5.2 (3.2-7.9)
10-15	57/264	4.1 (3.1-5.3)	33/199	3.1 (2.1-4.4)	24/65	7.1 (4.6-10.6)
15-20	55/253	4.1 (3.1-5.3)	49/217	4.2 (3.1-5.6)	6/36	3.2 (1.2-7.0)
20-25	38/181	4.1 (2.9-5.7)	28/133	4.2 (2.8-6.0)	10/48	4.0 (1.9-7.4)
25-30	54/242	4.4 (3.3-5.7)	11/77	3.0 (1.5-5.4)	43/165	4.9 (3.6-6.7)
30-35	35/167	4.0 (2.8-5.5)	6/24	5.1 (1.9-11.2)	29/143	3.8 (2.5-5.5)
35-40	42/230	3.6 (2.6-4.8)	4/33	2.5 (0.7-6.3)	38/197	3.7 (2.6-5.1)
40-45	52/262	3.8 (2.8-4.9)	5/34	3.1 (1.0-7.1)	47/228	3.9 (2.8-5.1)

45-50	55/301	3.5 (2.6-4.6)	7/28	5.1 (2.0-10.5)	48/273	3.4 (2.5-4.4)
50+	138/588	4.4 (3.7-5.2)	5/31	3.4 (1.1-7.9)	133/557	4.5 (3.8-5.3)
All	717/2918	4.7 (4.3-5.0)	303/1108	5.3 (4.7-5.9)	414/1810	4.3 (3.9-4.8)

TST reversion rates by BCG scar status from population surveys in the Karonga district, northern Malawi. BCG: Bacillus Calmette-Guérin; TST: Tuberculin skin test; PY: Person-years.

Evaluating the initial TST induration distribution revealed that individuals who experienced reversion exhibited a lower median induration compared to those who did not revert (12mm [IQR: 11-15] vs 14mm [IQR: 12-17], p < 0.001) (**Figure 3.3**).

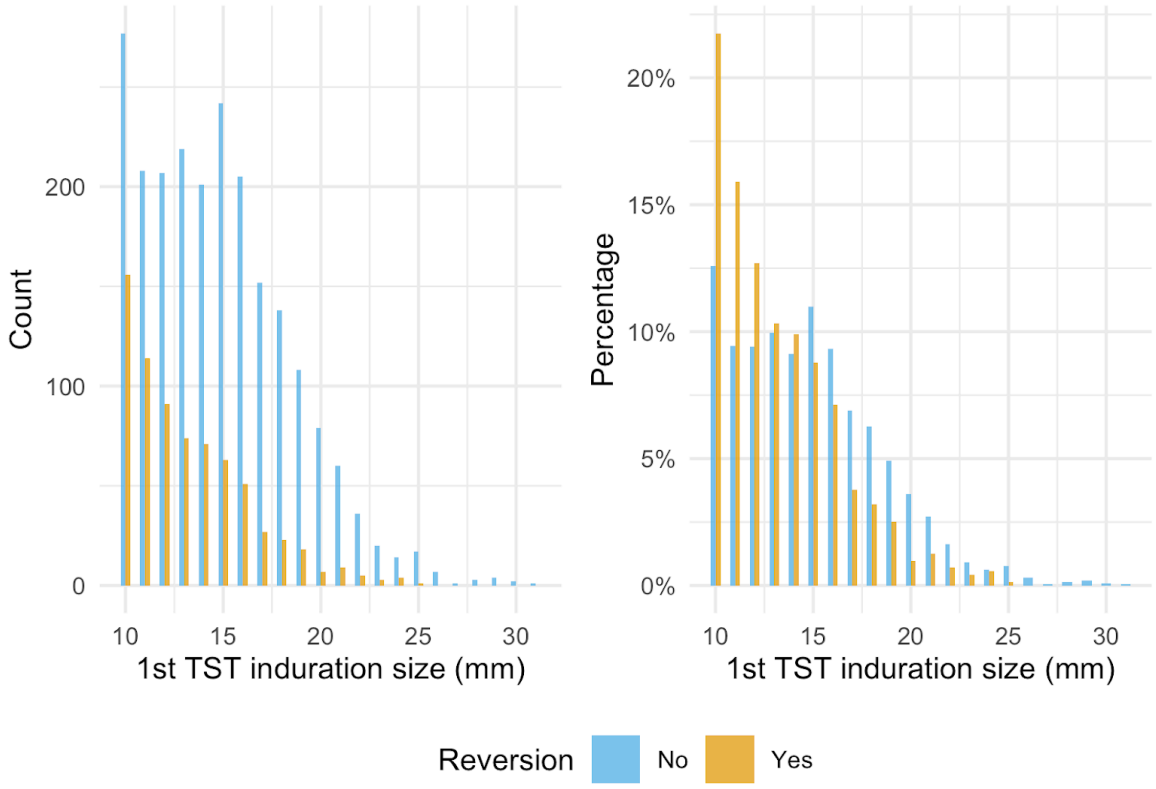

Figure 3.3 Induration distribution of initial TST by reversion status. Initial TST induration size distribution, as count and percentage, by the presence of reversion from population surveys in the Karonga district, northern Malawi. TST: Tuberculin skin test.

Among those without a BCG scar, 414 experienced TST reversion, resulting in a risk of 22.9% (95%CI: 20.9-24.9). Additionally, considering a follow-up time of 9,561 person-years, there was an annualised rate of 4.3 reversions (95%CI: 3.9-4.8) per 100 person-years. In contrast, those with a BCG scar presented a risk of 27.3% (95%CI: 24.8-30.1) and an annualised reversion rate

of 5.3 (95%CI: 4.7-5.9) per 100 person-years. There was strong evidence of a difference between TST reversion rates according to BCG scar status ($p < 0.001$), but none according to sex ($p = 0.185$). Additionally, evaluating reversion rates according to the interval between TSTs also revealed higher rates early after initial measurement as compared to later (**Table 3.2**).

Table 3.2 TST reversion rates by interval between tests

Interval between tests	Reversion	Follow-up (years)	Rate per 100py (95%CI)
> 2 to ≤ 3 years	12/47	124	9.7 (4.9-16.9)
> 3 to ≤ 4 years	91/388	1396	6.5 (5.2-8.0)
> 4 to ≤ 5 years	168/831	3920	4.3 (3.7-4.9)
> 5 to ≤ 6 years	290/1202	6529	4.4 (3.9-4.9)
> 6 years	156/450	3358	4.6 (3.9-5.4)

TST reversion rates by interval between tests from population surveys in the Karonga district, northern Malawi. TST: Tuberculin skin test; PY: Person-years.

There were 32 TB episodes among individuals without reversion (1.5%; 95%CI: 1.0-2.1) and 7 TB episodes among individuals with reversion (1.0%; 95%CI: 0.4-2.0). This difference was not statistically significant ($p = 0.435$), although it is worth noting that the power to detect such an association was low (17.5%).

By analysing the extensive TST data collected, we computed reversion rates along with their corresponding confidence intervals. Consistent with the observations made in the original study by Fine et al., we found that TST reversion is neither a rare nor a negligible phenomenon [13]. Additionally, rates are higher in younger populations and early after initial measurement, which is concordant with other studies evaluating TST reversion [18,19]. Notably, similar patterns are evident in immunoreactivity measured with IGRAs [20,21], indicating that the challenge of reversion has not been overcome even with the advent of newer diagnostic tools.

As explained before, awareness of *Mtb* immunoreactivity test reversion is critical to correctly estimating and interpreting the ARI [11]. Solely relying on tuberculous immunoreactivity largely underestimates the ARI, regardless of the population and tool employed [9,11,12,20]. In work described in this chapter, we estimated the true ARI to be at least 50% higher, considering the median estimates from the published Malawi cohort, than the naïve ARI (i.e., without accounting for reversion) [11]. By performing these additional analyses of the Malawi cohorts,

we were able to calculate reversion rates with its corresponding 95% confidence interval for individuals ages 8 to 12 years, as the most common targets for immunoreactivity surveys. Within this age group and the upper and lower bound of the reversion rates (6.3 reversions [95%CI: 4.1-9.2] per 100 person-years), the true to naïve ARI ratio was 2.9 (95%CI: 1.9-3.9).

There are some limitations to highlight. Firstly, it is important to note that reversion rates are highly contingent on the specific definition employed. As noted by Fine et al., different ARIs were derived based on which ATS guideline was followed [13]. Given that reversion is defined as the opposite of conversion, the discrepancies in threshold criteria and the required change in induration size inevitably lead to diverse reversion rate estimates. Similarly, here we considered a positive TST whether or not the value was above the threshold of 10mm and did not account for the change in induration. This approach was adopted because considering changes in induration would have required three, rather than two, TST measurements per participant. On the other hand, it is worth considering that reversion is likely underestimated since follow-up does not start from conversion, and some might have already reverted. Finally, despite access to over 115,000 TST measurements, most were a single instance, and those with subsequent tests occurred at variable intervals, ultimately leading to wide confidence ranges and were underpowered to evaluate certain associations.

3.4 Summary

This chapter examines the impact of immunoreactivity test reversion on ARI estimates, using a simple compartmental model of *Mtb* infection. Incorporating empirical reversion probabilities from TST and IGRA studies, the analysis reveals that ignoring reversion leads to significant underestimation of ARI, with true values being 2–5 times higher in surveyed children and compounding further in older populations. This underestimation distorts *Mtb* transmission intensity estimates, biases TB mathematical models, and risks misguiding public health interventions. The findings highlight the importance of integrating test- and age-specific reversion adjustments into ARI calculations, or at minimum, into its interpretation, to better inform TB strategies.

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Chapter 4: Global burden of viable *Mycobacterium tuberculosis* infection

In this chapter, the second research paper of the thesis is presented to address *Objective #2*: to estimate the global burden of viable *Mycobacterium tuberculosis* (*Mtb*) infection, incorporating reversion-adjusted and age-specific annual risk of infection (ARI) trends, as well as self-clearance of infection. The chapter opens with a concise overview of the research gap, followed by the preprint, supplementary material, and concludes with a brief summary.

4.1 Introduction

Determining the burden of *Mycobacterium tuberculosis* (*Mtb*) infection has always been a challenge. This is primarily because, in the absence of disease, its presence in the host cannot be directly measured, and instead relies on immunological memory of exposure to tuberculous antigens [1]. Consequently, previous estimates have centred on 'latent' tuberculosis infection (LTBI)—a non-disease, non-transmissible state—defined by immunoreactivity detected through a tuberculin skin test or an interferon-gamma release assay [1,2]. These studies suggest that approximately one-third to one-quarter of the global population has LTBI [3,4]. However, they actually represent a proportion of individuals who have been previously exposed to *Mtb* and exhibit tuberculous immunoreactivity, rather than necessarily viable *Mtb* infection, i.e. individuals capable of progressing to disease without re-infection [5]. Estimates of the latter accounts for the dynamic and transient nature of *Mtb* infection, providing useful insights into the population who would benefit from TB preventive therapy (TPT) [6].

Noting that the distinction between immunoreactivity and viable infection is critical, there are a number of assumptions to re-evaluate. Immunoreactivity, as a measure of past exposure, can be underestimated as it wanes or reverts [7]. Reversion reflects the decline of immune memory over time, which can occur due to the absence of ongoing exposure to *Mtb* antigens, assay variability, or changes in the host's immune status [7]. Previous studies have used trends in ARI, derived from immunoreactivity, to estimate current prevalence [3,4]. However, these studies have not accounted for the stark underestimation of the ARI caused by immunoreactivity reversion [8], as noted in the previous chapter. Furthermore, the ARI is often extrapolated from immunoreactivity surveys in children, even though they experience less *Mtb* transmission as compared to adults [9]. Lastly, evidence suggests that a substantial proportion of individuals infected may clear the infection without treatment, meaning they no longer harbour viable *Mtb* [5,10]. By addressing these assumptions, we can grasp a more refined understanding of viable *Mtb*, thereby providing actionable insights for TB prevention.

4.2 Research paper

The following pages contain the Research Paper Cover Sheet, the copyright license, the preprint of the research paper, and the supplementary material for: *Schwalb A, Dodd PJ, Rickman HM, Ugarte-Gil CA, Horton KC, Houben RMGJ. Estimating the global burden of viable Mycobacterium tuberculosis infection. SSRN. 2024. DOI:10.2139/ssrn.5017943* [11].

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	2004111	**Title**	Dr
First Name(s)	Alvaro		
Surname/Family Name	Schwalb		
Thesis Title	Estimating the burden of Mycobacterium tuberculosis infection and the impact of population-wide screening for tuberculosis		
Primary Supervisor	Prof Rein Houben		

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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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS Medicine
Please list the paper's authors in the intended authorship order:	Alvaro Schwalb, Peter J. Dodd, Hannah M. Rickman, César A. Ugarte-Gil, Katherine C. Horton, Rein M.G.J. Houben
Stage of publication	**Undergoing revision**

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 adapted the pipeline for the ARI data preparation and the Gaussian Process regression as developed by Pete Dodd and Rein Houben. I designed the methods to incorporate mixing and age-specific risks of infection with guidance from Pete Dodd. I calibrated self-clearance rates with help from Peter Dodd. I designed the model to implement all elements in collaboration with Katherine Horton, Pete Dodd and Rein Houben. I conducted the analysis and ran the model in the HPC with help from a co-worker (acknowledged in the preprint). 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.

SECTION E

Student Signature	Alvaro Schwalb
Date	7 January 2025

Supervisor Signature	Rein Houben
Date	7 January 2025

Estimating the global burden of viable *Mycobacterium tuberculosis* infection

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Keywords: annual risk of infection; immunoreactivity; self-clearance; prevalence

Abstract

Background: Estimating the proportion of individuals currently infected with *Mycobacterium tuberculosis* (*Mtb*) is key for informing global health policies. Although a substantial portion of the global population exhibit tuberculous immunoreactivity, not all have a viable infection that can progress to disease. Moreover, individuals with recent infections are at a higher risk of developing tuberculosis. Here, we present estimates of the global burden of viable *Mtb* infection, using new insights into the natural history of TB.

Methods: We constructed country-specific trends in annual risk of infection considering estimates of TB burden, immunoreactivity reversion, and age-specific mixing. We applied these trends to a deterministic mathematical model incorporating reinfection and self-clearance to estimate recent (within 2 years) and total viable *Mtb* infections. Self-clearance rates were informed by empirical data and modelling estimates; the robustness of the model to assumptions about long-term self-clearance rates was explored.

Findings: In 2022, 156 million people (95%UI:127-199) were recently infected with viable *Mtb*, equating to 2.0% (95% uncertainty interval [UI]:1.6-2.5) of the global population. Depending on assumptions regarding long-term self-clearance rates, we estimate that between 4.9% (95%UI:4.4-5.6) and 7.7% (95%UI:6.9-8.5) of the global population harbour a viable infection, corresponding to 387 (95%UI:347-441) and 606 (95%UI:549-670) million people, respectively. Of those recently infected, 11.5% (95%UI:10.5-12.3) were children under 15 years of age. Most recent infections were found in Southeast Asia (47.9%; 95%UI:37.6-59.4) and the Western Pacific regions (25.7%; 95%UI:17.6-35.8). India, China, and Indonesia had the highest burden with 41.7 (95%UI:22.3-76.7), 21.6 (95%UI:11.1-41.8), and 14.2 (95%UI:8.7-22.8) million recent Mtb infections, respectively.

Interpretation: Our findings offer the first global burden estimates of viable *Mtb* infection. New insights reveal a sizable population recently infected with viable *Mtb* and at high risk of progression to disease. New diagnostic tools that can detect individuals with viable *Mtb* —those who would benefit most from TB preventive therapy—are urgently needed.

Funding: European Research Council (ERC).

Research in context

Evidence before this study

We searched PubMed on 28 August 2024 for articles estimating the global burden of *Mycobacterium tuberculosis* (*Mtb*) infection, using the following search terms in the title or abstract, with no date or language restrictions: “(TB OR tuberc*) AND (infection) AND (global AND burden)." We identified 600 articles, two of which provided global estimates of 'latent' tuberculosis infection (LTBI), published in 1999 and 2016, estimating that approximately one-third and one-quarter of the global population were infected with *Mtb*, respectively. In parallel, we reviewed the estimates of the Global Burden of Disease study, which similarly suggest that, over the last decade, one-quarter of the global population has LTBI. These estimates of LTBI represent a proportion of individuals who have been previously exposed to *Mtb* and exhibit tuberculous immunoreactivity, rather than viable *Mtb*. Notably, these estimates were based on assumptions of permanent immunoreactivity and lifelong *Mtb* infection. Our search did not identify any prior studies that considered self-clearance in their estimates to account for the viability of infection.

Added value of this study

Our study introduces an estimate of the global population harbouring viable *Mtb* infection with a particular focus on those at high risk of progression to disease. To achieve this, we introduced several novel steps. Firstly, we constructed trends in the annual risk of infection (ARI), adjusting for immunoreactivity reversion and age-specific social mixing patterns; this approach addresses the underestimation of ARI in adults from using data in infection rates in children, providing a higher and more accurate representation of the force of infection. Secondly, we utilise evidence that a substantial portion of individuals may self-clear their infection, integrated this into a deterministic mathematical model, and thus provided an estimate of viable *Mtb* infection rather than an estimate of tuberculous immunoreactivity. Thirdly, we focused on recent infections, acknowledging that the highest risk of progression to disease occurs within the first two years since infection. Finally, we provide country-specific estimates for 171 nations, while also accounting for population dynamics.

Implications of all the available evidence

Our findings indicate that in 2022, 156 million people globally had a recent viable *Mtb* infection, highlighting a sizable population at high risk of progressing to disease. Additionally, we estimate that 5 to 8% of the global population was harbouring a viable *Mtb* infection in 2022, contrasting

with previous estimates of the proportion exposed to *Mtb*. These results underscore the need to develop tests that can detect viable *Mtb*, rather than relying on measures of immunological memory, as such tests would more accurately identify those who would benefit from preventive therapy.

Background

Estimates of *Mycobacterium tuberculosis* (*Mtb*) infection burden are fundamental in shaping global health strategies for tuberculosis (TB).[1] These estimates guide key interventions, such as the provision of TB preventive therapy (TPT) to individuals infected with *Mtb*, which is vital for reducing TB incidence.[2] Therefore, it is critical that estimates capture the number of individuals harbouring viable *Mtb* infection, i.e., an infection capable of progressing to disease.[3] Furthermore, these estimates should account for the recency of infection, as most infected individuals who progress to disease will do so within two years of infection.[4] Focusing on recent viable *Mtb* infection sets a medically actionable target for optimising the prevention cascade and the population to target with TPT.[1,3] Additionally, such estimates would offer deeper insights into the reservoir fuelling ongoing *Mtb* transmission in the coming years.[1]

Previous studies have estimated that a substantial portion of the global population had 'latent' TB infection (LTBI), an asymptomatic state defined by the presence of immunoreactivity to tuberculous antigens.[5–7] Although these estimates essentially reflect individuals exposed to *Mtb* and still exhibiting immunoreactivity, they are often used interchangeably to indicate current infection.[1,8] As our understanding of the natural history of TB has evolved,[9,10] long-standing assumptions that informed those estimates warrant reconsideration.

Firstly, estimates of LTBI used the annual risk of infection (ARI) as a metric for the force of infection experienced by a population. The ARI is derived from surveys of immunoreactivity prevalence, and assumes immunoreactivity persists over time;[11] however, immunoreactivity can wane and in several cases revert,[12] leading to significant underestimation of the actual ARI.[13,14] Secondly, the ARI is often extrapolated from surveys in children;[11] however, *Mtb* transmission to children is less common than adolescents and adults.[15] As a result, infection incidence (and the estimated ARI) may be underestimated in older age groups, who have higher contact rates with individuals with infectious TB.[14,15] Both reversion and contact patterns suggest that the true force of infection in adults is likely higher than previously assumed. If so, this would significantly increase the estimated global burden of infection, especially given the long-held assumption of lifelong *Mtb* infection. However, this assumption has been challenged by estimates suggesting that a large proportion (>90%) of individuals self-clear their infection without treatment and are no longer at risk of TB in the absence of reinfection.[8,9,16,17] Therefore, considering the phenomenon of self-clearance in our estimates would likely result in a lower global burden of infection than previously thought.[9]

These progressive insights underscore the need for estimates that account for the dynamic nature of *Mtb* infection. By incorporating these factors, more accurate assessments of the current global burden of viable *Mtb* infection can be made to guide effective TB prevention strategies. In this study, we estimate the global burden of viable *Mtb* infection using a mathematical modelling approach that incorporates recent insights into TB natural history.

Methods

Annual risk of infection

To estimate the burden of viable *Mtb* infection, we constructed national ARI trajectories spanning from 1950 to 2022, based on the methods used by Houben and Dodd.[6] The trajectories were constructed using a Gaussian process (GP) regression, a flexible, non-parametric framework combining different sources of estimates with the assumption of a normal approximation to the likelihood. These were fitted to 171 countries (comprising 99.6% of the world population) using two sources of ARI estimates. Direct ARI estimates were obtained from nationally representative immunoreactivity surveys identified in previous searches **(Table S1 and Supplementary Material SM1).** Most surveys used tuberculin skin test (TST) positivity prevalence and were conducted in children aged 6 to 9 years old. For estimates reported as a single value without presentation of uncertainty, an additional step is taken to quantify measurement precision **(Supplementary Material SM2).** Moreover, indirect ARI estimates were derived from TB prevalence estimates using the revised Styblo rule and adjusted to account for the influence of age and HIV on smear positivity **(Supplementary Material SM3)**. TB prevalence estimates were calculated by converting the most recent World Health Organization (WHO) TB incidence estimates (from 2000-2022) by applying an average duration of disease **(Supplementary Material SM4).** Furthermore, accounting for the impact of immunoreactivity reversion and that the true ARI is roughly 3 times higher than calculated, all ARI estimates are adjusted based on this underestimation.[13] Additionally, measurement uncertainty was also increased by 50% to account for this adjustment. The GP regression with a linear trend was applied to the reversion-adjusted data on ARI (on a log scale) and the measurement precision per country. For each country, 1,000 simulated ARI trajectories from 1950 to 2022 were generated.

Mixing and age-specific risks of infection

To address the higher risk of infection in adults compared to children, we used age-specific estimates of TB incidence as a proxy for TB prevalence and then applied contact mixing matrices to derive the corresponding hazard ratios for each age group. We defined three distinct age groups to encapsulate varying ARIs: under 15 years, 15 to 45 years, and 45 years and older. Using the estimated TB incidence disaggregated by age and country,[18] we calculated the relative TB incidence per capita, using the under-15-year-old age group as the reference, assuming that this age group has low infectiousness **(Figure S1)**. Similarly, by employing the synthetic country-specific contact mixing matrices developed by Prem et al.,[19] we obtained the average number of contacts between the defined age groups **(Figure S2)**. We then integrated these data to estimate the relative ARI for each age group, again using the under-15-year-old age group as the reference **(Figure S3)**. Finally, ARI trajectories were subdivided into three age groups and adjusted based on relative ARI; for countries with missing data, we applied the regional relative ARI.

Self-clearance rates

Using a Bayesian approach, self-clearance rates were calibrated by tracking an infected cohort over time, using a similar model structure as described above, but without accounting for infection or reinfection. Informed by the pathways described in the natural history of TB model by Horton et al.,[10] the proportions of the cohort that self-clear or recover (i.e., no longer harbour viable *Mtb* infection) at years 1 (95% CI: 80.1-81.7%), 2 (95% CI: 91.4-92.5%), and 10 (95% CI: 96.9-97.5%) were used as calibration targets. Due to the lack of data on the proportion after 10 years, we opted to assume a range of 98.5-99.5% as long-term proportion self-cleared and calibrated the associated post-10-year self-clearance rate under two different scenarios: one where this was reached by year 20 post-infection (high self-clearance) and another for year 50 (low self-clearance) **(Figure S4)**. All rates were assigned uninformed uniform priors and posterior estimates were calculated using a Markov chain Monte-Carlo algorithm in Stan via R statistical software.[20,21] We assumed that self-clearance rates were constant and were not influenced by age or year. Further details on calibration are available in the **Supplementary Material SM5**.

Model structure

We developed a deterministic model tracking *Mtb* infection and self-clearance of infection across five-year age groups **(Figure S5).** Parameters and descriptions can be found in **Table S2.** Once individuals are infected, they can progress through four infection states reflecting

various times since infection. In each infection state, individuals can self-clear infection and revert to not being infected. Individuals who have been distally infected (i.e. more than two years), are at risk of reinfection, adjusted by a protection factor.[22] The force of infection was determined by the reversion-adjusted and age-group specific ARI trajectory for each country. The self-clearance rates were obtained from the calibrated scenarios. The model was constructed using R version 4.3.2 for statistical computing and graphics.[21] Further details and model equations are available in the **Supplementary Material SM6-7**.

Model run and outputs

For each country, all 1,000 ARI trajectories from 1950 to 2022 were used to estimate the proportion of each age group harbouring viable *Mtb* at various times since infection. These proportions were combined with population estimates obtained from the United Nations World Population Prospects.[23] Estimates for absolute numbers and prevalence of viable *Mtb* infection were summarised and explored by age group, country, region, and globally. For the main results, we report the estimates based on the high self-clearance scenario as a conservative approach to estimating viable *Mtb* infection in 2022, with robustness compared against the low self-clearance scenario. All results are reported as medians with their corresponding 95% uncertainty intervals (95%UI), calculated as the 2.5% to 97.5% percentile range.

GATHER reporting

This study was reported in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).[24] **Figure 1** provides a comprehensive conceptual overview of the study including methods and data sources. The GATHER checklist is also available as **Supplementary Material.**

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Annual risk of infection estimates

Figure 2 shows the fitted ARI trajectories with and without reversion and age-specific adjustments for India, Indonesia, and China—countries with the highest estimated TB incidence

in 2022. Compared to the under-15-year-old population, the average relative ARI was 4.3 for the 15 to 45-year-old population and 3.3 for those aged 45 and older. Regional relative ARIs by age group are available in **Table S3**. For India, Indonesia, and China, the estimated ARI for the 15 to 45 years age group was 8.7% (95% UI: 4.3-17.8), 16.1% (95% UI: 8.1-30.5), and 3.6% (95% UI: 1.6-8.0), respectively. ARI estimates for 2022 for the remaining countries on the WHO's list of 30 high TB burden countries are shown in **Table S4**. When compared to the unadjusted ARI estimates for 2014 from Houben and Dodd,[6] the ARI for the under 15 years age group was 3.1 times higher (IQR: 2.6-4.0), reflecting the increase in the force of infection due to adjustments for reversion underestimation **(Table S5)**.

Global burden of infection estimates

We estimate that 2.0% (95%UI: 1.6-2.5) of the global population was recently infected with viable *Mtb*, amounting to approximately 155.6 million people (95%UI: 127.2-198.7) **(Table 1 and Table 2)**. Estimates of recently infected were robust across scenarios. In contrast, the overall infected population ranged between 4.9% (95%UI: 4.4-5.6) and 7.7% (95%UI: 6.9-8.5), depending on assumptions of long-term self-clearance rates.

Regional and country-level infection estimates

Of all recent infections, over 87% were found in the three regions of Southeast Asia (47.9%; 95%UI: 37.6-59.4), Western Pacific (25.7%; 95%UI: 17.6-35.8), and Africa (13.7%; 95%CI: 10.3-17.5) **(Table S5)**. At the country level, India, China, and Indonesia combined to about 50% of global recent infections, with 41.7 (95%UI: 22.3-76.7), 21.6 (95%UI: 11.1-41.8), and 14.2 (95%UI: 8.7-22.8) million recent *Mtb* infections, respectively **(Table S6)**. The remaining countries in the top 10 were all from the WHO's list of 30 high TB burden countries.[25] **Figure 3** shows the regional and country-level variation in the prevalence of recent viable *Mtb* infections. Here, the countries with the highest prevalence of recent viable *Mtb* infections were North Korea (9.3%; 95%UI: 4.8-16.3), The Philippines (8.5%; 95%UI: 4.4-16.4), and Cambodia (5.4%; 95%UI: 2.9-9.3) **(Table S7)**. Estimates of viable *Mtb* infection for all 171 countries are available in the **Supplementary File.**

Age trends

The proportions of individuals with viable *Mtb* infection by age group and region are shown in **Figure S6**. Across all regions, higher infection estimates are concentrated in the adult population younger than 45 years old, in line with the increased ARI. Among those recently

infected, 11.5% (95%UI: 10.5-12.3) were in children under 15 years of age, amounting to 17.6 million (95%UI: 14.5-22.2) **(Table 1 and Table 2)**. There was a substantial regional disparity in recent infections among children, ranging from 5.3% (95%UI: 4.8-6.0) in the European Region to 22.5% (95%UI :21.4-23.6) in the African Region, likely due to differences in population structure **(Table 2)**.

Discussion

Our findings provide an estimate of the global burden of viable *Mtb* infection, with approximately 156 million people, 2% of the world's population, recently infected and at immediate high risk of progression to disease, with significant geographical variability. Considering a reasonable range of long-term self-clearance rate assumptions, we estimate the total burden to lie between 5% and 8%. This underscores the need for enhanced diagnostic and management strategies to identify and treat these individuals, as only those with viable *Mtb* infection can possibly benefit from TPT.

Our estimates further highlight the important distinction between viable *Mtb* infection and positive immunoreactivity tests. Despite working on a similar construction of ARI trajectories, there is a stark numerical contrast between our viable *Mtb* infection estimates and the latest LTBI estimates.[6] The main contributor to this difference is the inclusion of self-clearance of infection in our model, and thus shifting the change of the estimate definition from (historical) exposure to *Mtb* (as measured by immunoreactivity) to viable *Mtb* infection. This was first suggested by Emery et al. where the population with viable *Mtb* infection was markedly smaller (up to 20%) than assumed in India, China, and Japan.[9] Similarly, our estimates indicate a lower overall proportion of *Mtb* infection, even after adjusting for the increased ARI experienced (considering immunoreactivity reversion and age-specific risks). Self-clearance is now widely acknowledged, as reflected by a shift in WHO reporting, which now describes the quarter of the population figure as "having been infected" rather than "currently infected".[1,18] Self-clearance therefore outweighed the increased force of infection generated by revised understanding of the true ARI underneath empirical measurements.[13,14] However, the shift in ARI has led to a higher estimate of the recently infected population are compared to previous (2.0 vs 0.8%), suggesting a rapid turnover of the population at risk of developing TB.[6]

While this study attempts to quantify the extent of viable *Mtb* infection, we remain unable to directly detect it. Current diagnostic tests for TBI, mainly TSTs and interferon-gamma release

assays (IGRA), detect immunoreactivity to tuberculous antigens but do not directly detect the presence of the organism itself.[26] Similarly, this pattern can also be observed in the diagnosis of TB among individuals with non-specific chest radiography abnormalities. Additionally, they are an inaccurate surrogate of viability as they can remain detectable (positive) after provision of TPT.[27] This poses a significant challenge for national TB programmes, as TPT is often offered to those with a single positive immunoreactivity test,[28] whereas the number of those that would truly benefit is likely smaller, especially in absence of an indicative patient history, such as recent contact with a TB patient. To improve and expand the use of TPT, there is a clear need for improved biomarkers for *Mtb* infection, with some having been explored recently.[29,30]

Our modelling study is not without limitations. Firstly, contemporary empirical ARI estimates are scarce, leading to substantial uncertainty for the ARI in recent years. While still requiring adjustments to account for reversion, recent surveys using IGRA or new TB antigen-based skin tests would improve ARI estimates, especially as they reduce false positive results among children who received Bacillus Calmette Guerin (BCG) vaccination.[26] Furthermore, in our attempt to capture a global estimate, we had to make several simplifications. For example, we treated all individuals as experiencing one of three age-specific ARIs, disregarding existing population and individual factors that could increase or decrease the force of infection. We also did not account for migration, assuming that all countries were epidemiologically independent. Additionally, the reversion underestimation factor was simplified; it was determined by a single value and applied uniformly to all ARI estimates. While reversion rates vary significantly across different ages and populations,[12] we opted for an average value and accounted for decreased measurement precision to reflect the additional uncertainty introduced by this assumption. Similarly, ARI estimates could have been further refined by breaking them down into distinct 5-year age groups, rather than using only three broad categories, which resulted in a coarse age group distribution in the estimates. However, as our results indicate, self-clearance of infection was the most significant operating factor in the model, suggesting that the added granularity would be unlikely to have provided qualitatively different findings. These necessary compromises may have introduced some biases in the accuracy of our results, but they were appropriate to ensure the feasibility of country, regional, and global burden assessments.

Our findings provide valuable global estimates of the burden of viable *Mtb* infection, emphasising the crucial distinction from positive immunoreactivity tests. By more accurately accounting for the true force of infection and the immune system's ability to clear infections, we

were able to better identify a sizeable population recently infected and at risk of progressing to disease. This approach underscores the importance of distinguishing viable *Mtb* infection as a prerequisite for TB disease,[31] as opposed to the concept of 'latency', most of which does not represent a dormant TB risk. There is an urgent need for enhanced diagnostic tools capable of detecting viable *Mtb* infection, allowing us to target those most likely to benefit from TB preventive therapy.

Author contributions: Conceptualisation: AS, PJD, and RMGJH; Data curation: AS; Formal analysis: AS and PJD; Writing – original draft: AS; Writing – review & editing: PJD, HMR, CAUG, KCH, and RMGJH; Supervision: PJD, KCH, and RMGJH.

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Conflict of interest: All authors declare no conflicts of interest.

Data availability: Data and analysis code are available on GitHub (https://github.com/aschwalbc/MtbInf).

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Table 1. Number of individuals with viable *Mycobacterium tuberculosis* infection in 2022.

WHO Region	Recent infections (M) [95%UI]	Recent infections in children (M) [95%UI]	All infections – high self-clearance scenario (M) [95%UI]	All infections – low self-clearance scenario (M) [95%UI]
AFR	21.3 [17.9–26.2]	4.8 [4.0–6.0]	53.3 [48.5–59.6]	80.3 [72.3–89.2]
AMR	5.4 [4.1–7.3]	0.4 [0.3–0.5]	14.6 [12.2–18.6]	44.1 [29.1–67.9]
EMR	8.5 [5.6–13.5]	1.7 [1.1–2.8]	22.2 [18.0–28.6]	43.9 [35.1–54.3]
EUR	5.2 [4.1–7.0]	0.3 [0.2–0.4]	17.3 [15.1–20.4]	46.8 [37.9–57.9]
SEA	74.3 [52.4–110.3]	7.5 [5.1–11.6]	173.6 [143.8–216.9]	225.6 [186.5–280.4]
WPR	39.4 [26.5–60.3]	2.8 [1.9–4.4]	103.6 [83.1–134.1]	160.2 [129.2–206.2]
GLOBAL	**155.6 [127.2–198.7]**	**17.6 [14.5–22.2]**	**387.0 [346.6–440.6]**	**605.5 [548.5–670.4]**

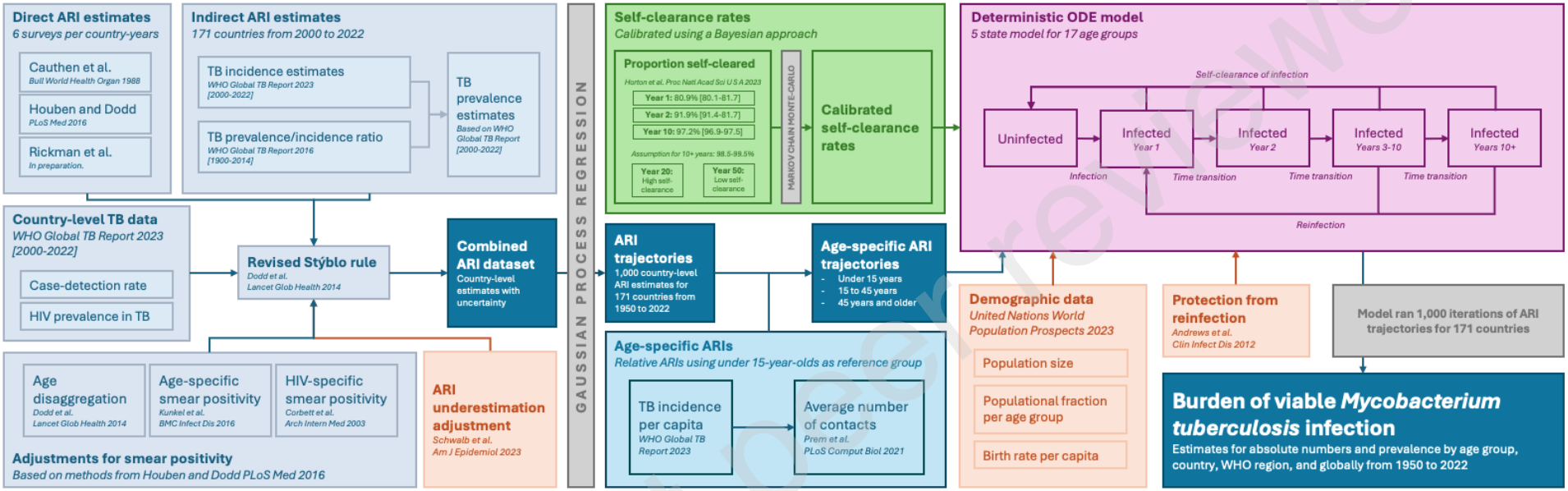
Absolute number of individuals globally and by WHO region infected with viable *Mycobacterium tuberculosis* in 2022. Numbers are in millions (M), with brackets indicating 95% uncertainty intervals (95%UI). Recent infection is defined as occurring within two years. Children are classified as individuals under 15 years of age. Estimates for all infections are provided and disaggregated based on different scenarios depending on assumptions about long-term self-clearance rates. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Table 2. Proportion of population with viable *Mycobacterium tuberculosis* infection in 2022.

WHO Region	Recent infection prevalence (%) [95%UI]	Proportion of recent infections in children (%) [95%UI]	All infections prevalence – high self-clearance scenario (%) [95%UI]	All infections prevalence – low self-clearance scenario (%) [95%UI]
AFR	1.8 [1.5–2.2]	22.5 [21.4-23.6]	4.5 [4.1-5.1]	6.8 [6.1-7.6]
AMR	0.5 [0.4–0.7]	7.4 [6.8-7.9]	1.4 [1.2-1.8]	4.3 [2.8-6.6]
EMR	1.1 [0.7–1.7]	20.2 [19.5-20.9]	2.9 [2.3-3.7]	5.7 [4.5-7.0]
EUR	0.6 [0.4–0.8]	5.3 [4.8-6.0]	1.9 [1.6-2.2]	5.0 [4.1-6.2]
SEA	3.6 [2.5–5.3]	7.1 [5.6-9.2]	8.4 [7.0-10.5]	10.9 [9.0-13.6]
WPR	2.0 [1.4–3.1]	10.0 [9.6-10.5]	5.4 [4.3-6.9]	8.3 [6.7-10.7]
GLOBAL	**2.0 [1.6–2.5]**	**11.4 [10.4-12.1]**	**4.9 [4.4-5.6]**	**7.7 [6.9-8.5]**

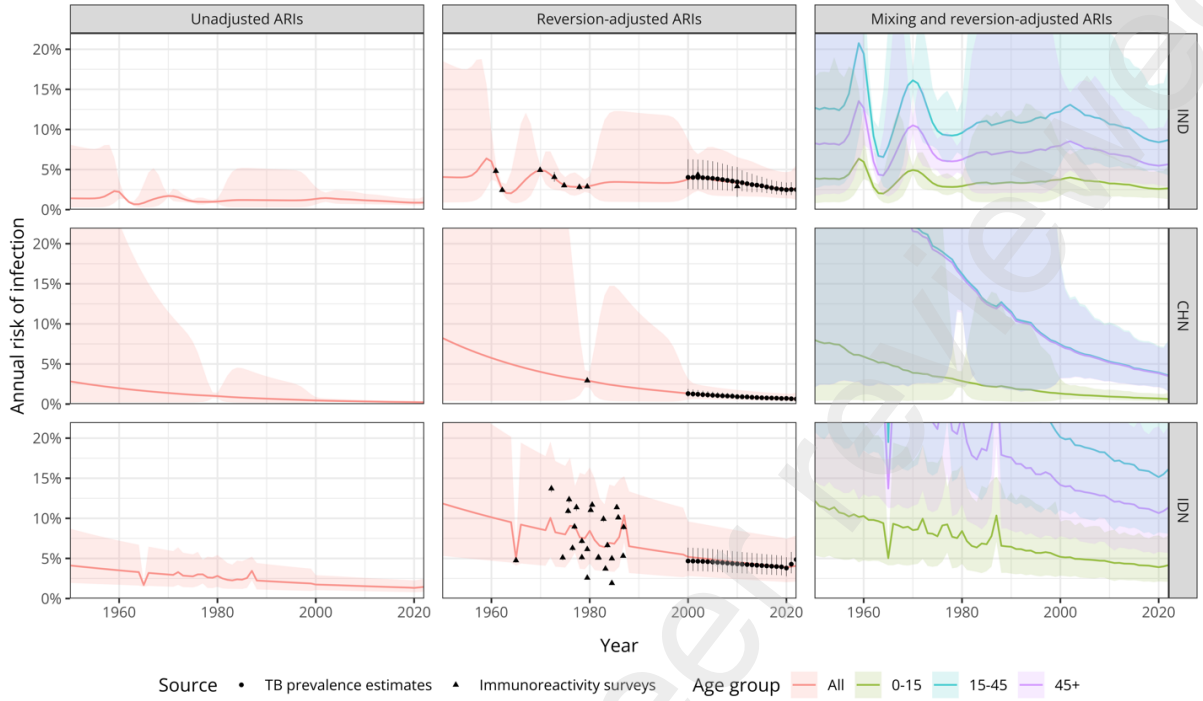
Proportion of population globally and by WHO region infected with viable *Mycobacterium tuberculosis* in 2022. Values are given percentages (%), with brackets indicating 95% uncertainty intervals (95%UI). Recent infection is defined as occurring within two years. Children are classified as individuals under 15 years of age. Estimates for all infections are provided and disaggregated based on different scenarios depending on assumptions about long-term self-clearance rates. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Figure 1. Diagram of conceptual overview of study.



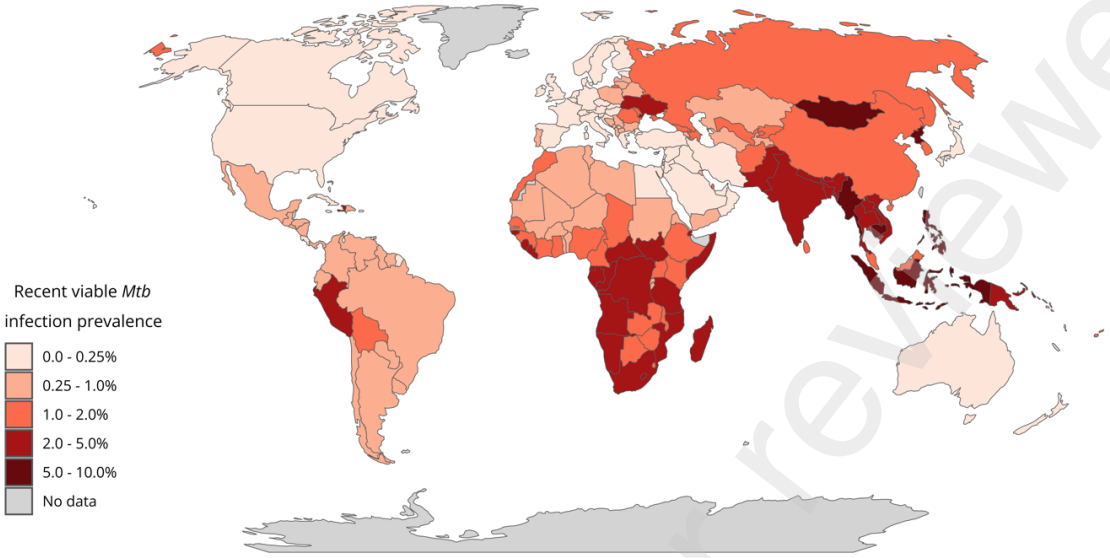
Conceptual overview of study as per Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).[24] ARI: Annual risk of infection; HIV: Human immunodeficiency virus; ODE: Ordinary differential equation; TB: Tuberculosis; WHO: World Health Organization.

Figure 2. Fitted trajectories for annual risk of infection and adjustments.



Fitted trajectories for the annual risk of *Mycobacterium tuberculosis* infection for selected countries and corresponding adjustments. The first column shows ARI trajectories without adjustment, the second column shows trajectories adjusted for immunoreactivity reversion, and the third column shows the ARI trajectories subdivided by age group, using children under 15 years of age as the reference group for relative ARIs. Greater uncertainty is observed in earlier years, which narrows as ARI data becomes available from immunoreactivity surveys or TB prevalence estimates. Data points represent available ARI data, with black circles representing TB prevalence estimates and black triangles representing nationally representative immunoreactivity surveys; error bars reflect measurement precision to ± one standard deviation. Lines represent the mean ARI, and the shaded area shows ± one standard deviation from the Gaussian process regression with a linear trend. ARI: Annual risk of infection; IND: India; CHN: China; IDN: Indonesia.

Figure 3. Prevalence of recent viable *Mycobacterium tuberculosis* infection in 2022.



Median estimated population prevalence of recent viable *Mycobacterium tuberculosis* infection by country in 2022. Recent infection is defined as occurring within two years.

SUPPLEMENTARY MATERIAL:

Estimating the global burden of viable *Mycobacterium tuberculosis* infection

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GitHub: https://github.com/aschwalbc/MtbInf

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Supplementary Methods:

SM1. Immunoreactivity surveys

Direct annual risk of infection (ARI) estimates were obtained from nationally representative immunoreactivity surveys, most of which used the tuberculin skin test (TST) and were implemented among children **(Table S1)**. The immunoreactivity surveys were conducted in 42 countries over approximately 250 years, resulting in 6 surveys per country-year. These surveys had been previously identified by Cauthen et al. and a systematic search by Houben and Dodd.[1,2] Additionally, we extracted nationally representative surveys from a systematic review by Rickman et al. (in preparation).

SM2. Uncertainty in annual risk of infection estimates

Typically, ARI estimates are reported as a point estimate, i.e. without presentation of uncertainty. Immunoreactivity surveys report the ARI alongside the sample size and the mean age of participants; this data can be used to conservatively estimate the precision associated with the study, as previously described by Houben and Dodd.[2] Using the information above, the precision can be conservatively estimated as: $\lambda/N\bar{a}$, where N is the sample size, $\bar{a}$ is the mean age of participants, and λ is the force of infection or ARI.

SM3. The Stýblo rule

In 1985, Dr. Karel Stýblo formulated a guiding rule for TB epidemiology.[3] The Stýblo rule assumes a fixed mathematical relationship, equating an ARI of 1% to an incidence of smear-positive disease of 50 per 100,000 inhabitants and a prevalence of smear-positive disease of 100 per 100,000 inhabitants.[3] This rule implies that one individual with smear-positive TB will cause in ten *Mtb* infections per year.[3] However, this widely used rule of thumb was derived from limited observations from the prechemotherapy era, and several studies have since suggested that it may no longer be applicable.[4–6] Transmission from one individual with smear-positive TB might be lower, for reasons such as prompt diagnosis and treatment, or if the individual is a child or has HIV infection, both of which reduce infectiousness, among other factors.[5,6] As seen in the study by Houben and Dodd,[2] a revised Stýblo rule was used by fitting a log-normal distribution to data from more recent ARI and TB prevalence estimates.[7] Additionally, ARI estimates were adjusted to account for the proportion of prevalent TB that is smear-positive in children and in people living with HIV.[2]

SM4. TB prevalence estimates

The World Health Organization (WHO) has published a global tuberculosis (TB) report annually since 1997.[8] This report includes WHO-generated estimates of TB mortality, incidence, among other metrics. While TB prevalence used to be featured in the document, the latest estimate provided dates back to 2014. We used the simple approximate relation of prevalence (P), incidence (I), and the average duration of disease ($\overline{D}$) to update TB prevalence estimates.[9] This is expressed as follows: $P = I \times \overline{D}$. We can then express the average duration of disease as the prevalence-to-incidence ratio. We obtained this value by averaging the estimated prevalence and incidence per each country from the last WHO database featuring prevalence estimates (available in the GitHub repository). The country-specific average duration of disease is then applied to current TB incidence estimates (2000-2022) to obtain TB prevalence estimates. This method opts to draw from TB incidence estimates that are constantly revised and, in some cases, incorporate findings from national TB prevalence surveys conducted.

SM5. Self-clearance rates calibration

We developed a transition matrix model using the same structure as described in the manuscript and above. The model tracked an infected cohort in '*Infected – Year 1*' as it experienced self-clearance and infection year transitions as competing risks, without accounting for infection or reinfection. Calibration targets reflected the proportion of the cohort that self-cleared at years 1 (80.9%; 95% CI: 80.1-81.7), 2 (91.9%; 95% CI: 91.4-92.5), and 10 (97.2%, 95% CI: 96.9-97.5), with an additional proportion (99.0%, 95% CI: 98.5-99.5) at either year 20 or year 50. Calibrated targets were modelled as being normally distributed. Self-clearance rates were drawn from exponential distributions with uninformed priors, assumed to be the same for '*Infected – Year 1*' and '*Infected – Year 2*', and then decreasing thereafter. Posterior estimates were calculated using a Markov chain Monte-Carlo algorithm in Stan via R statistical software.[10,11] For each scenario, we generated 80,000 parameter sets to be randomly sampled in each model run. The calibration fit was plotted for each scenario and is shown in **Figure S4.**

SM6. Model structure

We developed a deterministic compartmental model of *Mycobacterium tuberculosis* (*Mtb*) infection. The model captures the proportional population size of each country, and the structure is repeated across seventeen 5-year age groups until 80+ years.

The model structure explores the dynamics of *Mtb* infection, re-infection, and self-clearance of infection. Individuals in the '*Uninfected*' compartment are exposed to *Mtb* as informed by the ARI (symbolised as λ) of their corresponding age category. Upon infection, there is progression through a tunnel model of four '*Infected*' compartments describing consecutive progression since time from infection. Transitions between infection are fixed values: '*Infected - Year 1*' progresses to '*Infected – Year 2*' at rate $\kappa_1 = 1$, '*Infected – Year 2*' progresses to '*Infected – Years 3 to 10*' at $\kappa_2 = 1$, and '*Infected – Years 3 to 10*' progresses to '*Infected – Years 10+*' at rate $\kappa_3 = 1/8$. All '*Infected*' compartments can experience self-clearance of infection at varying rates γ_η (with $\eta = 1, \ldots, 4$) informed by calibration; self-clearance effectively returns individuals back to the '*Uninfected*' compartment. Individuals who have been distally infected (i.e. more than two years), '*Infected – Years 3 to 10*' and '*Infected – Years 10+*', are at risk of being reinfected at rate λ accounting for protection from reinfection π, and thus return to '*Infected - Year 1*'. The model was constructed using R version 4.3.2 for statistical computing and graphics.[11]

SM7. Model formulas

To describe the model, we have employed the following variable descriptions which represent:

- S_α: the proportion of the population in age group α that is '*Uninfected*'.
- I_α^η: the proportion of the population in in age group α that is in the '*Infected*' compartment for infection year η, where:
    - $\eta = 1$: '*Infected – Year 1*'
    - $\eta = 2$: '*Infected – Year 2*'
    - $\eta = 3$: '*Infected – Years 3 to 10*'
    - $\eta = 4$: '*Infected – Years 10+*'
- α: the seventeen 5-year age groups from 0-5 ($\alpha = 1$) to 80+ ($\alpha = 17$).
- fN_α: the fraction of the total population that belongs to age group α.
- δ_{ij}: the Kronecker delta, which is 1 when $i = j$ and 0 otherwise.
- π^η: the relative risk of reinfection at infection year η, where $\pi^\eta = 0$ for $\eta = 1$ and $\eta = 2$.
- θ_t: the birth rate per capita at time t.
- $\lambda_{\alpha,t}$: the force of infection at time t in age group α.
- γ_η: the self-clearance rate from infection year η.
- κ_η: the infection year η transition, where $\kappa_4 = 0$.

To describe the model, we have employed the following differential equations:

$$\frac{dS_\alpha}{dt} = \delta_{\alpha 1} \cdot \frac{\theta_t}{fN_{\alpha,t}} \cdot (1 - S_\alpha) - \lambda_{\alpha,t} \cdot S_\alpha + \sum_{\eta=1}^{4} (\gamma_\eta \cdot I_\alpha^\eta)$$

$$\frac{dI_\alpha^\eta}{dt} = \delta_{\eta 1} \cdot \lambda_{\alpha,t} \cdot S_\alpha - I_\alpha^\eta \cdot \left(\delta_{\alpha 1} \cdot \frac{\theta}{fN_{\alpha,t}} + \gamma_\eta + (1 - \delta_{\eta 4}) \cdot \kappa_\eta + \lambda_{\alpha,t} \cdot \pi^\eta \right) +$$
$$(1 - \delta_{\eta 1}) \cdot \kappa_{\eta-1} \cdot I_\alpha^{\eta-1} + \delta_{\eta 1} \cdot \lambda_{\alpha,t} \cdot \left(S_\alpha + \sum_{\eta'=1}^{4} \pi^{\eta'} \cdot I_\alpha^{\eta'} \right)$$

The force of infection ($\lambda_{\alpha,t}$) is derived from national annual risk of infection trajectories spanning from 1950 to 2022. These trajectories were subdivided into three age groups (under 15 years, 15 to 45 years, and 45 years and older) and adjusted based on relative ARI.

Supplementary Tables:

Table S1. Immunoreactivity surveys used for annual risk of infection estimates.

Country (ISO-3)	Survey years (Mid-point)	Number tested	Age (Mid-point)	ARI, % (95%CI)	Reference
Source: Cauthen et al. *Bull World Health Organ* 2002.[1]					
AFG	1963 (1963.5)	30,938	10.0	3.06	[12]
AFG	1982 (1982.5)	881	7.5	3.53	[13]
ARG	1960–1961 (1961.0)	1,259	7.5	0.53	[14]
ARG	1967–1968 (1968.0)	1,221	7.0	1.31	[15]
ARG	1967–1968 (1968.0)	3,196	7.0	0.57	[15]
ARG	1974–1975 (1975.0)	3,590	7.0	0.23	[15]
ARG	1974–1978 (1976.5)	26,902	6.5	0.56	[16]
ARG	1979–1980 (1980.0)	443	7.0	0.29	[15]
ARG	1979–1980 (1980.0)	2,125	7.0	0.23	[15]
ARG	1983 (1983.5)	325	7.0	0.26	[15]
BDI	1964 (1964.6)	202	17.5	2.66	[17]
BDI	1982–1984 (1983.5)	912	20.5	1.17	[18]
BHR	1969 (1969.5)	897	7.0	0.90	[19]
BHR	1981 (1981.4)	6,151	7.0	0.20	[19]
BRA	1983 (1983.5)	11,880	7.3	0.39	[20]
BRA	1983 (1983.5)	3,507	7.0	0.56	[20]
BWA	1956–1957 (1957.0)	1,450	6.6	5.79	[21]
BWA	1981–1982 (1982.0)	257	6.5	1.30	[22]
CHN	1979 (1979.5)	10,000*	7.5	1.01	[23]
CMR	1964 (1964.3)	326	7.5	1.32	[24]
CMR	1984 (1984.5)	860	8.5	0.64	[25]
DZA	1949–1952 (1951.1)	110,547	8.5	4.30	[26]
DZA	1976 (1976.5)	262	8.5	1.03	[27]
DZA	1980 (1989.9)	1,844	8.5	0.46	[27]

DZA	1981 (1981.5)	1,117	8.5	0.75	[27]
DZA	1980–1984 (1982.8)	7,514	8.5	0.48	[27]
DZA	1985 (1985.5)	2,378	8.5	0.27	[28]
ETH	1977 (1977.5)	185	8.5	3.81	[29]
ETH	1983 (1983.9)	1,251	8.6	1.30	[30]
GMB	1976 (1976.4)	2,397	9.4	1.92	[31]
IDN	1964–1965 (1965.0)	1,633	7.5	1.64	[32]
IDN	1972 (1972.2)	1,371	9.3	4.73	[33]
IDN	1974 (1974.5)	1,070	8.1	1.76	[34]
IDN	1975 (1975.6)	2,425	8.9	3.76	[34]
IDN	1975 (1975.8)	1,429	8.2	4.26	[34]
IDN	1976 (1976.5)	1,124	8.6	2.17	[35]
IDN	1976 (1976.9)	1,655	8.6	3.09	[35]
IDN	1977 (1977.3)	1,199	8.7	3.92	[34]
IDN	1978 (1978.4)	1,659	8.8	3.47	[33]
IDN	1978 (1978.4)	1,125	8.9	1.77	[34]
IDN	1979 (1979.5)	1,122	8.9	0.89	[34]
IDN	1979 (1979.5)	2,197	8.9	2.12	[34]
IDN	1980 (1980.2)	4,839	8.5	3.80	[34]
IDN	1980 (1980.5)	3,573	8.7	4.03	[34]
IDN	1981 (1981.7)	2,501	8.9	1.75	[35]
IDN	1981 (1981.8)	2,181	8.6	1.77	[35]
IDN	1982 (1982.8)	1,577	9.0	3.42	[34]
IDN	1983 (1983.2)	1,894	8.5	1.28	[34]
IDN	1983 (1983.6)	1,549	8.8	2.29	[33]
IDN	1984 (1984.5)	1,406	8.3	0.66	[34]
IDN	1984 (1984.5)	2,938	8.5	1.72	[34]
IDN	1985 (1985.5)	4,001	8.9	3.92	[34]

IDN	1985 (1985.8)	4,840	8.9	3.48	[34]
IDN	1986 (1986.8)	3,839	8.8	1.83	[35]
IDN	1986 (1986.9)	1,986	8.7	3.07	[35]
IND	1960–1961 (1960.9)	3,788	2.5	1.66	[36]
IND	1961–1963 (1962.2)	7,981	2.5	0.84	[37]
IND	1968–1971 (1969.9)	27,520	3.0	1.70	[38]
IND	1972 (1972.8)	679	3.0	1.40	[38]
IND	1974–1975 (1974.8)	3,805	2.5	1.04	[39]
IND	1977–1978 (1977.9)	1,492	2.5	0.97	[40]
IND	1979 (1979.5)	5,203	2.5	0.99	[39]
KOR	1965 (1965.5)	2,377	2.5	4.23	[41]
KOR	1975 (1975.5)	1,871	2.1	2.32	[41]
KOR	1980 (1980.5)	1,310	2.1	2.36	[41]
KOR	1985 (1985.5)	1,420	2.8	1.97	[42]
KWT	1972 (1972.5)	2,258	4.7	0.36	[43]
KWT	1973 (1973.5)	6,363	4.3	0.29	[43]
KWT	1974 (1974.5)	6,722	4.2	0.20	[43]
KWT	1975 (1975.5)	7,665	4.5	0.29	[43]
KWT	1976 (1976.5)	9,018	5.1	0.44	[43]
KWT	1977 (1977.5)	17,444	5.3	0.29	[43]
KWT	1972–1981 (1978.4)	131,846	5.1	0.26	[43]
KWT	1978 (1978.5)	20,843	5.2	0.31	[43]
KWT	1979 (1979.5)	22,674	5.3	0.24	[43]
KWT	1980 (1980.5)	16,149	5.1	0.12	[43]
KWT	1981 (1981.5)	22,710	5.2	0.22	[43]
LBY	1954 (1954.5)	188	7.5	3.68	[44]
LBY	1959 (1959.7)	361	7.5	2.39	[45]
LBY	1976–1977 (1977.0)	1,827	7.5	0.26	[46]

LBY	1976–1977 (1977.0)	361	7.5	0.26	[46]
LSO	1956–1957 (1957.0)	1,101	4.9	2.78	[21]
LSO	1962–1965 (1963.8)	10,216	4.9	2.83	[47]
LSO	1981–1982 (1982.0)	158	5.2	2.03	[22]
MYS	1976–1977 (1977.0)	1,429	5.5	0.37	[48]
PAK	1961–1962 (1962.0)	769	7.5	3.45	[49]
PAK	1974–1978 (1976.5)	2,289	7.5	1.84	[49]
PHL	1981–1983 (1982.5)	2,038	2.1	1.84	[50]
SYR	1960 (1960.8)	387	7.5	0.74	[51]
SYR	1978 (1978.8)	1,845	6.5	0.26	[52]
SYR	1983 (1983.8)	1,586	6.5	0.30	[52]
SYR	1983 (1983.8)	1,182	6.5	0.14	[52]
THA	1954 (1954.9)	1,578	10.5	2.52	[53]
TZA	1977 (1977.1)	383	9.7	0.92	[54]
TZA	1978 (1978.9)	1,329	10.2	1.30	[55]
TZA	1979 (1979.5)	1,817	10.0	2.16	[56]
TZA	1983–1987 (1985.6)	30,982	10.3	1.11	[57]
Source: Houben and Dodd *PLoS Med* 2016.[2]					
AFG	2005–2006 (2005.0)	11,413	20.4	0.80 (0.76–0.84)	[58]
BGD	1964–1966 (1965.0)	21,658	7.5	0.56 (0.48–0.64)	[59]
BGD	2007–2009 (2008.0)	9,357	7.0	1.50	[60]
BGD	2007–2009 (2008.0)	8,228	12.0	1.70	[60]
BTN	2009 (2009.0)	835	7.0	0.70 (0.50–0.90)	[61]
CAF	2011 (2011.0)	2,710	10.0	1.90 (1.70–2.20)	[62]
CAF	2011 (2011.0)	2,710	10.0	0.80 (0.70–0.90)	[62]
DJI	1994 (1994.0)	1,505	9.0	2.86	[63]
EGY	1995–1997 (1996.0)	14,766	6.7	0.32	[64]
ETH	1987–1990 (1989.0)	23,695	8.0	1.40	[65]

GMB	2011 (2011.0)	13,386	9.0	1.27 (1.09–1.49)	[66]
GRC	1981–1991 (1986.0)	544,210	21.0	0.89	[67]
IND	2000–2003 (2002.0)	83,746	4.0	1.50 (1.40–1.60)	[68]
IND	2009–2010 (2010.0)	18,400	4.0	1.00 (0.80–1.20)	[68]
KEN	1986–1990 (1988.0)	14,984	8.5	0.60	[69]
KEN	1994–1996 (1995.0)	7,556	9.0	1.10 (0.80–1.40)	[70]
KEN	2004–2007 (2006.0)	12,107	9.6	1.15 (0.84–1.48)	[71]
KHM	1995 (1995.0)	1,224	8.0	0.75 (0.56–0.96)	[72]
KHM	2002 (2002.0)	2,273	6.0	2.06 (1.77–2.40)	[73]
KOR	1990 (1990.0)	1,210	7.5	1.10	[74]
KOR	1995 (1995.0)	857	7.5	0.50	[75]
LAO	1996–1997 (1997.0)	4,035	8.4	1.10	[76]
MDG	1991–1994 (1993.0)	1,544	8.0	1.29 (0.97–1.59)	[77]
MWI	1994 (1994.0)	2,696	10.2	1.20 (1.00–1.40)	[78]
NPL	2006 (2006.0)	17,260	9.0	0.86 (0.49–1.23)	[79]
PHL	1997 (1997.0)	6,492	7.5	2.30	[80]
SOM	2006 (2006.0)	10,364	9.0	2.70 (2.5–2.9)	[81]
TZA	1983–1987 (1985.0)	34,427	10.4	1.20	[82]
TZA	1988–1992 (1990.0)	29,696	10.9	1.00	[82]
TZA	1993–1998 (1995.0)	20,592	11.3	0.90	[82]
TZA	2000–2003 (2002.0)	10,239	9.5	0.68 (0.55–0.81)	[83]
VNM	2006–2007 (2006.0)	21,487	10.0	1.70 (1.50–1.80)	[84]
YEM	2007 (2007.0)	28,499	9.5	0.05 (0.04–0.07)	[85]
Source: Rickman et al. *In preparation*.					
BEN	1987–1990 (1989.0)	17,390	7.9	0.44	[86]
BEN	1994 (1994.0)	23,476	8.1	0.50	[86]
BWA	1996 (1996.0)	783	2.3	3.10	[87]
HKG	1999–2000 (2000.0)	21,113	8.0	1.68 (1.61–1.74)	[88]

KOR	2006 (2006.0)	4,018	6.0	1.90	[89]
LKA	2010 (2010.0)	4,318	10.0	0.40 (0.20–0.70)	[90]
SAU	2010–2013 (2012.0)	1,369	26.3	0.36	[91]

Direct annual risk of infection (ARI) from immunoreactivity surveys per source used to identify. *Estimated value. ISO-3: International Organization for Standardization 3166-1 alpha-3 codes; AFG: Afghanistan; ARG: Argentina; BDI: Burundi; BEN: Benin; BGD: Bangladesh; BHR: Bahrain; BRA: Brazil; BTN: Bhutan; BWA: Botswana; CAF: Central African Republic; CHN: China; CMR: Cameroon; DZA: Algeria; DJI: Djibouti; EGY: Egypt; ETH: Ethiopia; GMB: Gambia; GRC: Greece; HKG: Hong Kong; IDN: Indonesia; IND: India; KEN: Kenya; KHM: Cambodia; KOR: South Korea; KWT: Kuwait; LAO: Laos; LBY: Libya; LKA: Sri Lanka; LSO: Lesotho; MDG: Madagascar; MWI: Malawi; MYS: Malaysia; NPL: Nepal; PAK: Pakistan; PHL: Philippines; SAU: Saudi Arabia; SOM: Somalia; SYR: Syria; THA: Thailand; TZA: Tanzania; VNM: Vietnam; YEM: Yemen.

Table S2. Model parameters.

Parameter	Description	Notes
λ	Annual risk of infection	Obtained from GP regression, varying by country, year, and age group
γ_η	Self-clearance rate	Obtained from MCMC calibration, varying by infection year
κ_η	Infection year transitions	Fixed values ($\kappa_1 = 1$; $\kappa_2 = 1$; $\kappa_3 = 1/8$)
π	Relative risk of reinfection	0.21(95%CI: 0.14–0.30),[92] sampled from a beta distribution

GP: Gaussian process; MCMC: Markov chain Monte-Carlo.

Table S3. Regional relative annual risk of infection as implied by mixing matrices.

WHO Region	Under 15 years*	15 to 45 years	45 years and older
AFR	1.00	2.82	1.82
AMR	1.00	4.51	3.42
EMR	1.00	3.89	2.09
EUR	1.00	5.63	4.72
SEA	1.00	4.20	3.21
WPR	1.00	4.45	3.77
GLOBAL	1.00	4.29	3.25

Age-specific relative annual risk of infection by WHO region, as implied by TB incidence and contact mixing matrices. Individuals under 15 years old were used as the reference age group. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Table S4. Adjusted annual risk of infection estimates by age group in 2022.

Country (ISO-3)	Annual risk of *Mycobacterium tuberculosis* infection (%) [95%UI]		
	Under 15 years	15 to 45 years	45 years and older
AGO	3.5 [1.4–8.6]	9.7 [3.9–24.1]	6.2 [2.5–15.4]
BGD	3.6 [1.6–8.8]	12.4 [5.3–29.9]	8.5 [3.7–20.7]
BRA	0.4 [0.2–1.0]	2.3 [1.1–5.1]	1.5 [0.7–3.4]
CAF	4.7 [2.0–12.0]	12.1 [5.2–31.0]	7.5 [3.2–19.3]
CHN	0.6 [0.3–1.4]	3.6 [1.6–8.0]	3.5 [1.6–7.8]
COD	3.8 [1.6–9.6]	9.0 [3.7–22.8]	6.4 [2.6–16.2]
COG	3.2 [1.4–8.4]	9.1 [3.9–23.6]	5.9 [2.5–15.3]
ETH	0.9 [0.5–1.6]	3.2 [1.8–5.4]	1.8 [1.0–3.0]
GAB	5.5 [2.5–12.3]	14.1 [6.3–31.3]	8.1 [3.6–18.1]
IDN	4.2 [2.1–7.9]	16.1 [8.1–30.5]	11.3 [5.7–21.4]
IND	2.7 [1.3–5.5]	8.7 [4.3–17.8]	5.7 [2.8–11.6]
KEN	1.6 [0.9–3.0]	5.5 [2.9–10.3]	3.6 [1.9–6.6]
LBR	3.5 [1.5–8.0]	10.6 [4.5–24.1]	7.3 [3.2–16.7]
LSO	3.4 [1.9–6.7]	11.4 [6.4–22.2]	7.6 [4.3–14.8]
MMR	4.1 [2.1–7.7]	16.5 [8.2–30.5]	11.6 [5.8–21.4]
MNG	5.1 [2.2–12.0]	16.6 [7.3–39.6]	9.7 [4.2–23.0]
MOZ	3.0 [1.2–7.3]	7.8 [3.1–19.4]	5.2 [2.1–13.0]
NAM	3.2 [1.5–7.0]	9.1 [4.3–19.7]	5.4 [2.5–11.7]
NGA	1.6 [0.7–3.9]	3.6 [1.4–8.7]	2.3 [0.9–5.6]
PAK	2.8 [1.3–5.7]	6.9 [3.2–14.3]	4.9 [2.2–10.1]
PHL	8.8 [4.0–19.9]	28.8 [13.1–65.4]	19.6 [8.9–44.4]
PNG	4.3 [1.7–10.5]	11.4 [4.5–27.7]	6.2 [2.4–15.0]
PRK	5.1 [2.2–10.8]	29.5 [12.7–62.6]	24.1 [10.4–51.3]

SLE	3.7 [1.6–8.8]	9.8 [4.3–22.9]	6.4 [2.8–15.0]
THA	1.7 [0.9–3.0]	10.1 [5.6–17.9]	10.7 [5.9–18.9]
TZA	2.6 [1.4–4.5]	6.9 [3.8–12.1]	5.0 [2.8–8.8]
UGA	1.3 [0.6–2.8]	3.1 [1.4–6.8]	2.1 [0.9–4.5]
VNM	2.2 [1.0–4.8]	9.9 [4.7–21.4]	7.6 [3.6–16.3]
ZAF	3.6 [1.8–6.9]	12.2 [6.3–23.6]	6.9 [3.5–13.4]
ZMB	2.0 [0.9–4.7]	5.5 [2.5–13.1]	3.8 [1.7–9.0]

Reversion-adjusted, age-specific annual risk of infection for WHO's top 30 high TB burden countries. ISO-3: International Organization for Standardization 3166-1 alpha-3 codes. AGO: Angola; BGD: Bangladesh; BRA: Brazil; CAF: Central African Republic; CHN: China; COD: Democratic Republic of the Congo; COG: Congo; ETH: Ethiopia; GAB: Gabon; IDN: Indonesia; IND: India; KEN: Kenya; LBR: Liberia; MMR: Myanmar; MNG: Mongolia; MOZ: Mozambique; NAM: Namibia; NGA: Nigeria; PAK: Pakistan; PHL: Philippines; PNG: Papua New Guinea; PRK: Democratic People's Republic of Korea; SLE: Sierra Leone; THA: Thailand; TZA: United Republic of Tanzania; UGA: Uganda; VNM: Viet Nam; ZAF: South Africa; ZMB: Zambia.

Table S5. Annual risk of infection estimates in 2014.

Country (ISO-3)	Annual risk of *Mycobacterium tuberculosis* infection (%) [95%UI]			
	Unadjusted[2]	Age-specific and reversion adjusted		
	All ages	Under 15 years	15 to 45 years	45 years and older
AGO	1.4 [0.7–2.8]	3.8 [2.0–7.3]	10.7 [5.4–20.3]	6.8 [3.5–12.9]
BGD	1.1 [0.6–2.3]	3.4 [1.8–6.6]	11.7 [6.2–22.4]	8.1 [4.3–15.5]
BRA	0.1 [0.1–0.3]	0.4 [0.2–0.8]	2.2 [1.2–4.1]	1.5 [0.8–2.7]
CAF	1.1 [0.5–2.2]	4.5 [2.3–8.6]	11.6 [6.0–22.3]	7.2 [3.8–13.8]
CHN	0.2 [0.1–0.5]	0.8 [0.4–1.6]	4.8 [2.5–9.2]	4.6 [2.5–9.0]
COD	1.5 [0.7–3.0]	3.9 [2.0–7.3]	9.4 [4.7–17.5]	6.6 [3.3–12.4]
COG	1.3 [0.7–2.7]	3.3 [1.7–6.2]	9.2 [4.8–17.5]	6.0 [3.1–11.4]
ETH	0.5 [0.3–1.0]	1.5 [0.9–2.3]	4.9 [3.1–7.6]	2.8 [1.8–4.3]
GAB	1.6 [0.8–3.3]	5.9 [3.1–11.5]	14.9 [7.9–29.2]	8.6 [4.5–16.8]
IDN	1.9 [1.0–3.4]	4.3 [2.3–8.0]	16.8 [8.7–30.9]	11.8 [6.1–21.7]
IND	0.6 [0.3–1.1]	3.1 [1.6–5.8]	10.2 [5.2–18.8]	6.6 [3.4–12.2]
KEN	0.6 [0.3–1.3]	2.8 [2.0–3.9]	9.5 [6.8–13.4]	6.1 [4.4–8.6]
LBR	1.4 [0.7–2.9]	3.4 [1.8–6.7]	10.3 [5.3–20.0]	7.2 [3.7–13.9]
LSO	1.6 [0.8–3.2]	4.2 [2.5–6.9]	14.1 [8.4–22.9]	9.4 [5.6–15.2]
MMR	1.2 [0.7–2.3]	4.8 [2.9–7.3]	18.9 [11.7–29.1]	13.3 [8.2–20.4]
MNG	0.6 [0.3–1.3]	4.9 [2.8–8.2]	16.2 [9.1–26.9]	9.4 [5.3–15.7]
MOZ	1.6 [0.8–3.2]	3.0 [1.5–5.9]	7.9 [4.0–15.6]	5.3 [2.7–10.5]
NAM	1.9 [0.9–3.8]	4.7 [2.7–8.1]	13.2 [7.6–22.8]	7.8 [4.5–13.5]
NGA	0.9 [0.5–1.6]	1.7 [0.9–3.2]	3.7 [1.9–7.0]	2.4 [1.2–4.5]
PAK	0.9 [0.5–1.7]	2.9 [1.6–5.7]	7.4 [4.0–14.4]	5.2 [2.8–10.1]
PHL	1.2 [0.6–2.1]	7.6 [4.3–13.9]	25.1 [14.1–45.9]	17.1 [9.6–31.2]
PNG	1.4 [0.7–3.0]	4.4 [2.3–8.4]	11.5 [6.0–22.1]	6.2 [3.3–12.0]

PRK	1.4 [0.6–3.3]	5.1 [2.7–9.4]	29.6 [15.8–54.8]	24.3 [12.9–44.9]
SLE	1.3 [0.6–2.6]	3.9 [2.1–7.6]	10.2 [5.4–19.7]	6.7 [3.5–12.9]
THA	0.7 [0.4–1.3]	1.9 [1.2–2.9]	11.5 [7.3–17.4]	12.2 [7.7–18.4]
TZA	1.5 [0.7–3.3]	2.9 [1.6–4.8]	7.7 [4.4–13.0]	5.6 [3.2–9.4]
UGA	0.3 [0.2–0.6]	1.4 [0.7–2.6]	3.3 [1.8–6.2]	2.2 [1.2–4.2]
VNM	0.6 [0.3–1.2]	2.8 [1.6–4.7]	12.4 [7.0–21.3]	9.5 [5.4–16.3]
ZAF	1.8 [0.9–3.7]	5.9 [3.8–9.8]	20.3 [13.2–33.5]	11.5 [7.5–18.9]
ZMB	1.1 [0.6–2.2]	2.8 [1.5–4.9]	7.6 [4.2–13.5]	5.2 [2.9–9.2]

Comparison of annual risk of infection estimates for WHO's top 30 high TB burden countries in 2014. Unadjusted estimates were extracted from ARI data from Houben and Dodd.[2] ISO-3: International Organization for Standardization 3166-1 alpha-3 codes. AGO: Angola; BGD: Bangladesh; BRA: Brazil; CAF: Central African Republic; CHN: China; COD: Democratic Republic of the Congo; COG: Congo; ETH: Ethiopia; GAB: Gabon; IDN: Indonesia; IND: India; KEN: Kenya; LBR: Liberia; MMR: Myanmar; MNG: Mongolia; MOZ: Mozambique; NAM: Namibia; NGA: Nigeria; PAK: Pakistan; PHL: Philippines; PNG: Papua New Guinea; PRK: Democratic People's Republic of Korea; SLE: Sierra Leone; THA: Thailand; TZA: United Republic of Tanzania; UGA: Uganda; VNM: Viet Nam; ZAF: South Africa; ZMB: Zambia.

Table S6. Regional distribution of viable *Mtb* infection in 2022.

WHO Region	Percentage of global burden of recent infection [95%UI]	Percentage of global burden of all infections – high self-clearance scenario [95%UI]	Percentage of global burden of all infections – low self-clearance scenario [95%UI]
AFR	13.7 [10.3–17.5]	13.8 [11.8–15.9]	13.3 [11.5–15.2]
AMR	3.4 [2.5–4.8]	3.8 [3.0–4.9]	7.3 [4.8–10.9]
EMR	5.5 [3.5–8.5]	5.7 [4.5–7.4]	7.2 [5.8–9.0]
EUR	3.4 [2.4–4.7]	4.5 [3.7–5.4]	7.8 [6.1–9.6]
SEA	47.9 [37.6–59.4]	45.1 [39.2–51.5]	37.6 [32.2–43.6]
WPR	25.7 [17.6–35.8]	26.8 [21.8–32.8]	13.3 [11.5–15.2]

Proportion of global viable *Mycobacterium tuberculosis* infection of population by WHO region in 2022. Values are given as percentages (%), with brackets indicating 95% uncertainty intervals (95%UI). Recent infection is defined as occurring within two years. Estimates for all infections are provided and disaggregated based on different scenarios depending on assumptions about long-term self-clearance rates. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Table S7. Top ten countries with the highest number of recent viable *Mtb* infections in 2022.

Country [ISO-3)	Recent infections (M) [95%UI]	All infections – high self-clearance scenario (M) [95%UI]	All infections – low self-clearance scenario (M) [95%UI]
India (IND)	41.7 [22.3–76.7]	103.8 [74.6–144.6]	141.5 [104.9–197.1]
China (CHN)	21.6 [11.1–41.8]	64.0 [45.0–93.9]	108.3 [78.0–150.6]
Indonesia (IDN)	14.2 [8.7–22.8]	31.7 [23.6–42.1]	37.3 [29.0–48.3]
Philippines (PHL)	9.7 [5.0–18.8]	18.9 [12.9–29.0]	20.5 [14.7–30.0]
Bangladesh (BGD)	7.0 [3.7–14.4]	15.7 [11.2–24.2]	19.4 [14.3–28.0]
Pakistan (PAK)	5.6 [3.0–10.4]	13.8 [9.8–19.9]	20.1 [14.5–27.4]
Viet Nam (VNM)	3.3 [1.8–6.4]	8.6 [6.2–12.3]	10.9 [8.3–14.4]
Thailand (THA)	3.0 [1.8–4.8]	7.1 [5.2–9.8]	8.7 [6.6–11.4]
Myanmar (MMR)	2.9 [1.6–4.8]	6.5 [4.6–9.1]	7.5 [5.7–10.1]
DR Congo (COD)	2.8 [1.4–6.2]	6.5 [4.5–10.3]	8.4 [5.9–12.2]

Absolute number of individuals per country infected with viable Mycobacterium tuberculosis in 2022, showing the top ten countries sorted in descending order by the number of recent infections. Numbers are in millions (M), with brackets indicating 95% uncertainty intervals (95%UI). Recent infection is defined as occurring within two years. Estimates for all infections are provided and disaggregated based on different scenarios depending on assumptions about long-term self-clearance rates. ISO-3: International Organization for Standardization 3166-1 alpha-3 codes.

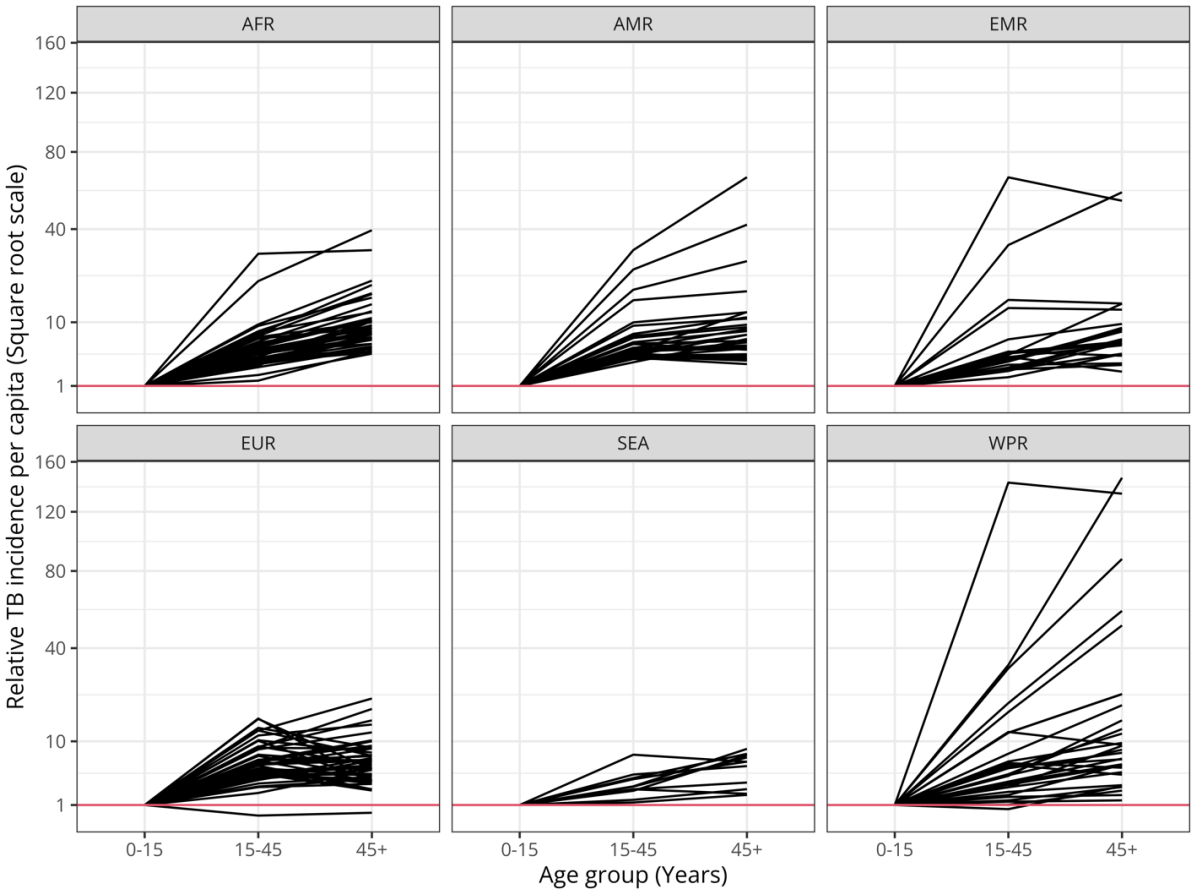
Table S8. Top ten countries with the highest prevalence of recent viable *Mtb* infections in 2022.

Country (ISO-3)	Recent infection prevalence (%) [95%UI]	All infections prevalence – high self-clearance scenario (%) [95%UI]	All infections prevalence – low self-clearance scenario (%) [95%UI]
DPR Korea (PRK)	9.3 [4.8–16.3]	18.4 [13.0–26.3]	19.4 [14.5–27.2]
Philippines (PHL)	8.5 [4.4–16.4]	16.5 [11.3–25.3]	17.9 [12.8–26.2]
Cambodia (KHM)	5.4 [2.9–9.3]	12.4 [8.8–17.3]	13.4 [9.8–18.2]
Timor-Leste (TLS)	5.4 [2.5–11.1]	11.7 [7.9–18.1]	13.2 [9.3–19.2]
Myanmar (MMR)	5.3 [2.9–8.8]	12.0 [8.6–16.8]	13.9 [10.5–18.8]
Indonesia (IDN)	5.2 [3.2–8.3]	11.5 [8.6–15.3]	13.6 [10.6–17.6]
Mongolia (MNG)	5.0 [2.4–10.3]	10.7 [7.4–17.4]	12.7 [9.3–18.8]
Gabon (GAB)	4.5 [2.3–8.9]	10.1 [7.0–15.2]	11.9 [8.8–16.7]
Bangladesh (BGD)	4.1 [2.2–8.5]	9.2 [6.6–14.2]	11.4 [8.4–16.5]
Lao PDR (LAO)	4.1 [2.2–7.2]	9.5 [6.8–13.4]	11.7 [8.8–15.4]

Proportion of population by country infected with viable *Mycobacterium tuberculosis* in 2022, showing the top ten countries sorted in descending order by the prevalence of recent infections. Values are given as percentages (%), with brackets indicating 95% uncertainty intervals (95%UI). Recent infection is defined as occurring within two years. Estimates for all infections are provided and disaggregated based on different scenarios depending on assumptions about long-term self-clearance rates. ISO-3: International Organization for Standardization 3166-1 alpha-3 codes.

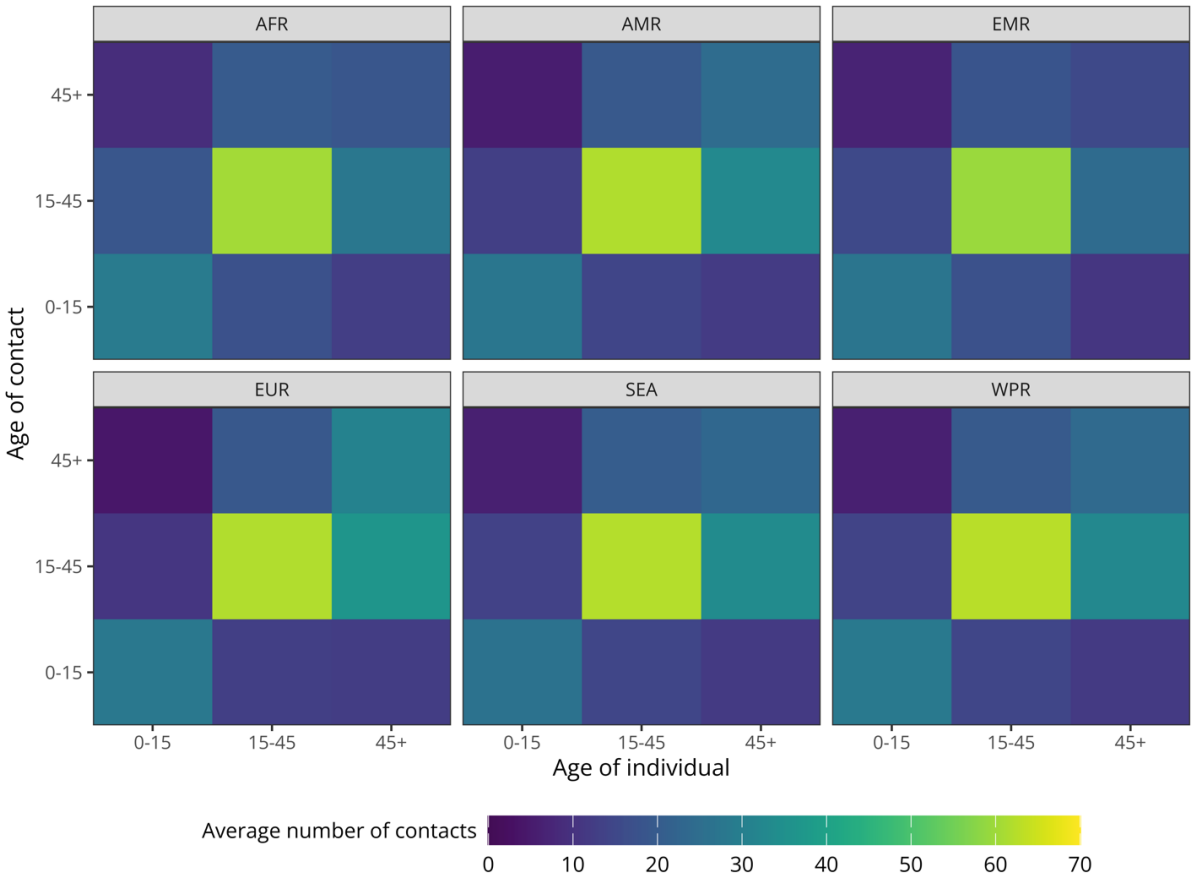
Supplementary Figures:

Figure S1. Relative TB incidence per capita in 2022.



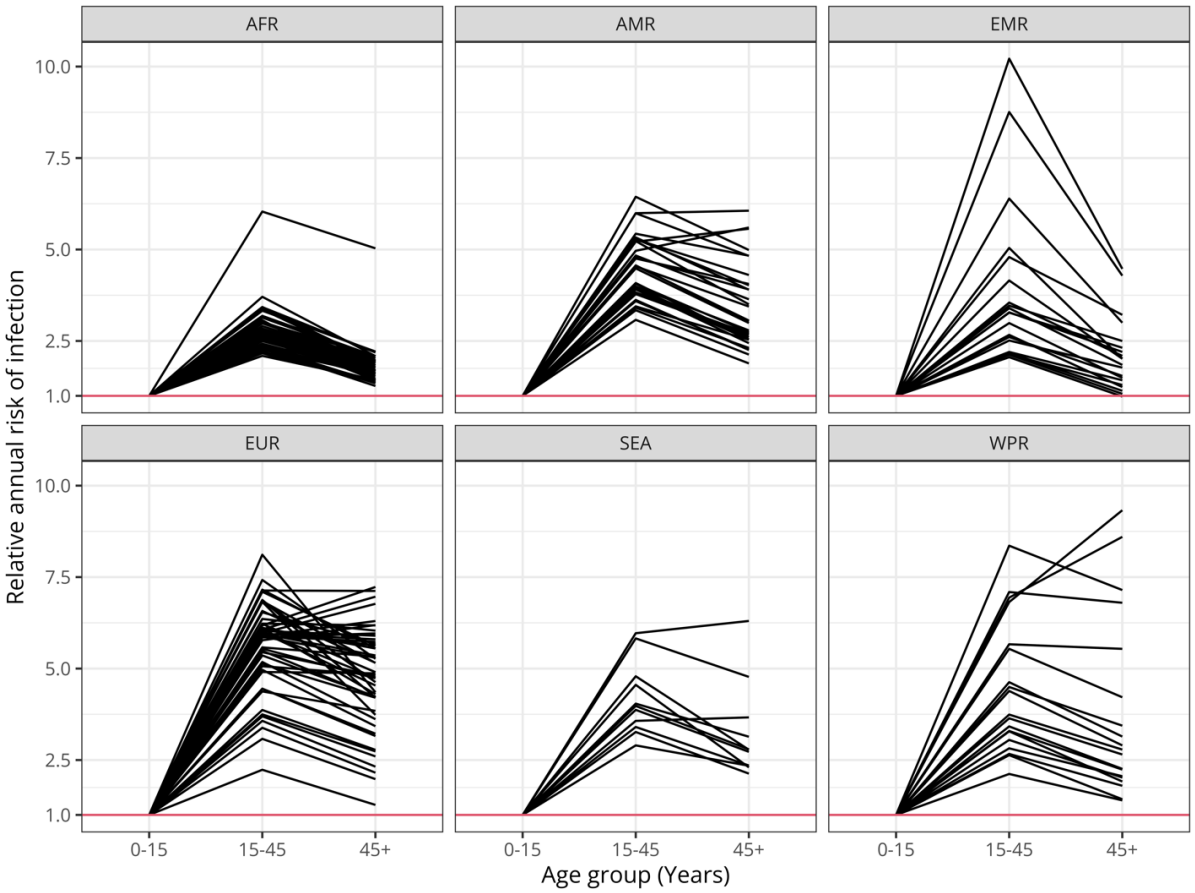
Country-specific relative TB incidence per capita by WHO region in 2022, using children under 15 years of age as the reference group, with the y-axis displayed on a square root scale. Age-specific TB incidence estimates were sourced from WHO,[93] and population data from the UN World Population Prospects.[94] WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region; UN: United Nations.

Figure S2. Average number of contacts per age group.



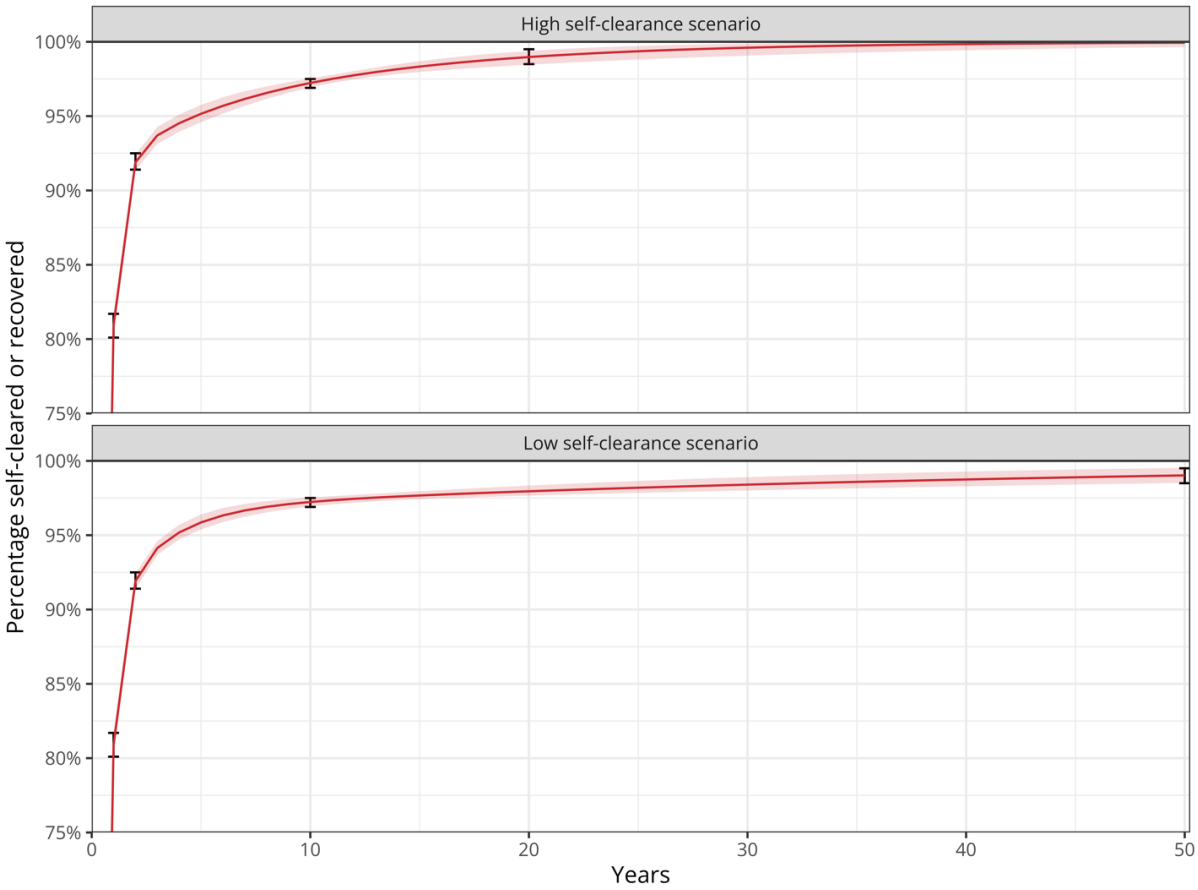
Average number of social contacts per age group by WHO region, based on synthetic country-specific contact mixing matrices developed by Prem et al.[95] WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Figure S3. Relative annual risk of infection as implied by mixing matrices.



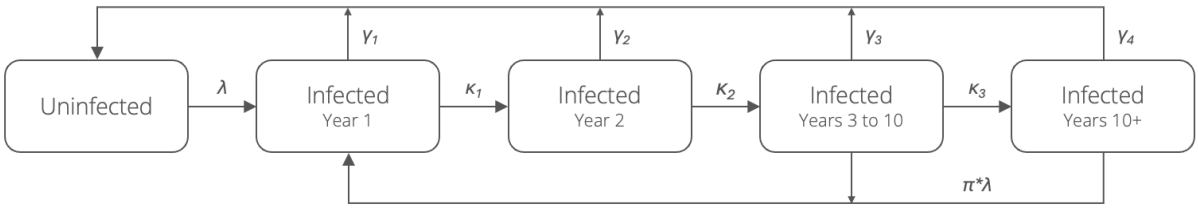
Relative annual risk of *Mycobacterium tuberculosis* infection per country by WHO region in 2022, using children under 15 years of age as the reference group. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

Figure S4. Calibration plots for self-clearance rates under different scenarios.



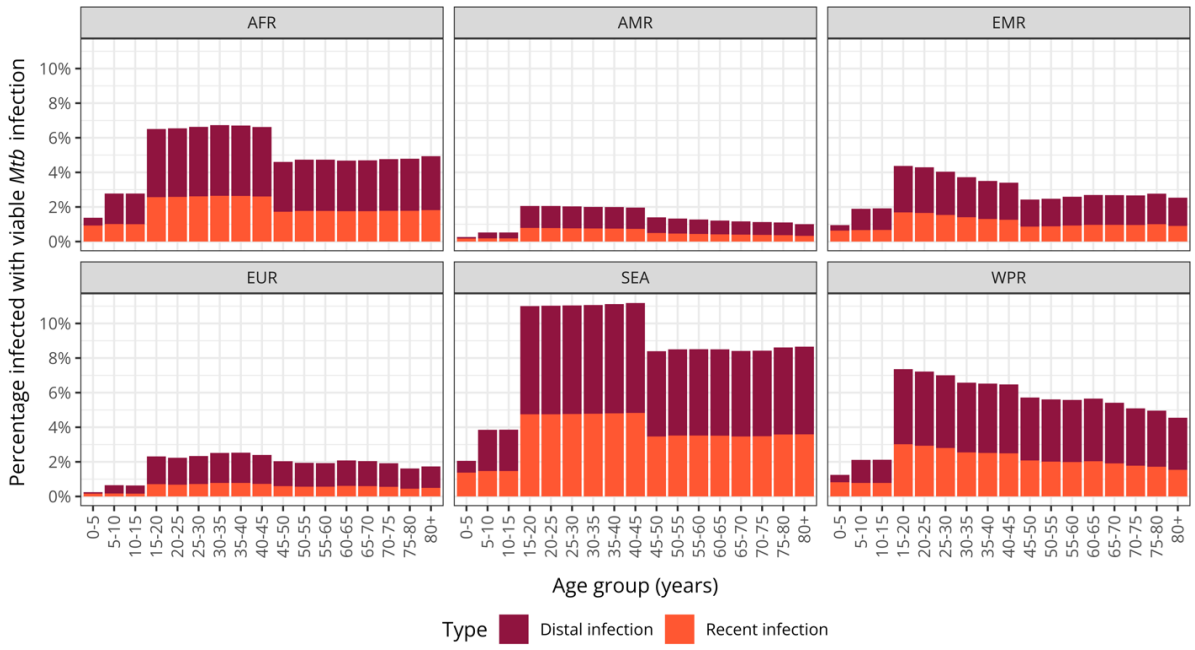
Percentage of an initially infected cohort that has effectively controlled or eliminated *Mycobacterium tuberculosis* infection without developing TB (self-cleared) or after developing TB (recovered), i.e., no longer harbouring viable infection.[96] Lines represent the median value, and the shaded area shows the lower (2.5% quantile) and upper (97.5% quantile) bounds. Error bars indicate calibration targets at years 1 (80.1– 81.7%), 2 (91.4– 92.5%), and 10 (96.9– 97.5%). Due to limited data beyond year 10, two scenarios were tested one assuming a range of 98.5-99.5% at year 20 (high self-clearance), and another at year 50 (low self-clearance).

Figure S5. Model structure.



The model structure for a single age group is illustrated. **λ:** Force of infection; **γ:** Self-clearance rates; **κ:** Infection year transitions; **π:** Protection from reinfection. Recent infection is defined as occurring within two years, i.e., '*Infected – Year 1*' and '*Infected – Year 2*'.

Figure S6. Prevalence of viable *M. tuberculosis* infection by age and WHO region in 2022.



Median estimated proportion of the population per age group and by WHO region infected with viable *Mycobacterium tuberculosis* in 2022. Values are presented as percentages (%). Recent infection is defined as occurring within two years, and distal infection as occurring after two years. The coarse age group distribution in the estimates reflects the annual risk of infection disaggregated into the following groups: under 15 years old, 15 to 45 years old, and 45 years and older. Estimates are based on scenario assuming high long-term self-clearance rates. WHO: World Health Organization; AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEA: South-East Asia Region; WPR: Western Pacific Region.

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Country-level viable Mtb infection estimates from Schwalb et al 2025, distributed under CC BY 4.0 license https://creativecommons.org/licenses/by/4.0/							
Country (ISO-3)	Absolute numbers, rounded to the nearest thousand (95%UI)				Prevalence of population as percentage (95%UI)		
	Recent infections	Recent infections in children	All infections - high self-clearance scenario	All infections - low self-clearance scenario	Recent infections	All infections - high self-clearance scenario	All infections - low self-clearance scenario
AFG	648,000 (323,000-1,311,000)	182,000 (91,000-373,000)	1,779,000 (1,228,000-2,719,000)	2,947,000 (2,066,000-4,070,000)	1.69 (0.84-3.45)	4.38 (3.03-6.70)	7.26 (5.09-10.03)
AGO	996,000 (461,000-2,134,000)	248,000 (113,000-540,000)	2,447,000 (1,710,000-3,757,000)	3,129,000 (2,170,000-4,467,000)	2.99 (1.40-6.26)	6.98 (4.88-10.72)	8.93 (6.19-12.75)
ALB	10,000 (5,000-21,000)	0 (0-1,000)	33,000 (23,000-63,000)	118,000 (32,000-265,000)	0.39 (0.19-0.77)	1.17 (0.79-2.20)	4.14 (1.12-9.29)
ARE	3,000 (2,000-6,000)	0 (0-0)	22,000 (10,000-112,000)	330,000 (34,000-783,000)	0.04 (0.02-0.07)	0.24 (0.11-1.19)	3.51 (0.36-8.32)
ARG	143,000 (90,000-231,000)	11,000 (7,000-17,000)	506,000 (345,000-902,000)	2,568,000 (1,192,000-4,823,000)	0.34 (0.21-0.53)	1.11 (0.76-1.99)	5.66 (2.63-10.63)
ARM	13,000 (7,000-26,000)	1,000 (0-2,000)	56,000 (38,000-86,000)	151,000 (72,000-247,000)	0.51 (0.26-1.00)	2.01 (1.38-3.10)	5.44 (2.58-8.87)
AUS	30,000 (14,000-60,000)	2,000 (1,000-3,000)	89,000 (59,000-219,000)	284,000 (77,000-2,404,000)	0.12 (0.06-0.24)	0.34 (0.23-0.84)	1.09 (0.29-9.23)
AUT	11,000 (5,000-21,000)	0 (0-1,000)	56,000 (34,000-160,000)	390,000 (80,000-881,000)	0.13 (0.07-0.25)	0.63 (0.38-1.79)	4.36 (0.90-9.86)
AZE	150,000 (77,000-314,000)	11,000 (6,000-24,000)	444,000 (312,000-663,000)	724,000 (424,000-1,084,000)	1.54 (0.79-3.18)	4.30 (3.02-6.42)	7.01 (4.11-10.50)
BDI	119,000 (67,000-218,000)	30,000 (17,000-56,000)	374,000 (258,000-558,000)	740,000 (503,000-1,052,000)	0.99 (0.57-1.88)	2.94 (2.03-4.39)	5.82 (3.96-8.27)
BEL	17,000 (8,000-35,000)	1,000 (0-2,000)	61,000 (37,000-172,000)	402,000 (60,000-1,123,000)	0.15 (0.08-0.32)	0.53 (0.32-1.47)	3.45 (0.52-9.65)
BEN	73,000 (37,000-152,000)	16,000 (8,000-34,000)	228,000 (155,000-356,000)	585,000 (326,000-1,016,000)	0.60 (0.30-1.25)	1.73 (1.17-2.70)	4.44 (2.47-7.72)
BFA	88,000 (43,000-189,000)	23,000 (11,000-50,000)	284,000 (186,000-485,000)	779,000 (270,000-1,521,000)	0.41 (0.20-0.89)	1.27 (0.83-2.17)	3.48 (1.20-6.79)
BGD	6,628,000 (3,473,000-13,681,000)	725,000 (373,000-1,535,000)	15,693,000 (11,213,000-24,167,000)	19,349,000 (14,345,000-28,035,000)	4.12 (2.16-8.48)	9.21 (6.58-14.19)	11.36 (8.42-16.46)
BGR	38,000 (20,000-77,000)	1,000 (0-2,000)	168,000 (112,000-265,000)	403,000 (235,000-650,000)	0.58 (0.30-1.21)	2.46 (1.65-3.88)	5.90 (3.44-9.51)
BHR	5,000 (2,000-9,000)	0 (0-0)	18,000 (12,000-33,000)	74,000 (38,000-129,000)	0.34 (0.17-0.69)	1.23 (0.80-2.24)	5.04 (2.59-8.79)
BIH	24,000 (12,000-46,000)	1,000 (0-1,000)	96,000 (65,000-147,000)	207,000 (128,000-315,000)	0.78 (0.40-1.51)	2.94 (2.01-4.52)	6.39 (3.93-9.71)
BLR	70,000 (36,000-135,000)	2,000 (1,000-5,000)	286,000 (195,000-426,000)	605,000 (368,000-926,000)	0.77 (0.41-1.53)	2.99 (2.04-4.47)	6.34 (3.85-9.69)
BOL	186,000 (91,000-396,000)	22,000 (11,000-47,000)	550,000 (385,000-840,000)	880,000 (594,000-1,297,000)	1.64 (0.78-3.37)	4.53 (3.17-6.91)	7.24 (4.89-10.68)
BRA	1,641,000 (856,000-3,346,000)	90,000 (47,000-185,000)	4,851,000 (3,296,000-7,992,000)	12,241,000 (6,885,000-20,846,000)	0.82 (0.44-1.65)	2.26 (1.53-3.72)	5.70 (3.20-9.70)
BTN	26,000 (13,000-49,000)	2,000 (1,000-3,000)	65,000 (47,000-91,000)	83,000 (61,000-113,000)	3.48 (1.78-6.79)	8.30 (6.02-11.73)	10.67 (7.77-14.50)
BWA	40,000 (23,000-66,000)	5,000 (3,000-9,000)	132,000 (98,000-180,000)	206,000 (157,000-272,000)	1.61 (0.95-2.74)	5.07 (3.76-6.89)	7.92 (6.02-10.43)
CAF	193,000 (91,000-414,000)	56,000 (26,000-122,000)	446,000 (303,000-727,000)	543,000 (383,000-790,000)	3.69 (1.79-8.00)	8.10 (5.50-13.21)	9.87 (6.97-14.36)
CAN	51,000 (26,000-109,000)	2,000 (1,000-3,000)	154,000 (103,000-434,000)	611,000 (137,000-3,437,000)	0.14 (0.07-0.30)	0.40 (0.27-1.13)	1.60 (0.36-8.98)
CHE	11,000 (5,000-23,000)	0 (0-1,000)	43,000 (28,000-130,000)	305,000 (43,000-880,000)	0.13 (0.07-0.28)	0.50 (0.32-1.49)	3.50 (0.49-10.10)
CHL	63,000 (32,000-122,000)	3,000 (1,000-5,000)	194,000 (129,000-373,000)	720,000 (193,000-1,683,000)	0.34 (0.17-0.67)	0.99 (0.66-1.91)	3.67 (0.98-8.59)
CHN	20,149,000 (10,429,000-39,243,000)	757,000 (389,000-1,489,000)	63,985,000 (44,984,000-93,917,000)	108,279,000 (78,018,000-150,552,000)	1.51 (0.78-2.93)	4.49 (3.15-6.59)	7.59 (5.47-10.56)
CIV	289,000 (149,000-541,000)	71,000 (37,000-134,000)	950,000 (648,000-1,392,000)	1,722,000 (1,110,000-2,364,000)	1.09 (0.57-2.08)	3.42 (2.33-5.01)	6.19 (3.99-8.50)
CMR	434,000 (236,000-782,000)	95,000 (51,000-174,000)	1,210,000 (859,000-1,718,000)	1,961,000 (1,380,000-2,743,000)	1.68 (0.90-3.01)	4.39 (3.12-6.24)	7.12 (5.01-9.95)
COD	2,688,000 (1,305,000-6,075,000)	766,000 (369,000-1,782,000)	6,503,000 (4,459,000-10,285,000)	8,413,000 (5,914,000-12,235,000)	2.91 (1.41-6.35)	6.68 (4.58-10.56)	8.64 (6.07-12.56)
COG	162,000 (78,000-357,000)	36,000 (17,000-80,000)	396,000 (270,000-625,000)	523,000 (356,000-725,000)	2.90 (1.37-6.26)	6.71 (4.58-10.60)	8.86 (6.03-12.27)
COL	399,000 (198,000-760,000)	26,000 (13,000-49,000)	982,000 (661,000-1,553,000)	1,937,000 (850,000-4,682,000)	0.81 (0.41-1.57)	1.90 (1.28-3.00)	3.74 (1.64-9.04)
COM	3,000 (2,000-7,000)	1,000 (0-2,000)	9,000 (6,000-15,000)	22,000 (8,000-58,000)	0.40 (0.19-0.85)	1.04 (0.69-1.77)	2.63 (0.97-6.98)
CPV	4,000 (2,000-8,000)	0 (0-1,000)	16,000 (11,000-24,000)	34,000 (17,000-51,000)	0.71 (0.36-1.47)	2.64 (1.85-4.09)	5.70 (2.85-8.72)
CRI	9,000 (5,000-19,000)	1,000 (0-1,000)	34,000 (20,000-83,000)	182,000 (31,000-463,000)	0.20 (0.10-0.39)	0.67 (0.39-1.60)	3.53 (0.60-8.97)
CUB	20,000 (10,000-43,000)	1,000 (0-1,000)	68,000 (45,000-179,000)	394,000 (66,000-1,104,000)	0.19 (0.09-0.41)	0.61 (0.40-1.59)	3.51 (0.59-9.84)
CYP	2,000 (1,000-4,000)	0 (0-0)	4,000 (3,000-10,000)	8,000 (4,000-105,000)	0.14 (0.07-0.30)	0.35 (0.23-0.76)	0.65 (0.29-8.44)
CZE	11,000 (5,000-22,000)	0 (0-1,000)	57,000 (33,000-182,000)	438,000 (75,000-1,004,000)	0.11 (0.06-0.23)	0.54 (0.31-1.73)	4.17 (0.72-9.56)
DEU	70,000 (36,000-144,000)	3,000 (2,000-6,000)	271,000 (174,000-1,001,000)	2,492,000 (275,000-8,294,000)	0.09 (0.05-0.19)	0.32 (0.21-1.20)	2.99 (0.33-9.94)
DJI	28,000 (14,000-61,000)	4,000 (2,000-8,000)	86,000 (62,000-125,000)	112,000 (85,000-154,000)	2.66 (1.34-5.76)	7.72 (5.58-11.25)	10.07 (7.62-13.84)
DNK	6,000 (3,000-12,000)	0 (0-0)	27,000 (16,000-87,000)	231,000 (27,000-539,000)	0.10 (0.05-0.21)	0.46 (0.27-1.48)	3.93 (0.46-9.18)
DOM	75,000 (36,000-157,000)	8,000 (4,000-16,000)	239,000 (161,000-392,000)	558,000 (230,000-958,000)	0.72 (0.33-1.46)	2.14 (1.44-3.51)	4.99 (2.06-8.57)
DZA	227,000 (121,000-429,000)	38,000 (20,000-71,000)	797,000 (543,000-1,275,000)	2,488,000 (1,376,000-4,387,000)	0.54 (0.29-1.04)	1.79 (1.22-2.86)	5.59 (3.09-9.85)

ECU	141,000 (69,000-299,000)	13,000 (6,000-27,000)	400,000 (275,000-634,000)	905,000 (377,000-1,583,000)	0.84 (0.42-1.73)	2.23 (1.54-3.54)	5.06 (2.10-8.84)
EGY	121,000 (61,000-256,000)	21,000 (11,000-45,000)	566,000 (334,000-1,565,000)	3,794,000 (682,000-8,389,000)	0.12 (0.06-0.25)	0.51 (0.30-1.42)	3.45 (0.62-7.62)
ERI	26,000 (14,000-49,000)	5,000 (3,000-10,000)	90,000 (58,000-141,000)	202,000 (130,000-299,000)	0.75 (0.41-1.41)	2.47 (1.59-3.85)	5.53 (3.55-8.18)
ESP	88,000 (42,000-175,000)	2,000 (1,000-5,000)	425,000 (269,000-997,000)	2,165,000 (502,000-4,669,000)	0.20 (0.10-0.40)	0.89 (0.57-2.10)	4.55 (1.05-9.81)
EST	3,000 (2,000-6,000)	0 (0-0)	19,000 (11,000-36,000)	65,000 (32,000-108,000)	0.23 (0.12-0.49)	1.40 (0.82-2.74)	4.90 (2.41-8.14)
ETH	1,188,000 (699,000-1,923,000)	214,000 (126,000-347,000)	4,091,000 (2,973,000-5,584,000)	7,510,000 (5,283,000-10,576,000)	1.04 (0.62-1.69)	3.36 (2.44-4.58)	6.16 (4.34-8.68)
FIN	5,000 (3,000-11,000)	0 (0-0)	24,000 (15,000-80,000)	212,000 (26,000-556,000)	0.10 (0.05-0.21)	0.44 (0.26-1.45)	3.82 (0.47-10.05)
FJI	10,000 (5,000-20,000)	1,000 (1,000-2,000)	21,000 (13,000-33,000)	25,000 (15,000-66,000)	1.14 (0.54-2.24)	2.25 (1.45-3.58)	2.69 (1.60-7.16)
FRA	101,000 (51,000-225,000)	4,000 (2,000-9,000)	366,000 (242,000-995,000)	2,133,000 (363,000-6,079,000)	0.17 (0.09-0.35)	0.57 (0.37-1.54)	3.30 (0.56-9.42)
GAB	102,000 (52,000-204,000)	21,000 (11,000-44,000)	240,000 (165,000-359,000)	281,000 (209,000-396,000)	4.53 (2.33-8.90)	10.14 (6.98-15.19)	11.88 (8.82-16.75)
GBR	107,000 (50,000-213,000)	5,000 (2,000-9,000)	411,000 (269,000-984,000)	2,436,000 (424,000-5,972,000)	0.17 (0.08-0.34)	0.61 (0.40-1.46)	3.61 (0.63-8.86)
GEO	54,000 (28,000-98,000)	3,000 (1,000-5,000)	200,000 (146,000-273,000)	308,000 (232,000-403,000)	1.53 (0.79-2.78)	5.32 (3.89-7.26)	8.19 (6.17-10.75)
GHA	587,000 (319,000-1,044,000)	106,000 (57,000-190,000)	1,634,000 (1,136,000-2,391,000)	2,551,000 (1,861,000-3,443,000)	1.88 (1.03-3.34)	4.93 (3.42-7.21)	7.69 (5.61-10.38)
GIN	242,000 (114,000-496,000)	58,000 (27,000-121,000)	642,000 (444,000-968,000)	957,000 (606,000-1,384,000)	1.89 (0.88-3.81)	4.69 (3.24-7.07)	6.99 (4.43-10.11)
GMB	16,000 (8,000-30,000)	4,000 (2,000-8,000)	51,000 (35,000-82,000)	132,000 (81,000-210,000)	0.62 (0.32-1.17)	1.92 (1.32-3.06)	4.94 (3.01-7.84)
GNB	63,000 (31,000-141,000)	14,000 (7,000-32,000)	154,000 (104,000-244,000)	194,000 (132,000-283,000)	3.21 (1.55-7.15)	7.38 (4.97-11.72)	9.32 (6.34-13.60)
GNQ	32,000 (15,000-67,000)	6,000 (3,000-13,000)	75,000 (50,000-119,000)	102,000 (63,000-162,000)	2.03 (0.94-4.26)	4.54 (3.00-7.21)	6.13 (3.82-9.81)
GRC	6,000 (4,000-11,000)	0 (0-0)	72,000 (32,000-196,000)	428,000 (232,000-674,000)	0.07 (0.04-0.12)	0.69 (0.31-1.88)	4.11 (2.23-6.48)
GTM	64,000 (31,000-134,000)	10,000 (5,000-20,000)	190,000 (123,000-322,000)	536,000 (169,000-1,220,000)	0.38 (0.18-0.79)	1.07 (0.70-1.82)	3.02 (0.96-6.88)
GUY	6,000 (3,000-12,000)	1,000 (0-1,000)	20,000 (14,000-31,000)	42,000 (19,000-71,000)	0.77 (0.38-1.59)	2.47 (1.72-3.82)	5.27 (2.35-8.78)
HKG	128,000 (70,000-234,000)	2,000 (1,000-4,000)	451,000 (328,000-604,000)	660,000 (514,000-846,000)	1.80 (1.02-3.27)	6.02 (4.38-8.06)	8.81 (6.86-11.29)
HND	38,000 (20,000-80,000)	5,000 (2,000-10,000)	152,000 (96,000-286,000)	475,000 (174,000-785,000)	0.39 (0.20-0.80)	1.46 (0.93-2.76)	4.58 (1.68-7.58)
HRV	4,000 (2,000-8,000)	0 (0-0)	45,000 (24,000-107,000)	190,000 (93,000-319,000)	0.10 (0.05-0.20)	1.11 (0.58-2.64)	4.71 (2.31-7.89)
HTI	270,000 (132,000-540,000)	28,000 (14,000-59,000)	762,000 (545,000-1,083,000)	1,032,000 (752,000-1,412,000)	2.48 (1.23-4.93)	6.61 (4.73-9.41)	8.96 (6.53-12.26)
HUN	13,000 (6,000-25,000)	0 (0-1,000)	102,000 (58,000-264,000)	452,000 (230,000-838,000)	0.14 (0.07-0.27)	1.05 (0.60-2.73)	4.67 (2.37-8.65)
IDN	13,635,000 (8,224,000-21,953,000)	1,306,000 (764,000-2,168,000)	31,692,000 (23,575,000-42,090,000)	37,286,000 (29,010,000-48,272,000)	5.17 (3.18-8.30)	11.54 (8.58-15.33)	13.58 (10.56-17.58)
IND	39,509,000 (21,058,000-73,574,000)	4,367,000 (2,310,000-8,236,000)	103,770,000 (74,594,000-144,547,000)	141,463,000 (104,935,000-197,102,000)	2.95 (1.58-5.43)	7.35 (5.28-10.23)	10.02 (7.43-13.96)
IRL	4,000 (2,000-9,000)	0 (0-0)	22,000 (13,000-76,000)	185,000 (24,000-468,000)	0.09 (0.05-0.18)	0.43 (0.26-1.53)	3.70 (0.48-9.35)
IRN	147,000 (75,000-298,000)	14,000 (7,000-28,000)	571,000 (364,000-1,450,000)	3,036,000 (553,000-7,474,000)	0.18 (0.09-0.35)	0.65 (0.41-1.64)	3.44 (0.63-8.47)
IRQ	83,000 (40,000-165,000)	20,000 (10,000-40,000)	324,000 (213,000-732,000)	1,408,000 (312,000-3,079,000)	0.20 (0.10-0.40)	0.74 (0.48-1.66)	3.20 (0.71-7.00)
ISR	3,000 (1,000-6,000)	0 (0-1,000)	17,000 (9,000-97,000)	284,000 (21,000-735,000)	0.03 (0.02-0.06)	0.19 (0.09-1.08)	3.17 (0.24-8.19)
ITA	64,000 (31,000-132,000)	2,000 (1,000-4,000)	246,000 (161,000-818,000)	1,714,000 (244,000-6,022,000)	0.12 (0.06-0.23)	0.42 (0.27-1.38)	2.90 (0.41-10.19)
JAM	1,000 (1,000-3,000)	0 (0-0)	6,000 (4,000-24,000)	51,000 (5,000-222,000)	0.05 (0.03-0.11)	0.20 (0.13-0.84)	1.80 (0.19-7.84)
JOR	4,000 (2,000-9,000)	1,000 (0-2,000)	17,000 (10,000-92,000)	167,000 (15,000-827,000)	0.04 (0.02-0.08)	0.15 (0.09-0.82)	1.49 (0.14-7.35)
JPN	244,000 (116,000-490,000)	8,000 (4,000-16,000)	1,174,000 (762,000-2,808,000)	5,901,000 (1,527,000-13,118,000)	0.21 (0.10-0.42)	0.94 (0.61-2.26)	4.75 (1.23-10.56)
KAZ	135,000 (81,000-219,000)	15,000 (9,000-25,000)	534,000 (363,000-794,000)	1,147,000 (781,000-1,701,000)	0.75 (0.45-1.21)	2.77 (1.88-4.11)	5.94 (4.05-8.82)
KEN	950,000 (524,000-1,651,000)	160,000 (87,000-283,000)	2,827,000 (2,047,000-3,998,000)	3,360,000 (2,504,000-4,824,000)	1.85 (1.01-3.25)	5.28 (3.83-7.47)	6.28 (4.68-9.02)
KGZ	90,000 (47,000-173,000)	15,000 (8,000-29,000)	252,000 (176,000-373,000)	416,000 (245,000-629,000)	1.45 (0.78-2.76)	3.83 (2.67-5.68)	6.33 (3.73-9.56)
KHM	865,000 (460,000-1,491,000)	100,000 (52,000-178,000)	2,066,000 (1,470,000-2,879,000)	2,231,000 (1,631,000-3,037,000)	5.39 (2.95-9.26)	12.39 (8.81-17.26)	13.37 (9.78-18.21)
KOR	876,000 (518,000-1,564,000)	14,000 (8,000-26,000)	3,227,000 (2,451,000-4,283,000)	4,721,000 (3,671,000-6,137,000)	1.78 (1.07-3.18)	6.23 (4.73-8.26)	9.11 (7.08-11.84)
KWT	12,000 (6,000-24,000)	1,000 (0-1,000)	47,000 (32,000-89,000)	226,000 (97,000-423,000)	0.29 (0.15-0.59)	1.11 (0.75-2.10)	5.33 (2.29-9.96)
LAO	288,000 (161,000-507,000)	36,000 (19,000-64,000)	713,000 (512,000-1,000,000)	873,000 (661,000-1,153,000)	4.08 (2.24-7.18)	9.53 (6.84-13.38)	11.67 (8.84-15.42)
LBN	7,000 (3,000-15,000)	1,000 (0-2,000)	22,000 (14,000-63,000)	77,000 (19,000-425,000)	0.13 (0.06-0.29)	0.39 (0.25-1.13)	1.39 (0.34-7.66)
LBR	168,000 (81,000-332,000)	34,000 (16,000-70,000)	393,000 (270,000-598,000)	485,000 (335,000-684,000)	3.39 (1.64-6.53)	7.48 (5.14-11.39)	9.25 (6.38-13.03)
LBY	37,000 (19,000-72,000)	5,000 (2,000-9,000)	109,000 (72,000-186,000)	366,000 (194,000-610,000)	0.59 (0.31-1.13)	1.61 (1.06-2.74)	5.40 (2.87-9.00)
LKA	251,000 (135,000-507,000)	20,000 (10,000-40,000)	689,000 (484,000-1,058,000)	1,248,000 (652,000-2,120,000)	1.22 (0.66-2.43)	3.16 (2.22-4.85)	5.72 (2.99-9.72)
LSO	80,000 (47,000-142,000)	12,000 (7,000-22,000)	205,000 (146,000-290,000)	255,000 (188,000-343,000)	3.66 (2.13-6.62)	8.94 (6.39-12.64)	11.12 (8.17-14.95)

LTU	21,000 (10,000-40,000)	1,000 (0-1,000)	90,000 (63,000-128,000)	179,000 (110,000-270,000)	0.83 (0.41-1.54)	3.27 (2.27-4.62)	6.48 (3.98-9.76)
LUX	1,000 (1,000-2,000)	0 (0-0)	3,000 (2,000-9,000)	18,000 (3,000-56,000)	0.18 (0.10-0.36)	0.54 (0.36-1.44)	2.76 (0.49-8.74)
LVA	9,000 (5,000-18,000)	0 (0-1,000)	48,000 (32,000-78,000)	112,000 (71,000-168,000)	0.51 (0.26-1.05)	2.60 (1.71-4.20)	6.01 (3.80-9.03)
MAC	10,000 (5,000-22,000)	0 (0-1,000)	34,000 (24,000-49,000)	54,000 (38,000-77,000)	1.61 (0.86-3.39)	4.96 (3.55-7.09)	7.87 (5.47-11.16)
MAR	389,000 (197,000-812,000)	44,000 (22,000-95,000)	1,111,000 (791,000-1,631,000)	2,061,000 (1,054,000-3,515,000)	1.11 (0.57-2.30)	2.98 (2.12-4.38)	5.53 (2.83-9.43)
MDA	54,000 (28,000-107,000)	3,000 (1,000-5,000)	165,000 (118,000-231,000)	250,000 (169,000-353,000)	1.87 (0.95-3.67)	5.40 (3.88-7.57)	8.20 (5.53-11.57)
MDG	868,000 (416,000-1,700,000)	164,000 (77,000-329,000)	2,129,000 (1,497,000-3,188,000)	2,755,000 (2,021,000-3,814,000)	3.13 (1.56-6.07)	7.28 (5.12-10.90)	9.42 (6.91-13.03)
MDV	3,000 (2,000-7,000)	0 (0-0)	10,000 (7,000-17,000)	25,000 (10,000-48,000)	0.70 (0.33-1.47)	1.94 (1.28-3.27)	4.82 (1.89-9.05)
MEX	497,000 (235,000-1,033,000)	44,000 (21,000-92,000)	1,272,000 (841,000-2,260,000)	2,968,000 (1,079,000-10,108,000)	0.41 (0.20-0.85)	1.00 (0.66-1.78)	2.34 (0.85-7.96)
MKD	5,000 (2,000-10,000)	0 (0-0)	25,000 (16,000-52,000)	102,000 (40,000-193,000)	0.25 (0.13-0.48)	1.18 (0.74-2.47)	4.84 (1.91-9.17)
MLI	101,000 (46,000-219,000)	29,000 (13,000-63,000)	312,000 (209,000-545,000)	801,000 (297,000-1,509,000)	0.48 (0.22-1.04)	1.40 (0.94-2.45)	3.60 (1.33-6.78)
MLT	3,000 (1,000-5,000)	0 (0-0)	5,000 (4,000-9,000)	6,000 (4,000-26,000)	0.49 (0.27-0.92)	1.02 (0.69-1.60)	1.22 (0.79-4.91)
MMR	2,727,000 (1,444,000-4,605,000)	247,000 (128,000-440,000)	6,478,000 (4,618,000-9,050,000)	7,516,000 (5,671,000-10,144,000)	5.30 (2.87-8.85)	12.00 (8.56-16.77)	13.92 (10.51-18.79)
MNE	2,000 (1,000-4,000)	0 (0-0)	7,000 (4,000-17,000)	29,000 (6,000-55,000)	0.28 (0.13-0.59)	1.11 (0.66-2.76)	4.56 (0.89-8.80)
MNG	160,000 (78,000-338,000)	25,000 (12,000-55,000)	362,000 (251,000-588,000)	429,000 (313,000-634,000)	5.01 (2.43-10.32)	10.74 (7.43-17.43)	12.71 (9.29-18.78)
MOZ	791,000 (368,000-1,683,000)	194,000 (89,000-417,000)	1,915,000 (1,294,000-3,063,000)	2,547,000 (1,704,000-3,720,000)	2.55 (1.15-5.47)	5.89 (3.98-9.42)	7.83 (5.24-11.44)
MRT	34,000 (17,000-65,000)	9,000 (5,000-18,000)	124,000 (83,000-189,000)	259,000 (165,000-365,000)	0.78 (0.39-1.48)	2.65 (1.77-4.05)	5.55 (3.52-7.81)
MUS	5,000 (3,000-11,000)	0 (0-0)	16,000 (11,000-29,000)	51,000 (15,000-119,000)	0.44 (0.22-0.91)	1.24 (0.83-2.25)	3.91 (1.17-9.14)
MWI	194,000 (116,000-338,000)	43,000 (26,000-75,000)	676,000 (471,000-989,000)	1,265,000 (879,000-1,718,000)	1.02 (0.61-1.76)	3.36 (2.34-4.91)	6.28 (4.36-8.53)
MYS	526,000 (265,000-1,003,000)	38,000 (19,000-74,000)	1,293,000 (902,000-1,911,000)	2,295,000 (1,413,000-3,653,000)	1.66 (0.83-3.15)	3.83 (2.67-5.66)	6.80 (4.19-10.82)
NAM	71,000 (36,000-139,000)	14,000 (7,000-27,000)	203,000 (150,000-290,000)	260,000 (199,000-351,000)	2.91 (1.48-5.77)	7.96 (5.88-11.36)	10.20 (7.81-13.77)
NER	190,000 (93,000-377,000)	59,000 (29,000-118,000)	618,000 (427,000-935,000)	1,307,000 (714,000-1,879,000)	0.78 (0.39-1.56)	2.40 (1.66-3.63)	5.08 (2.78-7.31)
NGA	2,578,000 (1,183,000-5,273,000)	707,000 (322,000-1,449,000)	6,644,000 (4,437,000-10,079,000)	11,114,000 (6,024,000-18,018,000)	1.25 (0.59-2.54)	3.08 (2.05-4.67)	5.15 (2.79-8.34)
NIC	36,000 (16,000-78,000)	4,000 (2,000-9,000)	107,000 (71,000-178,000)	268,000 (96,000-519,000)	0.54 (0.25-1.16)	1.56 (1.03-2.58)	3.89 (1.39-7.52)
NLD	19,000 (10,000-38,000)	1,000 (0-1,000)	82,000 (51,000-259,000)	677,000 (87,000-1,781,000)	0.12 (0.06-0.23)	0.47 (0.29-1.48)	3.86 (0.49-10.16)
NOR	4,000 (2,000-8,000)	0 (0-0)	18,000 (12,000-69,000)	173,000 (18,000-515,000)	0.08 (0.04-0.15)	0.34 (0.21-1.27)	3.20 (0.34-9.51)
NPL	971,000 (483,000-1,887,000)	100,000 (49,000-199,000)	2,567,000 (1,816,000-3,712,000)	3,253,000 (2,414,000-4,358,000)	3.40 (1.66-6.55)	8.45 (5.98-12.22)	10.71 (7.95-14.35)
NZL	7,000 (3,000-14,000)	0 (0-1,000)	25,000 (15,000-70,000)	157,000 (24,000-458,000)	0.14 (0.07-0.28)	0.48 (0.30-1.35)	3.03 (0.47-8.88)
OMN	6,000 (3,000-13,000)	0 (0-1,000)	23,000 (15,000-62,000)	139,000 (24,000-368,000)	0.15 (0.07-0.30)	0.51 (0.34-1.37)	3.06 (0.52-8.09)
PAK	5,313,000 (2,767,000-10,068,000)	1,085,000 (566,000-2,090,000)	13,760,000 (9,812,000-19,902,000)	20,045,000 (14,511,000-27,407,000)	2.41 (1.26-4.46)	5.89 (4.20-8.52)	8.58 (6.21-11.74)
PAN	25,000 (12,000-53,000)	2,000 (1,000-5,000)	77,000 (52,000-128,000)	200,000 (77,000-378,000)	0.59 (0.29-1.25)	1.75 (1.19-2.93)	4.57 (1.76-8.64)
PER	692,000 (333,000-1,474,000)	58,000 (27,000-129,000)	1,826,000 (1,239,000-2,766,000)	2,663,000 (1,734,000-3,876,000)	2.17 (1.03-4.62)	5.38 (3.65-8.16)	7.85 (5.11-11.43)
PHL	9,249,000 (4,742,000-17,782,000)	1,318,000 (650,000-2,673,000)	18,954,000 (12,933,000-28,989,000)	20,522,000 (14,659,000-30,027,000)	8.48 (4.38-16.37)	16.53 (11.28-25.28)	17.90 (12.78-26.19)
PNG	351,000 (173,000-750,000)	67,000 (33,000-146,000)	844,000 (586,000-1,304,000)	1,043,000 (738,000-1,530,000)	3.67 (1.79-7.73)	8.40 (5.84-12.98)	10.38 (7.34-15.22)
POL	115,000 (57,000-241,000)	3,000 (2,000-7,000)	531,000 (343,000-1,027,000)	1,890,000 (648,000-3,609,000)	0.32 (0.16-0.66)	1.39 (0.90-2.69)	4.94 (1.69-9.44)
PRI	1,000 (0-1,000)	0 (0-0)	6,000 (2,000-37,000)	124,000 (8,000-345,000)	0.02 (0.01-0.03)	0.18 (0.07-1.13)	3.83 (0.25-10.63)
PRK	2,321,000 (1,181,000-4,115,000)	111,000 (54,000-213,000)	4,776,000 (3,382,000-6,848,000)	5,047,000 (3,769,000-7,077,000)	9.28 (4.81-16.34)	18.35 (13.00-26.32)	19.39 (14.48-27.20)
PRT	45,000 (23,000-92,000)	1,000 (0-2,000)	191,000 (126,000-340,000)	563,000 (269,000-959,000)	0.47 (0.24-0.95)	1.86 (1.22-3.30)	5.48 (2.61-9.32)
PRY	46,000 (22,000-94,000)	5,000 (2,000-10,000)	121,000 (82,000-201,000)	243,000 (108,000-527,000)	0.72 (0.35-1.45)	1.80 (1.21-2.98)	3.60 (1.60-7.82)
PSE	0 (0-0)	0 (0-0)	1,000 (1,000-23,000)	61,000 (1,000-357,000)	0.00 (0.00-0.01)	0.03 (0.01-0.45)	1.17 (0.03-6.87)
QAT	38,000 (19,000-74,000)	1,000 (0-2,000)	102,000 (70,000-151,000)	180,000 (104,000-273,000)	1.49 (0.77-2.94)	3.80 (2.62-5.62)	6.70 (3.88-10.16)
ROU	241,000 (121,000-481,000)	8,000 (4,000-15,000)	922,000 (676,000-1,305,000)	1,499,000 (1,054,000-1,998,000)	1.31 (0.65-2.63)	4.79 (3.51-6.77)	7.78 (5.47-10.37)
RUS	1,553,000 (782,000-3,038,000)	64,000 (33,000-128,000)	5,387,000 (3,734,000-8,040,000)	10,236,000 (6,831,000-15,046,000)	1.14 (0.59-2.22)	3.72 (2.58-5.56)	7.07 (4.72-10.40)
RWA	71,000 (34,000-138,000)	13,000 (6,000-24,000)	233,000 (160,000-389,000)	605,000 (239,000-1,010,000)	0.55 (0.27-1.07)	1.71 (1.18-2.86)	4.44 (1.75-7.42)
SAU	51,000 (27,000-98,000)	5,000 (2,000-9,000)	226,000 (155,000-505,000)	1,336,000 (308,000-3,295,000)	0.15 (0.08-0.29)	0.63 (0.43-1.40)	3.70 (0.85-9.12)
SDN	242,000 (150,000-406,000)	62,000 (38,000-105,000)	886,000 (599,000-1,371,000)	2,323,000 (1,342,000-3,649,000)	0.55 (0.34-0.94)	1.91 (1.30-2.96)	5.02 (2.90-7.89)
SEN	168,000 (79,000-353,000)	45,000 (21,000-96,000)	485,000 (323,000-747,000)	871,000 (451,000-1,366,000)	1.04 (0.49-2.22)	2.84 (1.89-4.37)	5.10 (2.64-7.99)

SGP	100,000 (49,000-213,000)	2,000 (1,000-4,000)	248,000 (167,000-397,000)	401,000 (222,000-670,000)	1.78 (0.88-3.70)	4.16 (2.81-6.66)	6.74 (3.73-11.24)
SLB	6,000 (3,000-13,000)	1,000 (1,000-2,000)	18,000 (13,000-28,000)	35,000 (18,000-59,000)	0.89 (0.45-1.83)	2.55 (1.80-3.93)	4.95 (2.54-8.25)
SLE	262,000 (128,000-515,000)	57,000 (27,000-114,000)	638,000 (448,000-952,000)	806,000 (580,000-1,173,000)	3.25 (1.54-6.40)	7.49 (5.27-11.18)	9.47 (6.82-13.77)
SLV	37,000 (19,000-77,000)	3,000 (2,000-7,000)	101,000 (69,000-159,000)	154,000 (81,000-503,000)	0.62 (0.32-1.27)	1.60 (1.09-2.51)	2.44 (1.29-7.95)
SOM	532,000 (263,000-1,091,000)	113,000 (55,000-238,000)	1,334,000 (909,000-1,994,000)	1,657,000 (1,195,000-2,230,000)	3.24 (1.64-6.54)	7.70 (5.25-11.51)	9.56 (6.89-12.87)
SRB	26,000 (13,000-56,000)	1,000 (0-2,000)	127,000 (78,000-257,000)	391,000 (119,000-650,000)	0.39 (0.19-0.80)	1.75 (1.07-3.54)	5.38 (1.64-8.96)
SSD	278,000 (138,000-573,000)	70,000 (34,000-145,000)	695,000 (461,000-1,050,000)	895,000 (505,000-1,268,000)	2.70 (1.33-5.46)	6.42 (4.25-9.70)	8.26 (4.66-11.70)
SUR	3,000 (1,000-6,000)	0 (0-1,000)	7,000 (5,000-13,000)	15,000 (6,000-49,000)	0.47 (0.22-0.95)	1.22 (0.80-2.07)	2.45 (1.03-8.03)
SVK	3,000 (2,000-7,000)	0 (0-0)	30,000 (14,000-108,000)	226,000 (53,000-482,000)	0.06 (0.03-0.13)	0.55 (0.26-1.99)	4.15 (0.97-8.87)
SVN	2,000 (1,000-5,000)	0 (0-0)	16,000 (9,000-44,000)	94,000 (28,000-208,000)	0.12 (0.06-0.23)	0.73 (0.42-2.09)	4.43 (1.34-9.80)
SWE	10,000 (5,000-19,000)	0 (0-1,000)	37,000 (25,000-122,000)	193,000 (34,000-958,000)	0.10 (0.05-0.19)	0.35 (0.24-1.16)	1.84 (0.33-9.11)
SWZ	17,000 (10,000-30,000)	3,000 (2,000-6,000)	62,000 (43,000-88,000)	95,000 (69,000-125,000)	1.49 (0.86-2.64)	5.18 (3.63-7.33)	7.92 (5.78-10.48)
SYR	33,000 (17,000-65,000)	5,000 (3,000-10,000)	125,000 (79,000-314,000)	923,000 (351,000-1,877,000)	0.16 (0.08-0.32)	0.58 (0.37-1.45)	4.27 (1.62-8.70)
TCD	203,000 (98,000-403,000)	57,000 (28,000-115,000)	534,000 (366,000-797,000)	887,000 (494,000-1,377,000)	1.23 (0.59-2.45)	3.06 (2.10-4.57)	5.08 (2.83-7.89)
TGO	31,000 (17,000-58,000)	6,000 (3,000-11,000)	108,000 (75,000-184,000)	326,000 (127,000-651,000)	0.38 (0.21-0.70)	1.24 (0.85-2.11)	3.72 (1.45-7.44)
THA	2,791,000 (1,688,000-4,680,000)	88,000 (52,000-151,000)	7,106,000 (5,190,000-9,803,000)	8,737,000 (6,625,000-11,401,000)	4.11 (2.45-6.73)	9.92 (7.24-13.68)	12.20 (9.25-15.91)
TJK	77,000 (38,000-151,000)	17,000 (9,000-34,000)	277,000 (185,000-421,000)	565,000 (321,000-820,000)	0.83 (0.41-1.63)	2.81 (1.88-4.28)	5.73 (3.26-8.32)
TKM	48,000 (24,000-95,000)	6,000 (3,000-13,000)	162,000 (111,000-251,000)	356,000 (184,000-540,000)	0.79 (0.40-1.59)	2.53 (1.73-3.93)	5.58 (2.88-8.46)
TLS	68,000 (31,000-144,000)	12,000 (5,000-26,000)	156,000 (106,000-241,000)	176,000 (124,000-256,000)	5.40 (2.51-11.06)	11.72 (7.94-18.09)	13.18 (9.29-19.19)
TTO	4,000 (2,000-8,000)	0 (0-0)	12,000 (8,000-25,000)	33,000 (11,000-134,000)	0.28 (0.14-0.58)	0.77 (0.51-1.61)	2.14 (0.71-8.79)
TUN	57,000 (27,000-124,000)	5,000 (3,000-12,000)	144,000 (96,000-244,000)	245,000 (119,000-926,000)	0.49 (0.23-1.04)	1.17 (0.78-1.98)	1.99 (0.97-7.52)
TUR	137,000 (64,000-277,000)	11,000 (5,000-22,000)	574,000 (359,000-1,409,000)	3,166,000 (611,000-7,578,000)	0.17 (0.08-0.34)	0.67 (0.42-1.66)	3.72 (0.72-8.91)
TZA	1,378,000 (878,000-2,250,000)	329,000 (208,000-549,000)	3,516,000 (2,506,000-5,151,000)	5,214,000 (3,768,000-7,074,000)	2.28 (1.45-3.70)	5.45 (3.88-7.98)	8.08 (5.84-10.96)
UGA	483,000 (225,000-949,000)	127,000 (59,000-252,000)	1,342,000 (899,000-1,976,000)	2,386,000 (1,218,000-3,656,000)	1.10 (0.51-2.12)	2.88 (1.93-4.24)	5.12 (2.62-7.85)
UKR	864,000 (432,000-1,731,000)	27,000 (13,000-55,000)	2,502,000 (1,765,000-3,532,000)	3,797,000 (2,633,000-5,352,000)	2.12 (1.07-4.17)	5.77 (4.07-8.15)	8.76 (6.08-12.35)
URY	21,000 (10,000-44,000)	1,000 (0-2,000)	52,000 (34,000-86,000)	85,000 (43,000-272,000)	0.65 (0.31-1.35)	1.52 (1.00-2.51)	2.47 (1.26-7.95)
USA	172,000 (84,000-354,000)	7,000 (3,000-15,000)	808,000 (469,000-3,866,000)	10,959,000 (840,000-32,490,000)	0.05 (0.03-0.11)	0.24 (0.14-1.15)	3.25 (0.25-9.63)
UZB	332,000 (162,000-692,000)	40,000 (19,000-84,000)	993,000 (699,000-1,521,000)	1,966,000 (1,054,000-3,088,000)	1.02 (0.51-2.12)	2.89 (2.04-4.43)	5.72 (3.07-8.99)
VEN	155,000 (73,000-319,000)	16,000 (8,000-33,000)	376,000 (246,000-621,000)	688,000 (318,000-2,226,000)	0.58 (0.29-1.16)	1.34 (0.88-2.21)	2.45 (1.13-7.94)
VNM	3,176,000 (1,656,000-6,070,000)	222,000 (114,000-436,000)	8,620,000 (6,188,000-12,350,000)	10,856,000 (8,295,000-14,449,000)	3.41 (1.81-6.58)	8.81 (6.32-12.62)	11.10 (8.48-14.77)
YEM	131,000 (66,000-255,000)	34,000 (17,000-67,000)	444,000 (296,000-818,000)	1,372,000 (472,000-2,474,000)	0.42 (0.21-0.81)	1.33 (0.89-2.46)	4.12 (1.42-7.43)
ZAF	2,202,000 (1,224,000-3,995,000)	277,000 (150,000-514,000)	6,062,000 (4,491,000-8,421,000)	7,207,000 (5,624,000-9,653,000)	3.89 (2.12-6.92)	10.16 (7.53-14.12)	12.08 (9.43-16.18)
ZMB	346,000 (172,000-715,000)	79,000 (39,000-165,000)	1,032,000 (744,000-1,529,000)	1,512,000 (1,085,000-2,025,000)	1.85 (0.93-3.81)	5.23 (3.77-7.74)	7.66 (5.50-10.25)
ZWE	170,000 (93,000-312,000)	33,000 (18,000-62,000)	616,000 (446,000-907,000)	1,086,000 (786,000-1,473,000)	1.12 (0.61-2.07)	3.81 (2.76-5.62)	6.72 (4.87-9.12)

4.3 Additional analyses

We used the '*Infected'* tunnel states structure to track an infected cohort as it experienced self-clearance and infection year transitions as competing risks, without accounting for infection or reinfection. Self-clearance rates by year per tunnel state were ascertained using a Markov chain Monte-Carlo algorithm (**Table 4.1**).

Table 4.1 Calibrated self-clearance rates by year.

Parameter	Description	Scenarios	
		High self-clearance	**Low self-clearance**
γ_1	Infected – Year 1	1.39 (1.18 – 1.68)	1.61 (1.32 – 1.97)
γ_2	Infected – Year 2	3.92 (2.63 – 5.61)	2.70 (1.74 – 4.08)
γ_3	Infected – Years 3 to 10	0.14 (0.03 – 0.25)	0.29 (0.20 – 0.41)
γ_4	Infected – Years 10+	0.09 (0.05 – 0.30)	0.02 (0.01 – 0.04)

Self-clearance rates by year per tunnel state for each scenario.

4.4 Summary

In this chapter, I used mathematical modelling to account for immunoreactivity reversion, age-specific social mixing patterns, and self-clearance of infection to estimate the global burden of viable *Mtb* infections and their recency. By focusing on recent infections—when the risk of disease progression is highest—we provide a medically actionable target for prioritising populations for TPT. These advancements represent a step forward in understanding the reservoir of infection driving transmission and disease.

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Chapter 5: Tuberculosis screening in the Kolín study

In this chapter, the third research paper of the thesis is presented to address *Objective #3*: to re-evaluate the impact of a historical mass chest radiography (CXR) screening intervention on the reduction of tuberculosis (TB) prevalence. The chapter opens with a concise overview of the research gap, followed by the published paper, and concludes with a brief summary.

5.1 Introduction

Even before the advent of antimicrobial treatment, mass screenings for TB were conducted in cities then considered to have a high TB burden [1]. These interventions aimed to identify individuals earlier in their disease pathway, in an effort to reduce TB mortality and isolate those with TB to curb transmission [1,2]. Typically, these interventions involved large-scale CXR campaigns, which were carried out in various cities and isolated communities from the 1930s to the 1960s [1]. These mass screening efforts were symptom-agnostic, targeting the entire population or specific risk groups regardless of the presence of symptoms commonly associated with TB. Coupled with improved social conditions and housing, these interventions are thought to have contributed to substantial reductions in TB burden, ultimately leading to their discontinuation [3]. However, mass screening faced challenges; while CXR was a useful initial tool for identifying potential lung abnormalities, it was not sufficiently reliable on its own for diagnosing TB [3,4]. Individuals who screened positive on CXR films were typically referred for further investigation, including bacteriological studies, before initiating treatment [3,4]. Additionally, the logistics of sustaining such large-scale efforts proved problematic [3,4].

In 1974, a World Health Organization (WHO) Expert Committee on TB concluded that mass CXR screening had “no significant effect on the occurrence of subsequent smear-positive cases” and deemed it an ineffective and overly costly tool for interrupting transmission [5]. This conclusion shifted focus towards symptom- and bacteriology-based TB diagnosis, stimulated by the availability of treatment, and led to the development of a binary approach to TB. This paradigm dichotomises TB into: latent TB infection, characterised by immunoreactivity without clinical symptoms or microbiological evidence of disease, and active TB disease, marked by symptoms and transmissibility [6,7]. While this framework offered simplicity for diagnosis and treatment allocation, it overlooked the complex natural history of TB, including intermediate states and the infectious period preceding overt disease, thereby limiting its effectiveness in reducing transmission [8].

The historical mass CXR screening programme in Kolín, Czechoslovakia, was among the key studies that informed the report by the Expert Committee [4,9,10]. However, in light of the recognition of the spectrum of TB disease, it is worth reconsidering whether its perceived ineffectiveness was accurately understood [11]. Recent advancements in CXR technology, such as computer-aided detection, along with reduced costs and increased portability of CXR units, have sparked renewed interest in mass CXR screening for TB [3]. As optimal algorithms for population-wide screening are re-evaluated, revisiting the historical evidence of the impact of these interventions on TB burden is both timely and essential.

5.2 Research paper

The following pages contain the Research Paper Cover Sheet, the copyright license, and the published research paper for: *Schwalb A, Emery JC, Houben RMGJ. Use of chest radiography screening for TB: a re-evaluation of the Kolín study. Int J Tuberc Lung Dis. 2022;26: 983–985* [12].

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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	2004111	**Title**	Dr
First Name(s)	Alvaro		
Surname/Family Name	Schwalb		
Thesis Title	Estimating the burden of Mycobacterium tuberculosis infection and the impact of population-wide screening for tuberculosis		
Primary Supervisor	Prof Rein Houben		

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?	International Journal of Tuberculosis and Lung Diseases		
When was the work published?			
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	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 reviewed the published studies on the Kolín study and discussed the findings with Rein Houden. I recreated one of the figures used with help from Jon Emery. 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	Alvaro Schwalb
Date	7 January 2025

Supervisor Signature	Rein Houben
Date	7 January 2025

INT J TUBERC LUNG DIS 26(10):983–985

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LETTER

Use of chest radiography screening for TB: a re-evaluation of the Kolín study

Dear Editor,

Current TB care and prevention policies have resulted in a slow (<2%) annual decline in disease incidence,[1] meaning we are not on track to reach the 2030 Sustainable Development Goals.[2] Historically, mass chest radiography (CXR) screening programmes were widely used, in part because of their sensitivity for pulmonary TB.[3] However, following a 1974 WHO Expert Committee report, mass CXR screening was mostly abandoned in the past half-century. It was concluded that mass CXR screening had "no significant effect on the occurrence of subsequent smear-positive cases" and, given the resource requirements, was not a cost-effective tool to interrupt transmission.[4] One of the key sources cited in support of this viewpoint are the results from a carefully conducted long-term study on mass CXR screening and TB epidemiology in the district of Kolín, Czechoslovakia, from 1960 to 1972.[5–7]

However, because costs for mass CXR screening are rapidly dropping (due to technological advances, such as digitalisation and computer-aided detection of pulmonary abnormalities), we felt it timely to re-evaluate the Kolín study; specifically, whether or not the idea that mass CXR screening does not add epidemiological value still holds up. We re-examined the data from two key publications to address the questions: 1) whether or not there was a decline in TB incidence during the study period, and 2) if there was a decline, to what extent was this due to mass CXR screening. Before the study, the TB burden in Czechoslovakia was high.[6] Kolín District housed approximately 100,000 inhabitants across rural and urban areas, with an annual TB incidence of 151.8 per 100,000 in 1955–1959.[6] The study's objective was to observe epidemiological trends in a region covered by a TB programme over the 12-year study period, which included, among other measures, systematic Bacillus Calmette-Guérin vaccination and treatment, follow-up of cases and repeated mass CXR surveys of the population aged of ≥15 years.[6,7] During the study period, five mass CXR surveys were conducted to obtain several point-prevalence estimates. CXR films were independently and blindly evaluated by two physicians and stored for comparison in subsequent surveys.[6]

To address our first question, we extracted data from a plot of the period prevalence of bacillary pulmonary TB, defined as the number of notified cases (through study procedures) within a calendar year, for the whole study period (Krivinka et al.,[7] p 64). The graph used a logarithmic scale (replicated in the Figure, left), which visually underestimates the decline of total and new cases.[7] However, plotting the data on a linear scale and fitting a linear regression curve to the logarithm of the cases by the least-squares approach (Figure, right), we see that the total number of cases declined annually by 13.6% (95% CI 9.4–17.9). It is worth mentioning that TB prevalence increased noticeably in 1961 due to the first mass examination of the study; further peaks also correspond to years when mass CXR screening took place. The final year of the curve in 1972 also corresponds to a mass screening year, which implies that 1973 would have seen a further drop, mirroring previous patterns. A slightly lower decrease in the number of new cases was observed (annual decline of 10.8%, 95% CI 3.9–18.0). Although the study mainly attributed the overall decline to a drop in prevalence due to the effective treatment of chronic patients (annual decline of 42.8%, 95% CI 37.7–48.2), a substantial reduction in new TB cases was also observed over the whole period. The decline in TB burden also coincided with a period of national economic growth, impacting the socio-economic status of the study population.[8] It is useful to note that the annual decline differed between the two study periods, with a steeper decline in total cases occurring in 1960–1964 (annual decline of 17.2%, 95% CI 9.3–51.3) compared to 1965–1972 (10.6%, 95% CI 1.1–20.9), which suggests that interventions in the study had the largest impact shortly after implementation. Although less striking, it still exceeds the current annual global decline in TB five-fold.[1] Thus, either impact would be welcomed by most, if not all, TB programmes today.

The second question is the extent to which the decline of TB experienced in Kolín was due to mass CXR screening. Ascribing causality is challenging, but it is important to work through. Ideally, CXR screening would identify new cases early, during what we now refer to as the subclinical phase (i.e., before systems develop). Furthermore, the smear status of new cases is more likely to be smear-negative (i.e., have contributed less to transmission).[9] For the period 1960–1964, mass CXR contributed to the

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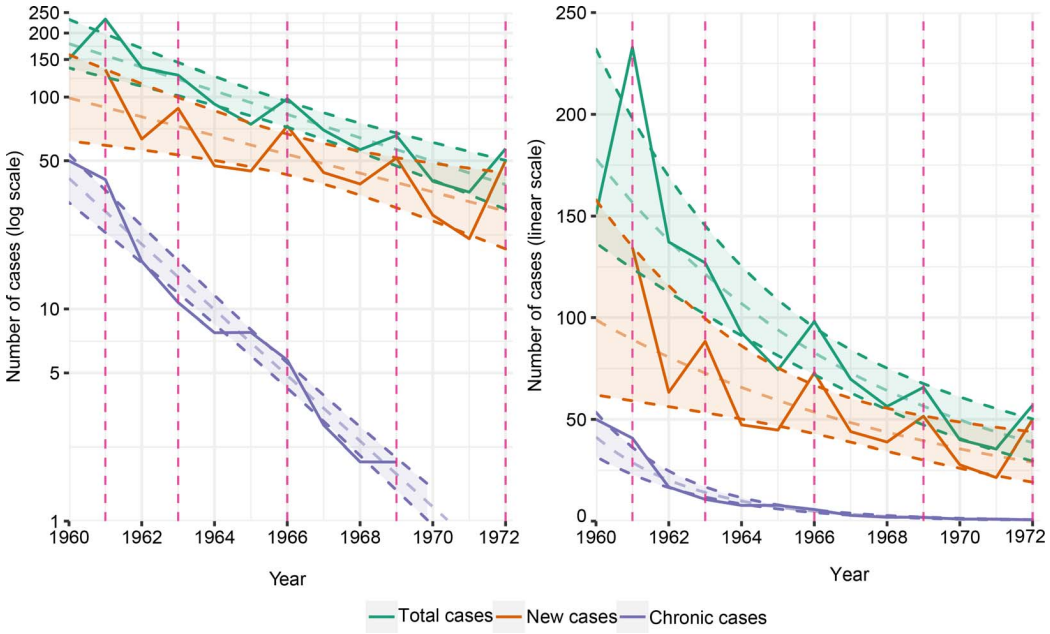

Figure Bacillary pulmonary TB cases in Kolín, Czechoslovakia, 1960–1972. Number of bacillary pulmonary TB cases detected in Kolín, Czechoslovakia, from 1960 to 1972, categorised as total, new (newly discovered cases in a calendar year) and chronic (continuous bacillary excretion for 2 years) cases, with corresponding regression lines. The original figure from Krivinka et al. is shown on the left (log scale), and the adapted figure is shown on the right (linear scale).[7] Dotted vertical lines indicate the year when a mass CXR screening took place. CXR = chest X-ray.

detection of 61% (148/241) of new TB cases, of which (16%, 23/148) were smear-positive (see Appendix Table 10 in Stýblo K, et al.[6]). For the period 1965–1972, the contribution to the detection of new cases declined to 38% (102/270); however, a larger proportion were smear-positive (29%, 30/102; see Table 2 in Krivinka R, et al.[7]). These numbers were interpreted to show that CXR was ineffective at detecting smear-positive cases. However, it is worth highlighting that even in that period, symptom-based passive case-finding contributed to 48% (129/270) of new cases, of which 43% (56/129) were smear-positive cases. One could therefore argue that the effectiveness of CXR screening for detecting new smear-positive cases was not substantially inferior, and nor was it irrelevant for the observed decline. In contrast, the conclusions surrounding the "impracticality" of CXR were fixed on its lack of detection of smear-positive cases. However, this focus prioritised interrupting rather than preventing intensive transmission and therefore warrants closer scrutiny.

As defined in a chapter in *Toman's Tuberculosis*, case detection is the early detection of individuals discharging and transmitting tubercle bacilli that is "carried out in order to treat the sources of infection so as to alleviate their suffering and to render them non-infectious".[5] Based on this description, CXR perfored well by primarily identifying early cases, most of which are less infectious (non-smear-positive), and providing them with timely treatment to prevent future suffering. Nevertheless, in the same chapter Toman considers the Kolín study an example against the effectiveness of mass CXR screening. We would argue that identifying smear-negative, asymptomatic cases could, and maybe should, be regarded as a benefit instead of a limitation.

Aside from the Kolín study, mass CXR screening has shown promise as an effective measure in other settings. In Cape Town, South Africa (1950–1970), a temporary decrease in TB notification rates coincided with population-wide active case-finding using miniature CXR.[10] Since then, the increased availability and reduced cost of CXR have allowed for its wider use, especially in regions with precarious healthcare systems.[3] It may be particularly valuable in settings with a high TB and HIV burden, as CXR is a cost-effective tool for TB screening in HIV-positive individuals.[11] Additionally, complementary use of molecular testing for TB further reduces requirements on infrastructure and costs.[12]

As the TB community looks for new solutions for the persistent global TB problem, we should revisit our beliefs about what historical data can tell us. Although mass CXR screening has challenges, we show here that its historical performance was better than originally perceived.

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5.3 Summary

In this chapter, I re-evaluated the historical mass CXR screening campaign in Kolín, Czechoslovakia, and argue that mass screening played a significant role in reducing TB burden by identifying and treating early TB disease, which, while likely less infectious, still contributed to transmission. Given recent advancements in CXR technology and accessibility, this work highlights the value of reconsidering CXR as a vital tool in current population-wide screening interventions, to prevent transmission and reduce TB prevalence.

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Chapter 6: Population-wide screening for tuberculosis

In this chapter, the fourth research paper of the thesis is presented to address *Objective #4*: to assess the cost-effectiveness of various population-wide screening algorithms and durations using a natural history model of the spectrum of tuberculosis (TB) disease. The chapter opens with a concise overview of the research gap, followed by the preprint, supplementary material, and concludes with a brief summary.

6.1 Introduction

Globally, the net reduction in TB incidence from 2015 to 2023 was 8.3% [1]. During this period, millions of individuals were diagnosed and treated for TB, reflecting substantial efforts in TB care and control [1]. However, this represents a limited decline, far short of the 90% reduction required by 2035 to meet the *End TB Strategy* targets—equivalent to an estimated constant reduction of 10% per year [2]. This slight decline is likely due to an overreliance on passive detection, where diagnosis and care are restricted to individuals experiencing symptoms who then seek and access healthcare [3,4]. Through this approach, individuals are diagnosed and treated after an extended period of infectiousness, contributing to ongoing transmission [5]. Furthermore, this approach does not reach the total people that have fallen ill with TB, with an estimated 40% undiagnosed [1]. Thus, in order to achieve the *End TB Strategy* targets, relying solely on passive detection is insufficient [2,3,5]. In contrast, population-wide screening aims to find and treat individuals with TB disease earlier in their disease pathway or those who would otherwise not have sought care [3,6]. Symptom-agnostic population-wide screening extends access to care to vulnerable populations and can overcome patient costs associated with diagnosis, which often hinder access to healthcare [8]. When implemented intensively and consistently over multiple years within a community, it has also been shown to reduce TB prevalence by shortening the period of infectiousness and cutting onward transmission [6,7].

Viet Nam is listed among the 30 high TB burden countries with estimates pointing to over 10,000 individuals falling ill with TB annually [1,9]. Despite concerted efforts to assess and address the TB burden, it has only decreased marginally over a 10-year period as shown in the TB prevalence surveys conducted between 2007 and 2017 [10–12]. In the search for more effective strategies, the ACT3 trial was undertaken, implementing annual, community-wide screenings across a span of three years [13]. It employed the Xpert MTB/RIF (Cepheid, USA) assay, a nucleic acid amplification test (NAAT), taking a symptom-agnostic approach that is similar to historic mass screening implementations [13]. Notably, ACT3 resulted in a significant reduction

in the prevalence of pulmonary TB within communities where the intervention was conducted, compared to those relying on passive detection [13]. However, despite the evident promise of this intervention, its implementation as a central component of TB elimination strategies remains under debate. The challenge lies in determining the optimal implementation of population-wide screening—including the ideal duration and algorithm—which is crucial to ascertain the most cost-effective approach to reducing the TB burden.

6.2 Research paper

The following pages contain the Research Paper Cover Sheet, the copyright license, the preprint of the research paper, and the supplementary material for: *Schwalb A, Horton KC, Emery JC, Harker MJ, Gosce L, Veeken LD, et al. Potential impact, costs, and benefits of population-wide screening interventions for tuberculosis in Viet Nam: a mathematical modelling study. medRxiv. 2024. DOI: 10.1101/2024.12.30.24319770* [14].

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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	2004111	**Title**	Dr
First Name(s)	Alvaro		
Surname/Family Name	Schwalb		
Thesis Title	Estimating the burden of Mycobacterium tuberculosis infection and the impact of population-wide screening for tuberculosis		
Primary Supervisor	Prof Rein Houben		

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?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The Lancet Global Health
Please list the paper's authors in the intended authorship order:	Alvaro Schwalb, Katherine C. Horton, Jon C. Emery, Martin J. Harker, Lara Goscé, Lara D. Veeken, Frances L. Garden, Hai Viet Nguyen, Thu-Anh Nguyen, Khanh Luu Boi, Frank Cobelens, Greg J. Fox, Dinh Van Luong, Hoa Binh Nguyen, Guy B. Marks, Rein M.G.J. Houben

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 led the conceptualisation of this study together with Rein Houben and Guy Marks. I developed the methodology in consultation with several of my co-authors. I adapted the spectrum of TB model with Jon Emery, based on the work by Katherine Horton. I conducted the model calibration with assistance from Andrew Iskauskas (acknowledged in the paper). I designed the screening algorithms in collaboration with Katherine Horton and Rein Houben. I revised and established specific test positivity values in collaboration with Lara Veeken, Katherine Horton, and Rein Houben. I performed the analysis, model runs, and sensitivity analyses for the study. For the cost-effectiveness analysis, I received guidance on conducting, interpreting, and reporting from Martin Harker and Lara Gosce. I prepared the results and drafted the first complete version of the paper, subsequently revising it based on feedback from co-authors. Finally, I submitted the manuscript to the preprint server.

SECTION E

Student Signature	Alvaro Schwalb
Date	7 January 2025

Supervisor Signature	Rein Houben
Date	7 January 2025

Potential impact, costs, and benefits of population-wide screening interventions for tuberculosis in Viet Nam: a mathematical modelling study

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Keywords: active detection; cost-effectiveness; subclinical; TB elimination

Abstract

Background: Population-wide screening may accelerate the decline of tuberculosis (TB) incidence, but the optimal screening algorithm and duration must weigh resource considerations.

Methods: We calibrated a deterministic transmission model to TB epidemiology in Viet Nam. We designed three population-wide screening algorithms from 2025: sputum nucleic acid amplification tests (NAAT, Xpert MTB/RIF Ultra) only; chest radiography (CXR) followed by NAAT; and CXR-only without microbiological confirmation. We determined the annual screening rounds required to reduce pulmonary TB prevalence below 50 per 100,000 people. Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs), representing the additional costs (in US$) per disability-adjusted life year (DALY) averted compared to business-as-usual by 2050. Additionally, we evaluated the impact of NAAT cartridges costing US$1 each.

Findings: NAAT-based algorithms required at least six rounds to reach the prevalence threshold, while CXR-only required three. NAAT-only achieved a prevalence reduction consistent with the ACT3 trial after three rounds. The CXR+NAAT algorithm averted 4.29m DALYs (95%UI:2.86-6.14) at US$225 (95%UI:85-520) per DALY averted compared with business-as-usual. The front-loaded investment of US$161m (95%UI:111-224) annually during the intervention resulted in average annual cost savings of US$12.7m (95%UI:6.7-21.4) up to 2050 compared to the business-as-usual counterfactual. Reducing the cost of NAAT to US$1 led to a 50% and 15% reduction in budget impact and a 63% and 26% reduction in the estimated ICER for the NAAT-only and CXR+NAAT algorithms, respectively.

Interpretation: In Viet Nam, population-wide screening could achieve ambitious policy goals. Substantial front-loaded investment is immediately followed by persistent cost savings and could be further offset by more affordable NAATs.

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Research in context

Evidence before this study

Community-wide screening interventions for tuberculosis (TB) have historically been implemented in countries that are now considered low-burden. It has been hypothesised that such interventions could significantly alter TB epidemiology in current high-burden settings if applied with multiple screening rounds and broad coverage. A recent systematic review identified two contemporary cluster-randomised trials evaluating the effect of screening interventions on TB prevalence. The ACT3 trial in Viet Nam demonstrated a significant reduction in microbiologically confirmed TB prevalence after three annual rounds of screening with Xpert MTB/RIF for all, regardless of symptoms. In contrast, the ZAMSTAR trial in Zambia and South Africa, which used symptom-based screening with sputum smear microscopy, did not show a reduction in TB prevalence, highlighting that the screening algorithm employed plays a role in the impact of the intervention.

Added value of this study

This study assessed the impact and cost-effectiveness of annual rounds of different population-wide screening algorithms using a mathematical model calibrated to TB epidemiology in Viet Nam. The model incorporated recent insights into the spectrum of TB disease, including self-clearance of *Mycobacterium tuberculosis* infection, the presence of unconfirmed, asymptomatic infectious, and symptomatic infectious TB, and the relative contribution of asymptomatic TB to transmission. We evaluated the epidemiological impact—assessed by cumulative TB incidence, TB deaths, and DALYs—along with the associated costs, including budget impact, the cost of front-loading for the duration of the intervention, and average annual cost savings over the time horizon, to inform policy decisions in a high TB burden setting. Additionally, sensitivity analyses allowed us to assess the impact of using alternative tests and reducing their associated costs.

Implications of all the available evidence

A substantial reduction in TB prevalence may be achieved by repeated annual rounds of symptom-agnostic, population-wide screening. A two-step algorithm, which uses chest radiography as an initial screen followed by sputum nucleic acid amplification test, is expected to avert 1.31 million individuals developing incident TB and 171,000 dying from TB by 2050. Despite an estimated budget impact of US$1,478 million and annual intervention-specific costs of US$161 million, annual savings of US$12.7 million begin immediately after the intervention

ends and are expected to be sustained well beyond 2050. These findings underscore the need to integrate proactive strategies into existing TB prevention and care practices and consider long term financial and health benefits. Furthermore, they illustrate how rapid achievement of ambitious policy goals can be accomplished through front-loaded investments.

Introduction

Despite a slight decline in tuberculosis (TB) incidence of approximately 2% over the past decade, an estimated 10 million people still fall ill with TB each year.[1] Worldwide, the conventional approach to TB prevention and care is passive detection, where diagnosis and treatment are only provided to individuals with symptoms who seek and receive healthcare.[2–4] This approach results in a large gap of undiagnosed individuals,[1] as not everyone with TB experiences symptoms or is able to access care.[5] Furthermore, due to the long duration and undulating pattern of TB, it also results in onward transmission before diagnosis and treatment.[6] Thus, in order to achieve ambitious *End TB Strategy* targets,[7] relying solely on passive detection is insufficient.[3,6] In contrast, population-wide screening aims to interrupt transmission by finding and treating individuals with TB disease who otherwise would be diagnosed later or not at all through the usual patient-initiated pathway.[2,3] Theoretically, when implemented intensively and consistently over multiple years, this approach could reduce TB prevalence and incidence by providing earlier treatment, shortening the period of infectiousness and breaking the chain of transmission.[2,8,9]

Population-wide screening is not a novel approach; it has previously been employed in countries now considered to have a low TB burden.[10] Screening campaigns using mobile chest radiography (CXR) units were conducted as early as the 1930s, with remarkable results across different settings.[10–15] More recently, the ACT3 trial, conducted in Viet Nam from 2014 to 2018, implemented annual, community-wide screening over three years, using a symptom-agnostic approach similar to historic screening efforts.[16] Notably, the trial demonstrated a significant reduction in the prevalence of pulmonary TB in the communities where screening was employed, compared with those utilising routine, passive detection methods alone.[16] It also observed a 57% reduction in incident TB episodes over three successive annual cohorts.[17] This outcome provides contemporary evidence of the tangible impact of population-wide screening, underscoring the importance of introducing proactive measures into current approaches to TB prevention and care.

Although population-wide screening shows evident promise, its implementation as a central component of TB elimination strategies in high TB burden countries like Viet Nam remains under debate. A major challenge lies in determining the optimal way to implement these strategies—including the ideal duration and frequency of repeated screening, and the most appropriate screening algorithm. Resolving these factors is crucial to ascertaining the most

effective approach to reducing the TB burden, both in terms of incident TB and deaths averted. Furthermore, population-wide screening requires significant investment, thus scaling up its implementation must consider the substantial front-loaded costs, including financial and human resources.[9] We sought to identify the most effective algorithm and duration of population-wide screening necessary to achieve a significant reduction in TB prevalence in Viet Nam, while weighing the short-term economic costs with long-term savings of reduced incident TB episodes.

Methods

Model structure

Previous modelling work has emphasised the need for enhanced TB screening and diagnosis of individuals;[17–19] nonetheless, it did not fully account for the spectrum of TB disease and the nature of transmission from individuals with asymptomatic TB.[20–22] To address this, we developed a deterministic transmission model of TB natural history that incorporates recent advances in quantifying the spectrum of TB disease,[20,23] including self-clearance of *Mycobacterium tuberculosis* (Mtb) infection and the relative contribution of asymptomatic TB to transmission.[22,24] We represented the natural history of TB using nine compartments, reflecting the progression of *Mtb* infection along a spectrum from susceptibility to various states for disease and treatment (**Figure 1**). The three disease states were defined as follows: (i) unconfirmed TB, representing individuals with inflammatory pathology prior to bacteriological evidence of TB disease or symptoms; (ii) asymptomatic TB, representing individuals with bacteriological evidence of TB disease who do not report symptoms during screening; and (iii) symptomatic TB, representing individuals with bacteriological evidence of TB disease who do report symptoms during screening. The disease state classification was informed by the ICE-TB framework, and naming follows current World Health Organization (WHO) definitions.[25,26] Additional model states, parameterisation, and model equations are described in detail in **Supplementary Materials SM1-2**. The model was constructed using R v4.2.3 for statistical computing and graphics.[27]

Model calibration

We calibrated the model to TB epidemiological data from Viet Nam using history matching with emulation, facilitated by the *hmer* R package (further details in the **Supplementary Materials SM3**).[28] Calibration targets included TB prevalence, TB mortality rate, TB notification rate, and the proportion of prevalent infectious disease that is asymptomatic, each set for at least two

distinct years (**Table S1**).[22,29–32] Ranges for priors and sources are shown in **Table S2**. Posterior parameter sets are presented as median values with corresponding 95% uncertainty intervals (95% UI), calculated as the 2.5th to 97.5th percentiles of the parameter sets, to quantify uncertainty.

Interventions

We simulated the population impact of different screening algorithms and durations as compared with the business-as-usual (BAU) counterfactual (see details in **Supplementary Materials SM4**). In the counterfactual scenario, we assumed that TB trends would follow the calibration trajectory, reflecting the ongoing provision of TB treatment and prevention services through routine passive detection, including a limited amount of individual or high-risk group-focused screening interventions (i.e., contact tracing, HIV screening) currently offered by the National TB Programme (NTP) of Viet Nam. Compared with the BAU baseline, we evaluated three population-wide screening intervention algorithms, all implemented regardless of whether individuals reported symptoms: (i) using a nucleic acid amplification test (NAAT, Xpert MTB/RIF Ultra) only, (ii) a two-step approach using digital CXR with computer-aided diagnosis software interpretation, followed by NAAT for those with imaging abnormalities and (iii) using CXR only. NAAT-based algorithms were performed upon expectorated sputum. For all three algorithms, a positive screen led to treatment initiation, with no additional bacteriological test or clinical assessment performed prior to treatment. We selected 2025 as the earliest year when population-wide screening interventions could be implemented and assumed the entire adult population of Viet Nam would be eligible for screening. The population was uniformly screened across all model states, with no increased probability of screening for individuals with TB disease. Additionally, we assumed that every individual with infectious TB (i.e. asymptomatic and symptomatic) would be able to provide a sputum sample, but only 60% of those with other model states would be able to do so.[16] An exception was made under the CXR+NAAT algorithm, where we assumed that all individuals who screened positive to CXR would also be able to provide sputum, given radiological evidence of disease.

Probability of a positive test

Screening was implemented based on the probability of a positive test for each model state according to the screening tool used; for the two-step algorithm, these probabilities were multiplied (**Table 1** and **Table S3**). Probabilities were independently sampled from uniform distributions for each model run.

Epidemiological outcomes

We sought to determine the number of repeated annual rounds of population-wide screening needed for the TB prevalence to fall below 50 per 100,000 people using each algorithm. To assess this, we focused solely on the median value of the model outputs, deeming the threshold met if the median fell below or was within 10% above the target, regardless of the uncertainty interval. Once the TB prevalence threshold was reached, we assumed the screening intervention would cease, and the model would revert to the BAU standard of care. We estimated the number of incident TB episodes and deaths averted compared with the BAU counterfactual. TB prevalence was defined as the sum of individuals with asymptomatic and symptomatic TB, while incident TB referred to the flow into symptomatic TB. To evaluate the performance of each screening algorithm, we also estimated the ratio of true positives (positive tests for unconfirmed, asymptomatic, and symptomatic TB) to false positives (positive tests for non-disease states) treated. Additionally, we compared our model outputs with the results of the ACT3 trial by assessing the proportional reduction of TB prevalence after three rounds of community-wide screening with NAAT compared with BAU.[16] We set a time horizon of 2050 to balance recency with a sufficient duration for benefits to accrue.

Cost outcomes

We took a simple and conservative provider approach to cost outcomes, broadly considering treatment and diagnosis in BAU and the various screening algorithms. To estimate the costs for the BAU passive detection counterfactual, we obtained cost estimates per individual from the NTP in Viet Nam (**Table S4**). These included the average cost of TB treatment, covering expenditure for TB drugs, personnel, bacterial monitoring and overheads; it did not include costs associated to the management of adverse events due to treatment. The average cost of passive TB diagnosis accounted for the number needed to test, personnel costs, infrastructure, and actual test costs. All costs were categorised based on drug susceptibility i.e., drug-susceptible or drug-resistant TB. Population-wide screening costs for each intervention algorithm were provided from the ACT3 trial and the ongoing ACT5 trial (**Table S5**).[16,33] These unit costs account for the number of tests performed, field staff, lab technicians, data managers, and consumables. For the main analysis, all cost estimates were independently sampled from gamma distributions, generated using the mean cost and a standard deviation of 20% of the mean value. All costs are presented in 2023 United States dollar (US$).

Summary health outcomes

We estimated disability-adjusted life years (DALYs) averted in the simulated algorithms compared with the BAU baseline to quantify the health gains achieved by population-wide screening interventions (see details in **Supplementary Materials SM5**). Both DALYs due to symptomatic TB and post-TB sequelae were considered, using country-specific data on total DALYs in 2019 from Menzies et al.[34] We calculated the estimated lifetime DALYs per person with TB by accounting for the number of incident TB in Viet Nam in 2019.[30,34] We then used the weighted average age of individuals with TB in Viet Nam and estimated the proportion of the lifetime that would be lived from 2025 to 2050. We estimated that 6.6 DALYs (95%CI: 4.8-9.0) would be incurred per incident TB episode (including the resulting post-TB sequelae) in 2025, varying depending on the age at which they experience TB. No disability weights were applied for other disease or treatment states and transitions. DALYs were independently sampled from a uniform distribution of the ranges discounted at 3% per year.[31] We did not account for DALYs accrued during earlier disease states or due to adverse events associated to treatment.

Summary cost-outcomes

We calculated the budget impact of each algorithm and the BAU counterfactual as the cumulative costs of treatment and screening/diagnosis for both BAU and the intervention up to 2050. The cost of front-loading was defined as the intervention-specific screening and treatment costs incurred, presented both as total cumulative costs and as annual averages over the intervention period. Additionally, we defined annual cost savings as the difference between BAU-specific diagnosis and treatment costs under the screening algorithms and the BAU counterfactual, averaged across the time horizon.

Cost-effectiveness analysis

We calculated the incremental cost-effectiveness ratio (ICER) for each screening algorithm relative to the BAU counterfactual as well as in comparison with one another. The resulting ICERs were expressed as the cost per DALY averted associated with the screening intervention and these were evaluated in relation to an estimated cost-effectiveness threshold range of US$2,176 to US$3,283 in Viet Nam, based on a GDP per capita of US$3,817 in 2023.[35] We excluded interventions from consideration based on simple dominance, where an alternative intervention was both more effective and less costly than the comparator, and extended dominance, where an alternative was more effective and more costly but offered better value for money (i.e., lower ICER) than the comparator.[37]

Sensitivity analyses

We performed several sensitivity analyses to test our model and assumptions. Firstly, we evaluated the cost effectiveness of reducing the unit price of NAAT cartridges from US$8 to US$1 (**Table S5**); no price reduction was applied for CXR use. Secondly, for each algorithm we explored the number of rounds needed and the resulting impact on disease burden and cost-effectiveness of targeting two alternative TB prevalence thresholds: 100 or 20 per 100,000 people. Thirdly, we assessed the performance of using Xpert MTB/RIF instead of Xpert MTB/RIF Ultra in an alternative NAAT-only algorithm to evaluate the impact of a lower probability of a positive test on non-disease states (due to higher specificity) and disease states (due to lower sensitivity) (**Table S3**). Fourthly, we evaluated the impact of further investigation for individuals who screened positive in each algorithm, assuming that in practice additional steps such as further investigation, additional imaging, or sputum culture would be performed prior to initiating treatment. These measures are intended to guide appropriate treatment decisions, ensuring effective resource utilisation and minimising potential harm to individuals. In absence of clear data from the literature, we used performance of prolonged cough as a proxy (see **Table S3**) and assumed a fixed cost of US$2 per individual. Finally, we evaluated CXR-based algorithms, assuming reduced CXR test positivity for unconfirmed and asymptomatic TB, equivalent to its performance in individuals who have recovered or been treated (**Table 1** and **Table S3**).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Model calibration

Model calibration generated 1,000 non-implausible parameter sets. **Figure 2** shows model runs with fitted parameters compared against calibration targets. The median and corresponding 95% uncertainty intervals (95%UI), calculated as the 2.5th to 97.5th percentiles, of the posterior parameter distributions, are presented in **Table S2**.

Rounds required to reach TB prevalence thresholds

At least six annual rounds of population-wide screening were needed to reach a TB prevalence of 50 per 100,000 people under the NAAT-only algorithm and eight for the CXR+NAAT algorithm (**Table 2** and **Figure S2**). In contrast, under the CXR-only algorithm, treating everyone with radiological abnormalities without microbiological confirmation resulted in a similar decline of TB prevalence after three annual rounds. Under BAU, the threshold was not reached within the time horizon. Additionally, we compared the performance of the NAAT-only algorithm, as simulated by our model, with the observed impact of the ACT3 clinical trial, which utilised the same screening algorithm. After three years of population-wide screening with the NAAT-only algorithm, we estimated a proportional reduction in TB prevalence of 58.7% (95%UI: 52.9-65.0), which sits between the reduction in prevalence seen in the intervention clusters and the comparison with the control clusters observed in the ACT3 trial of 67.7% (95%UI: 64.0-71.2) and 42.1 (95%UI: 36.7-47.1%), respectively (**Figure S3**).

Epidemiological impact of interventions

All screening algorithms resulted in lower cumulative TB incidence, TB deaths, and DALYs compared with BAU between 2025 and 2050 (**Table 2**). The cumulative TB incidence under both NAAT-based algorithms was similar, with 0.95 million (95%UI: 0.63-1.31) and 0.93 million (95%UI: 0.63-1.29) individuals projected to fall ill with TB under the NAAT and CXR+NAAT algorithms, respectively. Notably, TB incidence was further reduced under the CXR-only algorithm, with a cumulative TB incidence of 0.51 million (95%UI: 0.36-0.71). A similar trend was observed in cumulative TB deaths and DALYs (**Table 2**). Although implemented for only three annual rounds, the CXR-only algorithm correctly diagnosed 1.17 million (95%UI: 0.80-1.56) individuals with TB, with the majority having unconfirmed TB (0.93 million; 95%UI: 0.60-1.31). However, this algorithm also resulted in a high number of diagnoses among non-disease individuals, with 31.6 million (95%UI: 24.2-38.2) individuals screened positive, yielding a true-positive (TP) to false positive (FP) ratio of 1:27. In contrast, the NAAT-based algorithms detected around half as many individuals with TB: 555 thousand (95%UI: 411-688) under the NAAT algorithm and 578 thousand (95%UI: 419-736) under the CXR+NAAT algorithm. The NAAT-only algorithm also diagnosed more FPs (2.8 million; 95%UI: 2.1-3.7) than TPs, resulting in a TP:FP ratio of 1:5. However, the two-step CXR+NAAT algorithm reduced the number of FPs overall (1.7 million; 95%UI: 1.0-2.7), leading to a TP:FP ratio of 1:3.

Cost impact of interventions

Total intervention costs were substantial, with the CXR-only algorithm requiring US$3.0 billion (95%UI: 1.9-4.4), followed by the NAAT-only algorithm at US$2.8 billion (95%UI: 2.0-3.8) and the two-step CXR+NAAT algorithm at US$1.5 billion (95%UI: 1.1-2.0) (**Table 2**). The cost of front-loading for the CXR-only algorithm was estimated at US$949 million (95%UI: 606-1,415) per year for the three years of the intervention, with projected annual cost savings of US$15.6 million (95%UI: 9.2-24.7) on average from 2025 to 2050. Similarly, the NAAT-only algorithm incurred US$427 million (95%UI: 299-599) in annual intervention-specific costs during the six years of intervention, resulting in average annual cost savings of US$12.3 million (95%UI: 6.5-21.4). The CXR+NAAT algorithm required US$1.3 billion (95%UI: 1.0-1.8) of intervention-specific costs, averaging US$161 million (95%UI: 111-224) per year for the first eight years, before becoming cost saving at US$12.7 million (95%UI: 6.7-21.4) annually compared to the BAU counterfactual (**Table 2** and **Figure S4**). Trends of annual cost savings suggest they will continue beyond the 25-year time horizon. For NAAT-based algorithms, the majority of costs were associated with screening procedures, accounting for 88.9% (95%UI: 81.6-93.2) of total costs in the NAAT-only algorithm and 84.2% (95%UI: 72.7-91.1) in the CXR+NAAT algorithm. In contrast, in the CXR-only algorithm, only 9.3% (95%UI: 5.4-15.8) of the total costs were related to screening, with the vast majority spent on treating individuals who screened positive.

Cost-effectiveness analysis

Estimated ICERs against the BAU for all algorithms were below the estimated cost-effectiveness threshold range for Viet Nam. The CXR+NAAT algorithm averted 4.29 million DALYs (95%UI: 2.86-6.14) compared with BAU at an additional cost of US$967 million (95%UI: 523-1,488), giving an ICER of US$225 (95%UI: 85-520) per DALY averted. The CXR-only algorithm provided even greater effectiveness by averting an additional 1.61 million DALYs (95%UI: 0.86-2.56) compared with CXR+NAAT, but at double the total cost (US$2,954 million; 95%UI: 1,909-4,370), leading to an ICER of US$927 (95%UI: 393-1,124) per DALY averted compared with the CXR+NAAT algorithm (**Table 2** and **Table 3**), which is also well below the cost-effectiveness threshold range. The NAAT-only algorithm was dominated by the other two alternatives, which were collectively cheaper and more effective.

Sensitivity analyses

The performance of the algorithms under the different sensitivity analyses are shown in **Table 2** and **Table S6-9**. Firstly, lowering the unit price of NAAT to US$1 reduced screening costs, bringing the total costs to US$1.3 billion (95%UI: 1.0–1.8) and US$1.2 billion (95%UI: 0.9–1.6) in

the NAAT-only and CXR+NAAT algorithms, respectively—an approximate reduction of 50% and 15% (**Table 2**). In terms of ICERs, this reduction was 63% for the NAAT-only algorithm and 26% for the CXR+NAAT algorithm (**Table 2**). In the cost-effectiveness analysis, the NAAT-only algorithm was still dominated despite this reduction in cartridge unit cost, with CXR-only remaining cost effective compared to all alternatives (**Table S10**). Secondly, the relative epidemiological impact of the algorithms—assessed by cumulative TB incidence, TB deaths, and DALYs—remained consistent across different TB prevalence thresholds. However, the number of annual rounds required varied, ranging from two to three to achieve a prevalence of 100 per 100,000 and from four to twelve to achieve 20 per 100,000 (**Tables S6 and S7**). Thirdly, the use of Xpert MTB/RIF in an alternative NAAT-only algorithm was found to be less effective and more expensive than all three standard algorithms in the cost-effectiveness analysis (**Table S10**). Fourthly, the addition of further investigation post-screening reduced the cumulative number of FPs across all algorithms, particularly in the CXR-only algorithm, where apparent FPs decreased by 90% compared to the main analysis (**Table S8**). Given the reduced costs associated with the reduction in people treated, the CXR-only algorithm resulted in an ICER of US$113 (95%UI: 28-278) per DALY averted when compared to the BAU. For this analysis, CXR+NAAT averted more DALYs than CXR-only, at an ICER of US$1,293 (95%UI: 1,153-1,555) per DALY averted, while NAAT-only was marginally the most effective, but at a high additional cost, giving an ICER compared on CXR+NAAT well above the cost-effectiveness threshold range (**Table S10**). Finally, with revised CXR sensitivity, the CXR+NAAT algorithm required one additional round to reach the 50 per 100,000 people TB prevalence threshold (**Table S9**). Despite this, it only resulted in slight increase of the ICER compared to the BAU of US$283 (95%UI: 113-640) per DALY averted (**Table S10**).

Discussion

The study evaluates the implementation of various population-wide screening algorithms in order to achieve considerable reductions in TB prevalence in Viet Nam. While ambitious, these goals are aligned with the *End TB Strategy* targets,[7] to which Viet Nam has committed. All three screening algorithms significantly reduced the TB burden compared to BAU, with the CXR-only algorithm achieving the greatest reductions in TB incidence, deaths, and DALYs. However, its high overtreatment rates made the two-step algorithm—combining CXR with a confirmatory NAAT—a more efficient option, averting a substantial number of DALYs at a relatively low cost. These outcomes are contingent on substantial front-loaded investments during the intervention, although reductions in NAAT cartridge costs can help offset these expenses.

Ultimately, all interventions resulted in persistent annual cost savings compared to the BAU counterfactual up to 2050, with trends suggesting sustained savings beyond this period. The findings from this modelling exercise underscore the effectiveness of symptom-agnostic population-wide screening and provide guidance for implementing such large-scale strategies in high TB burden settings.

At face value, the CXR-only algorithm appears to be the most cost-effective option, achieving the greatest TB burden reduction with an ICER below the estimated cost-effectiveness threshold range.[35] However, several factors raise legitimate concerns about its suitability. Firstly, its epidemiological impact results in treating a large number of individuals with FP screens, which, while occurring in very few cases, carries risks such as serious adverse events, including hepatotoxicity,[50] potentially offsetting the DALYs averted and leading to higher ICERs. Secondly, the CXR-only algorithm is the most expensive intervention over the 25-year time horizon, requiring substantial front-loaded investment of nearly US$1 billion annually during the initial years. While cost savings would be realised after the short intervention period, such funding demands in the medium-term could pose challenges. In contrast, the CXR+NAAT algorithm reduces the annual economic strain to US$160 million per year, albeit over a longer duration, ultimately resulting in a lower budget impact. Lastly, while the investment appears cost-effective within the estimated threshold range of US$2,176 to US$3,283,[35] Viet Nam has no official policy threshold, and judgements on what is affordable must therefore be made by national health decision-makers.

When comparing against the outcomes of the ACT3 trial, we observed that our model shows a similar impact in the proportional reduction of TB prevalence.[16] Given this, our model was able to extrapolate empirically validated methods for rapidly reducing TB burden to explore various algorithms and durations for population-wide screening interventions in Viet Nam. However, our modelling focused on screening but did not explore other used measures that could be implemented on top of population-wide screening, such as TB preventive therapy for household contacts, social protection, or a generally more holistic approach that also addresses other structural determinants of TB.[41–43] Furthermore, our modelling assumed that after achieving intended TB prevalence thresholds, population-wide screening interventions are stopped, and TB care and prevention return to BAU. However, to sustain the momentum, alternative, more targeted approaches may then enable prevalence to decline to the level required for TB elimination, in accordance with the *End TB Strategy* targets.[7] Interventions such as contact and

cluster investigations and targeted treatment of *Mtb* infection are likely to be more successful and more feasible in the context of the substantial reduction in both prevalence and incidence of TB once the threshold has been reached. Furthermore, we did not account for the catastrophic costs prevented, the economic contributions of individuals who remain healthy or alive, or the accumulating benefits beyond 2050 under BAU. Hence, the realistic long-term benefits of the intervention are likely strongly underestimated in this analysis.

Opting to use symptom-independent diagnostic methods helps to overcome the considerable limitations of conventional diagnostic and referral pathways. However, a challenge encountered relates to the diagnostic accuracy of these test—particularly specificity—in the context of population-wide screening interventions.[44] The cost-effectiveness of mass screening is linked to the ability of a test to accurately diagnose, as false positive diagnoses can drive up treatment costs, as illustrated by the CXR only scenario.[45] This could largely be overcome by explicitly introducing further investigations post-screening as shown in our sensitivity analysis or by implementing confirmatory sputum culture for those testing positive on NAAT, coupled with ongoing surveillance for those who are negative on culture. As a case study, while our results indicate that CXR alone could rapidly reduce TB prevalence after a few annual rounds, this strategy is not feasible at present without an affordable, ideally non-sputum confirmatory test to establish the presence of viable *Mtb* as the cause of the pathology. Furthermore, the health consequences and social unacceptability of large-scale overtreatment would currently impede its recommendation.

A major strength of our study is that the natural history TB model used recognises earlier states of disease before symptomatic disease, adapting features of previously published models,[20,23] and its use matches empirical data of community screening.[16] Encompassing the spectrum of TB within this framework provides insight into the impact of screening interventions according to disease state. This is not only the case for asymptomatic TB and its recognised contribution to transmission,[22] but also that of unconfirmed TB, a state where macroscopic evidence of disease can be detected and there is risk of further progression. An example of the large reservoir of unconfirmed TB disease can be seen as the bounce back in prevalence once screening rounds stopped, reflecting the importance of detection and treatment beyond infectious TB disease.[47]

Our study also has limitations. Firstly, our study highlighted how we have limited insight into test performance when used in communities. Estimates based on pooled diagnostic accuracy from clinical settings tend to underestimate the specificity of the test when applied to a community setting;[48] thus values for non-disease states were used based on the performance of the test in selected population studies.[44,49] Similarly, clinic-based estimates likely overestimate sensitivity.[48] Sensitivity analyses, incorporating changes to test positivity or the addition of a further investigation step after screening, help to explore and validate the potential impact of these interventions. Secondly, our study did not account for the DALYs accrued due to overtreatment of the screened population as discussed above. Nonetheless, we are also likely underestimating the impact of screening on averting DALYs, as we only accounted for incident symptomatic TB, but did not look into the effect of these interventions on early TB disease diagnosis. Thirdly, our costing approach was simple in that we opted to obtain costs per individual screened and treated. Further granularity of the cost components would provide a deeper understanding of both the distribution of the intervention costs as well as that of costs averted under BAU. Additionally, our costing assumptions for conducting the interventions were centred around consumables and human resources but overlooked other sources of costs, including training and other scale-up activities prior to commencing the intervention. These costs are not negligible, especially in the start-up phase,[51] and should be reflected for investment case for screening interventions. Fourthly, our model does not encompass or adjust based on key drivers of TB. Tuberculosis is a biosocial problem that unevenly impacts people of low socioeconomic status, likely given the greater exposure to many risk factors such as malnutrition, air pollution, and overcrowding.[52,53] Lastly, further exploration of post-TB respiratory disease is warranted. The number of TB survivors is immense, and proper assessment of healthcare-associated use and costs due to lingering morbidity of existing and not-prevented TB episodes under BAU needs to be considered especially when implementing large interventions.[54]

Conventional symptom-centred, facility-based TB detection is insufficient.[6] Instead, proactive screening should complement existing routine passive detection. While Viet Nam currently implements active screening of limited high-risk populations, such as people living with HIV and close contacts of people with diagnosed TB, screening will need to extend beyond high-risk groups that only represent a limited fraction of prevalent TB. Sustained, multiple rounds will be required to ensure effectiveness.[8] Continuing the current strategy without significant enhancements is likely to result in a grave cost of inaction, causing TB to remain as serious a

threat as it currently stands.[38,39] Instead, the resources required to sustain BAU care would be better invested in a short-term strategy of repeated population-wide screenings. Immediate efforts must focus upon overcoming initial logistical challenges to scaling-up, such as developing infrastructure and human resource capacity required to support population-wide screening. In parallel, efforts to enhance acceptability of large-scale screening by the community should be conducted. Prioritising population-wide screening will make significant strides towards reducing TB prevalence and would set an example for global TB elimination efforts. In conclusion, this modelling study has demonstrated pathways to rapidly reducing TB prevalence in Viet Nam, through population-wide screening. The cost of front-loading in these interventions promises to reduce morbidity and mortality and realise the *End TB Strategy* at a time when BAU is unlikely to reach the agreed targets.

Contributors

Conceptualisation: GBM and RMGJH. Methodology: AS, KCH, JCE, MJH, LG, LDV, and RMGJH. Data curation: AS, KCH, JCE, MJH, LG, LDV, and RMGJH. Investigation: AS, KCH, JCE, MJH, LG, LDV, and RMGJH. Formal analysis: AS and JCE. Supervision: KCH, GBM, and RMGJH. Writing - original draft: AS. Writing - review & editing: KCH, JCE, MJH, LG, LDV, FLG, HVN, TN, KLB, FC, GJF, DVL, HBN, GBM, and RMGJH.

Declaration of interests

The authors have declared that no competing interests exist.

Data sharing

Data and analysis code is available at GitHub (https://github.com/aschwalbc/ACF-VN).

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Table 1. Probability of a positive test per model state for each screening tool.

Test	State	Value (Range)	Description
Nucleic acid amplification test (NAAT, Xpert MTB/RIF Ultra)	Susceptible	0.006 (0.005 – 0.008)	(1 − specificity) for individuals in the community[49]
	Infected	0.006 (0.005 – 0.008)	(1 − specificity) for individuals in the community[49]
	Cleared	0.006 (0.005 – 0.008)	(1 − specificity) for individuals in the community[49]
	Recovered	0.040 (0.020 – 0.060)	(1 − specificity) for individuals with a history of TB[55]
	Unconfirmed TB	0.044 (0.026 – 0.070)	(1 − specificity) for individuals with presumptive TB[48]
	Asymptomatic TB	0.775 (0.676 – 0.856)	Sensitivity for smear-negative pulmonary TB[48]
	Symptomatic TB	0.909 (0.862 – 0.947)	Sensitivity for pulmonary TB[48]
	Treated	0.040 (0.020 – 0.060)	(1 − specificity) for individuals with a history of TB[55]
Chest radiography with CAD software interpretation (CXR)	Susceptible	0.085 (0.069 – 0.134)	Proportion of individuals with abnormal CXR[5]
	Infected	0.085 (0.069 – 0.134)	Proportion of individuals with abnormal CXR[5]
	Cleared	0.085 (0.069 – 0.134)	Proportion of individuals with abnormal CXR[5]
	Recovered	0.503 (0.481 – 0.524)	Proportion of individuals reporting previous TB treatment with abnormal CXR[56]
	Unconfirmed TB	0.677 (0.626 – 0.712)	Midpoint between values for Recovered/Treated and Symptomatic TB
	Asymptomatic TB	0.677 (0.626 – 0.712)	Midpoint between values for Recovered/Treated and Symptomatic TB
	Symptomatic TB	0.850 (0.770 – 0.900)	Sensitivity for bacteriologically confirmed TB[4]
	Treated	0.503 (0.481 – 0.524)	Proportion of individuals reporting previous TB treatment with abnormal CXR[56]

Probability of a positive test result for each screening diagnostic tool for each state in the model. Probabilities were independently sampled from uniform distributions for each model run. Further descriptions on the probability of a positive test, including values for Xpert MTB/RIF and further investigation, are provided in **Table S3**. CAD: Computer-aided diagnosis; TB: Tuberculosis.

Table 2. Performance of population-wide screening interventions to reach TB prevalence threshold of 50 per 100,000 people.

Screening algorithm	BAU	NAAT		CXR+NAAT		CXR
Rounds required to reach threshold	Not reached	6 annual rounds		8 annual rounds		3 annual rounds
Cumulative TB incidence	2.25m (95%UI: 1.57-3.04)	0.95m (95%UI: 0.63-1.31)		0.93m (95%UI: 0.63-1.29)		0.51m (95%UI: 0.36-0.71)
Cumulative TB deaths	273k (95%UI:123-475)	104k (95%UI: 44-184)		99k (95%UI: 42-175)		60k (95%UI: 27-106)
Cumulative DALYs	8.12m (95%UI: 5.85-10.83)	3.74m (95%UI: 2.64-4.99)		3.85m (95%UI: 2.75-5.13)		2.21m (95%UI: 1.59-3.01)
Cumulative TPs diagnosed through screening	N/A	555k (95%UI: 411-688)		578k (95%UI: 419-736)		1,165k (95%UI: 791-1,555)
Cumulative FPs diagnosed through screening	N/A	2,779k (95%UI: 2,059-3,696)		1,717k (95%UI: 959-2,698)		31,619k (95%UI: 24,240-38,207)
Unit price of NAAT	N/A	US$8	US$1	US$8	US$1	N/A
Cost of diagnosis/screening	363m (95%UI: 222-578)	2,428m (95%UI: 1,675-3,465)	991m (95%UI: 693-1,360)	1,211m (95%UI: 845-1,719)	962m (95%UI: 679-1,335)	350m (95%UI: 251-474)
Cost of treatment	138m (95%UI: 86-209)	336m (95%UI: 220-511)		253m (95%UI: 152-393)		2,609m (95%UI: 1,552-3,941)
Budget impact	505m (95%UI: 328-757)	2,766m (95%UI: 1,965-3,782)	1,345m (95%UI: 999-1,755)	1,478m (95%UI: 1,066-1,996)	1,225m (95%UI: 894-1,614)	2,954m (95%UI: 1,909-4,370)
Annual cost of front-loading	N/A	427m (95%UI: 299-599)	190m (95%UI: 138-258)	161m (95%UI: 111-224)	129m (95%UI: 92-174)	949m (95%UI: 606-1,415)
Annual cost savings	N/A	12.3m (95%UI: 6.5-21.4)		12.7m (95%UI: 6.7-21.4)		15.6m (95%UI: 9.2-24.7)
ICER compared with BAU (US$ per DALY averted)	N/A	516 (95%UI: 233-1,073)	189 (95%UI: 71-426)	225 (95%UI: 85-520)	167 (95%UI: 57-380)	410 (95%UI: 178-929)

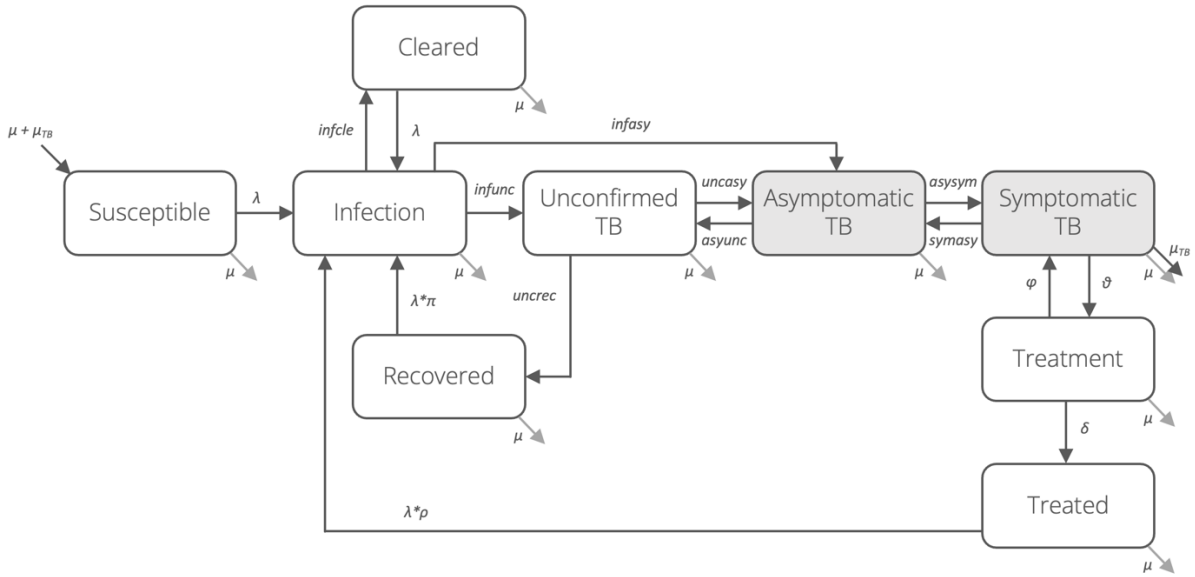
Epidemiological performance and economic impact of population-wide screening interventions in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 50 per 100,000 people. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. Budget impact includes cumulative costs of screening/diagnosis and treatment for both BAU and the intervention algorithm up to 2050. The cost of front-loading refers to intervention-specific screening and treatment costs, presented as the annual average during the intervention period. Annual cost savings are defined as the difference in BAU-specific diagnosis and treatment costs between the intervention algorithm and the BAU counterfactual, averaged over the time horizon. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; FP: False positive; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; TP: True positive; UI: Uncertainty interval; US$: United States dollar.

Table 3. Cost-effectiveness of population-wide screening interventions for TB.

Screening algorithm	DALYs averted vs BAU	Additional costs (US$) vs BAU	Incremental DALYs	Incremental costs (US$)	ICER (US$ per DALY averted)
CXR+NAAT	4.29m (95%UI: 2.86-6.14)	0.97b (95%UI: 0.52-1.49)	4.29m (95%UI: 2.86-6.14)	0.97b (95%UI: 0.52-1.49)	225 (95%UI: 85-520)
NAAT	4.36m (95%UI: 3.09-6.23)	2.25b (95%UI: 1.45-3.31)	Removed due to extended dominance with respect to CXR-only		
CXR	5.94m (95%UI: 4.18-7.97)	2.44b (95%UI: 1.41-3.88)	1.61m (95%UI: 0.86-2.56)	1.49b (95%UI: 0.34-2.87)	927 (95%UI: 393-1,124)

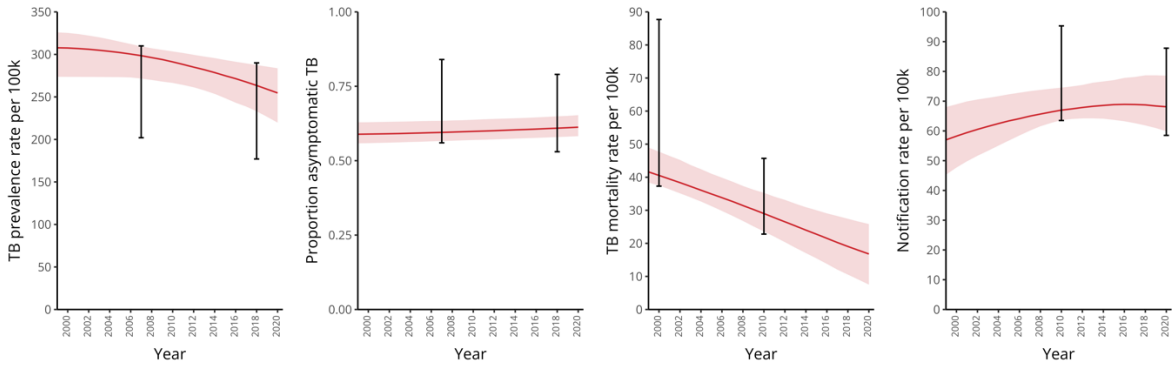
Cost-effectiveness of population-wide screening interventions in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 50 per 100,000 people. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; UI: Uncertainty interval; US$: United States dollar.

Figure 1. TB natural history model structure.



A closed population, compartmental model of tuberculosis natural history, adapting features of previously published models.[20,23] The model is depicted using nine compartments allowing for *Mycobacterium tuberculosis* infection through. Shaded compartments indicate those that contribute to transmission. The force of infection (depicted with λ) depends upon the contact parameter and the prevalence of infectious disease (i.e., asymptomatic and symptomatic TB), accounting for the relative infectiousness of asymptomatic TB.

Figure 2. Model outputs compared against calibration targets of TB in Viet Nam.



Fitted parameter sets were obtained by calibrating TB epidemiological data of Viet Nam using history matching with emulation. The red lines and shaded areas represent the median outputs and corresponding 95% uncertainty interval, respectively. Error bars reflect the time-specific calibration targets, with their values and sources specified in **Table S1**.

SUPPLEMENTARY MATERIAL:

Potential impact, costs, and benefits of population-wide screening interventions for tuberculosis in Viet Nam: a mathematical modelling study

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Keywords: active detection; cost-effectiveness; subclinical; TB elimination

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Supplementary Methods:

SM1. Baseline model structure

We developed a compartmental model of tuberculosis (TB) natural history, adapting features of previously published models [1]. The model structure is shown in **Figure 1** on the manuscript. Model parameters used and their definitions are provided in **Table S2** in a later section within this document. This model was run from 1500 to 2020 with some time-varying parameters. The model tracked a closed population of 100,000 adults (≥15 years old).

We represented TB natural history with nine distinct compartments allowing for *Mtb* infection through an annual risk of infection (ARI). Disease state classification was informed by the ICE-TB framework, and naming follows current World Health Organization (WHO) definitions [2,3]:

- Unconfirmed TB disease (uTB): individuals with inflammatory pathology (evidenced through imaging methods) prior to the onset of bacteriological evidence of TB disease or symptoms of active TB disease.
- Asymptomatic TB disease (aTB): individuals with bacteriological evidence of TB disease who do not report symptoms of active TB disease on screening.
- Symptomatic TB disease (sTB): individuals with bacteriological evidence of TB disease with symptoms of active TB disease.
- Infectious disease: refers to bacteriologically positive disease; as such, it includes asymptomatic and symptomatic disease.
- TB disease: Any state of unconfirmed, asymptomatic, or symptomatic disease.

The ARI λ depends upon the contact parameter β and the prevalence of infectious disease (i.e., asymptomatic and symptomatic TB). Additionally, the relative infectiousness κ of asymptomatic TB is also considered. The formula for the ARI λ is presented later in this document. Individuals in the *Susceptible* (S) compartment could become infected with *Mtb* and progress to the *Infection* (I) compartment. From *Infection* (I), three pathways are possible: (i) self-clearance of infection (i.e. *Cleared* (C)) at rate *infcle*, (ii) progression to *Unconfirmed* (uTB) at rate *infunc*, and (iii) progression to *Asymptomatic* (aTB) at rate *infasy*. TB transmission in the model (i.e., transition into the *Infected* (I) compartment) can occur via the ARI λ through four distinct routes: through first infection from *Susceptible* (S), through reinfection after self-clearance from *Cleared* (C), through reinfection after self-cure from *Recovered* (R) accounting for protection from reinfection π, and through reinfection after treatment from *Treated* (Tr) accounting for increased risk of reinfection ρ. TB disease states are sequentially depicted in the

model in the *Unconfirmed* (uTB), *Asymptomatic* (aTB), and *Symptomatic* (sTB) compartments, allowing progression (denoted with parameters *uncasy* and *asysym*) and regression (denoted with parameters *asyunc* and *symasy*). For the *Unconfirmed* (uTB) compartment, individuals can transition out of disease states by self-cure into the *Recovered* (R) compartment at rate *uncrec*; here, reinfection can occur via the ARI but we assume there is protection from reinfection π. The model assumes that TB diagnosis and treatment only occur for individuals in the *Symptomatic* (sTB) compartment at rate θ. Furthermore, it accounts for TB-specific mortality μ_{TB} in this compartment. Once in *Treatment* (Tx), there can be treatment failure at rate ϕ and treatment completion at rate δ. Finally, in the *Treated* (Tr) compartment, reinfection can occur via the ARI λ parameter.

The model also accounts for background mortality having a fixed rate μ (representing an age expectancy of 70 years) in each compartment. As a closed population model, the sum of all background and TB-specific mortality is fed back into the *Susceptible* compartment through the ω parameter.

SM2. Baseline model equations

A series of ordinary differential equations were set in place to represent the model structure mathematically. Parameter symbols and descriptions are outlined in **Table S2**. Parameter names indicate direction (i.e., *infcle* denotes from *Infection* to *Cleared*), and subscript *t* denotes parameters that vary over time. All nine compartments are represented: *Susceptible* (S), *Infected* (I), *Cleared* (C), *Recovered* (R), *Unconfirmed* (uTB), *Asymptomatic* (aTB), *Symptomatic* (sTB), *Treatment* (Tx), *Treated* (Tr). Given N = 100,000, then:

$$\frac{dS}{dt} = \mu \cdot (N - S) + \mu_{TB,t} \cdot sTB - \lambda \cdot S$$

$$\frac{dI}{dt} = \lambda \cdot (S + C + \pi \cdot R + \rho \cdot Tr) - I \cdot (infcle + infunc + infasy + \mu)$$

$$\frac{dC}{dt} = infcle \cdot I - C \cdot (\lambda + \mu)$$

$$\frac{dR}{dt} = uncrec \cdot uTB - R \cdot (\lambda \cdot \pi + \mu)$$

$$\frac{duTB}{dt} = infunc \cdot I + asyunc \cdot aTB - uTB \cdot (uncrec + uncasy + \mu)$$

$$\frac{daTB}{dt} = I \cdot (infasy + uncasy) + symasy \cdot sTB - aTB \cdot (asyunc + asysym + \mu)$$

$$\frac{dsTB}{dt} = asysym \cdot aTB - sTB \cdot \left(symasy + \theta_t + \mu_{TB,t} + \mu\right) + \varphi_t \cdot Tx$$

$$\frac{dTx}{dt} = \theta_t \cdot sTB - Tx \cdot (\varphi_t + \delta + \mu)$$

$$\frac{dTr}{dt} = \delta \cdot Tx - Tr \cdot (\lambda \cdot \rho + \mu)$$

As mentioned before, the ARI λ depends upon the contact parameter β and the prevalence of infectious disease (i.e., asymptomatic and symptomatic TB) and its equation is expressed below.

$$\lambda = \frac{\beta \cdot (\kappa \cdot aTB + sTB)}{N}$$

SM3. Calibration methodology

We calibrated the model using history matching with emulation, a calibration method that explores high-dimensional parameter spaces efficiently [4]. History matching refers to the exploration of the ranges of parameters given and identifying parameter sets that give rise to model outputs that match empirical data [4]. History matching progresses through multiple iterations (referred to as waves), where implausible areas of parameters (i.e., values where no match is found) are identified and discarded [4]. This process is made efficient with the use of emulators, which provide approximations of model outputs orders of magnitudes faster than the model [4]. As a result of multiple waves, the implausible space is reduced, resulting in parameter sets that match calibration targets.

History matching with emulation was implemented using the *hmer* package in R [5]. Calibration targets were TB epidemiological and demographic data of Viet Nam (S1 Table). The model comprised 23 dynamic parameters which are described in **Table S2**. The parameter ranges (priors) and sources are outlined. The non-implausible points (posteriors) were calculated as the median and corresponding 95% uncertainty intervals, calculated as the 2.5th to 97.5th percentiles of the parameter sets.

SM4. Screening model structure

We expanded the baseline TB natural history model described above to incorporate population-wide screening interventions from 2020 to 2050. The model structure remains mostly unchanged except for the transitions which occur during the years where the screening is

applied in various annual rounds from 2025 (see dashed lines in **Figure S2**). When screened, each compartment transitions into a treatment compartment and after completion transitions back into its original compartment except *Infection* (I) which transitions into *Cleared* (C) and the disease compartments (*Unconfirmed* (uTB), *Asymptomatic* (aTB), and *Symptomatic* (sTB)) which transition into *Treated* (Tr). Individuals in the *Treatment* (Tx) compartment are not screened as part of screening interventions. The rates of transitions per compartment are outlined in **Table 1** according to the tool used. The model is no longer a closed-population model and now accounts for birth and mortality rates for Viet Nam from 2020 to 2050 [6].

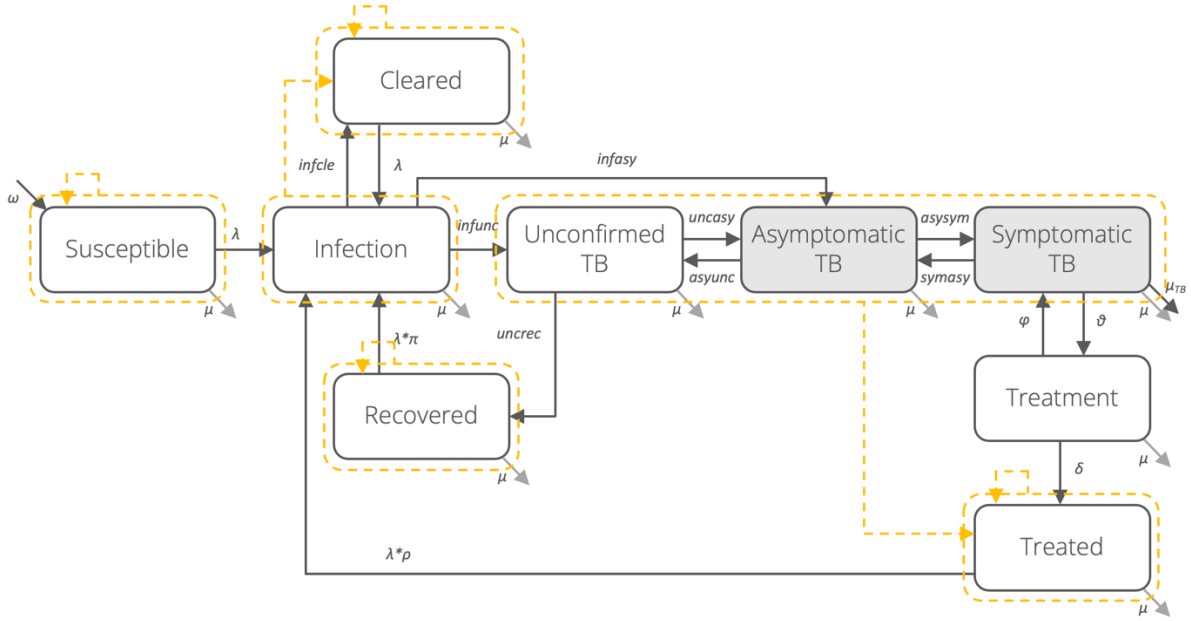
SM5. Disability-adjusted life years calculations

Since our compartmental model does not track ageing, we opted to estimate mean lifetime disability-adjusted life years (DALYs) per incident TB. For this, we used the total DALYs for TB disease (0.40 million; 95%CI: 0.33-0.49) and post-TB (0.85 million; 95%CI: 0.57-1.22) in Viet Nam in 2019, as estimated by Menzies et al [6]. Then, considering the number of incident TB estimated in Viet Nam in 2019 (169,000), we calculated the point value for lifetime DALYs per incident TB: 2.4 (95%CI: 2.0-2.9) for TB disease and 5.0 (95%CI: 3.4-7.2) for post-TB [7,8].

To estimate the DALYs lived with post-TB, we used the weighted average age of individuals with TB in Viet Nam (49 years) from the WHO Global TB Report and obtained the life expectancy at that age (29.5 years) from the United Nations World Population Prospects [6,8]. Next, we estimated the proportion of an individual's remaining lifetime that would occur between the start of the population-wide screening interventions in 2025 and the time horizon of 2050, a period chosen to align with the duration of the implementation of the intervention and evaluation timeframe. Ultimately, lifetime DALYs per incident TB were calculated as the DALYs due to TB disease episode plus the DALYs lived with post-TB, discounted at a rate of 3% per year from 2025 [9].

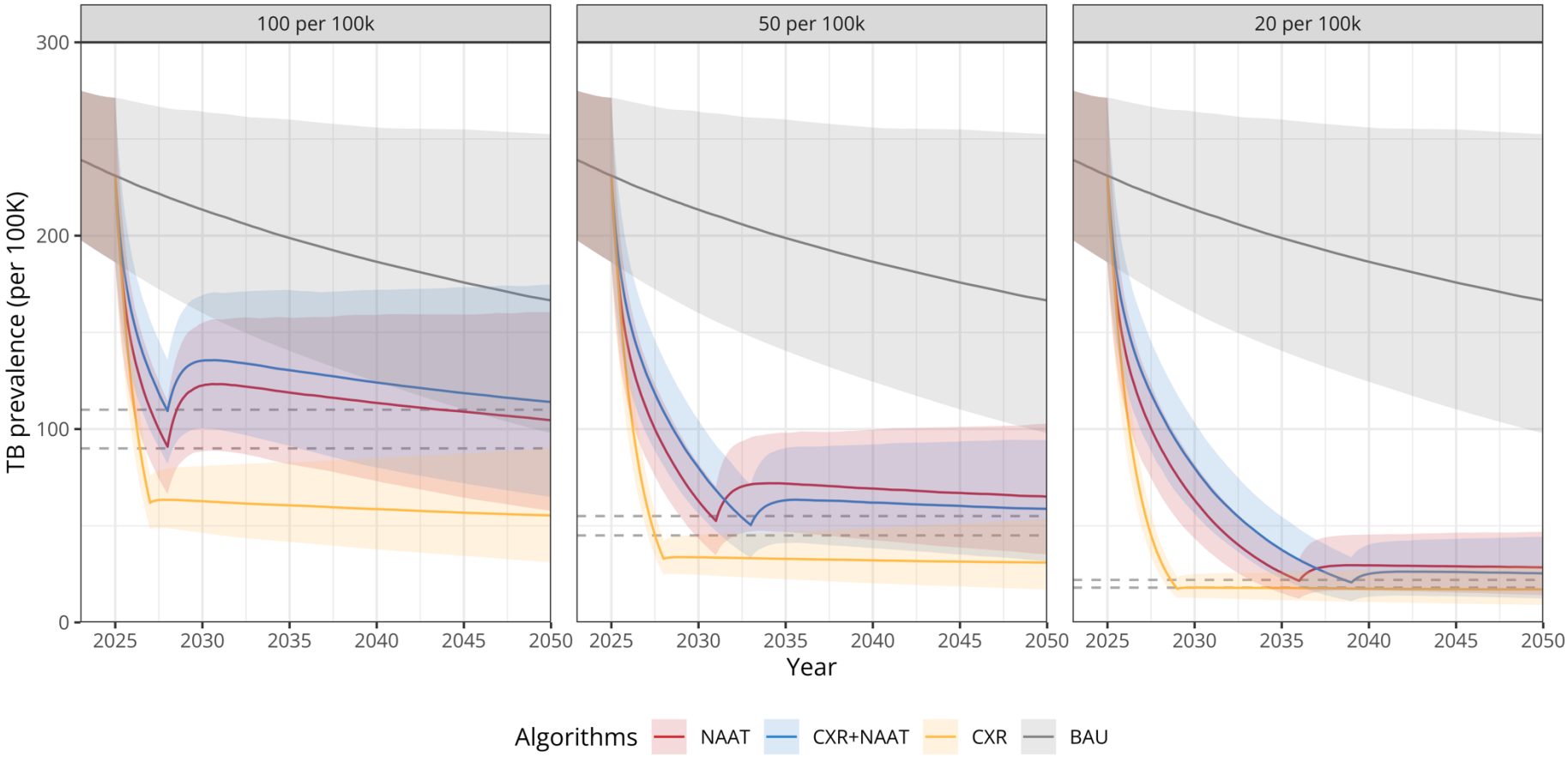
Supplementary Figures:

Figure S1. TB natural history model under population-wide screening.



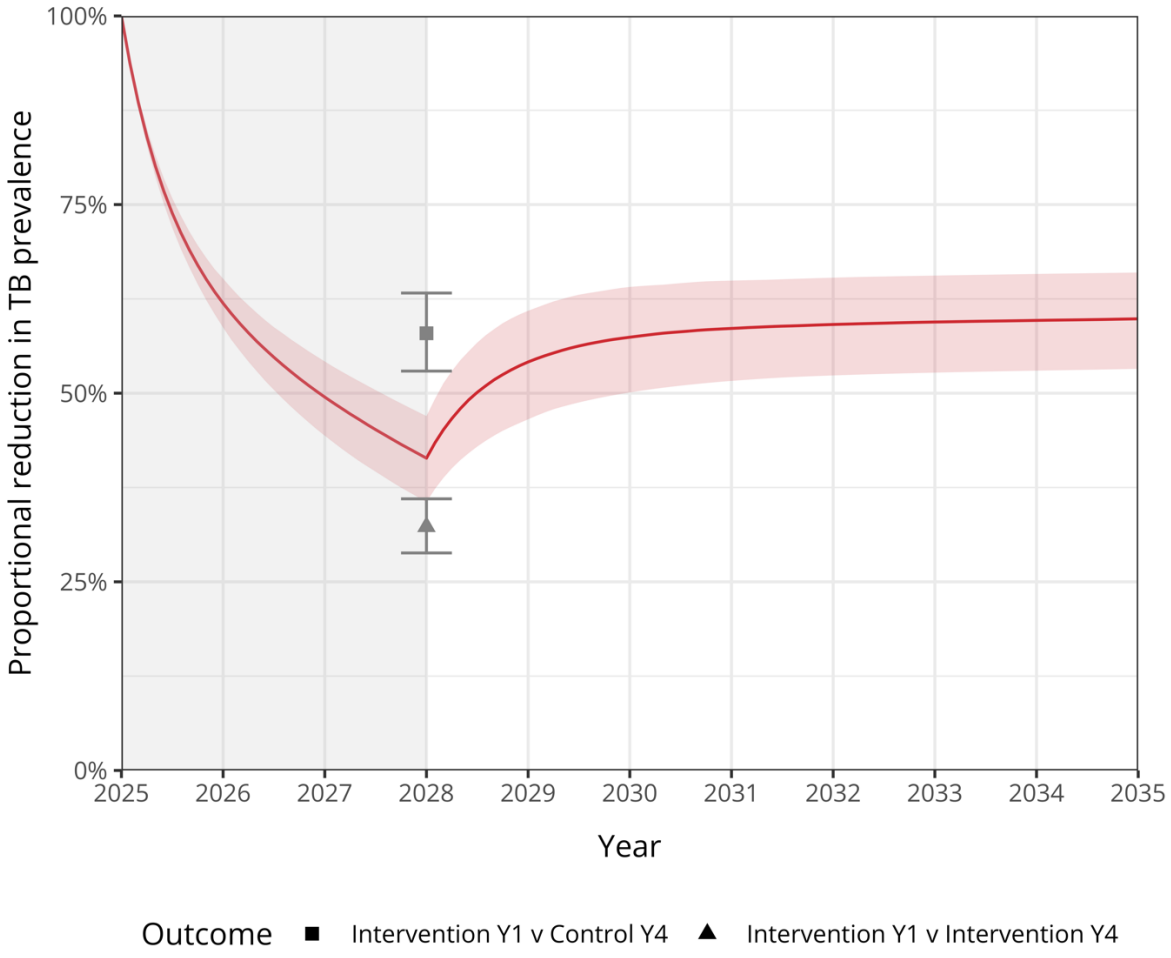
A compartmental model of tuberculosis natural history, adapting features of previously published models [1,10]. The model is depicted using nine compartments allowing for *Mycobacterium tuberculosis* infection through. Shaded compartments indicate those that contribute to transmission. The force of infection (depicted with λ) depends upon the contact parameter and the prevalence of infectious disease (i.e., asymptomatic and symptomatic TB), accounting for the relative infectiousness of asymptomatic TB. Dashed lines symbolise compartment flow after TB treatment.

Figure S2. TB prevalence reduction under population-wide screening algorithms.



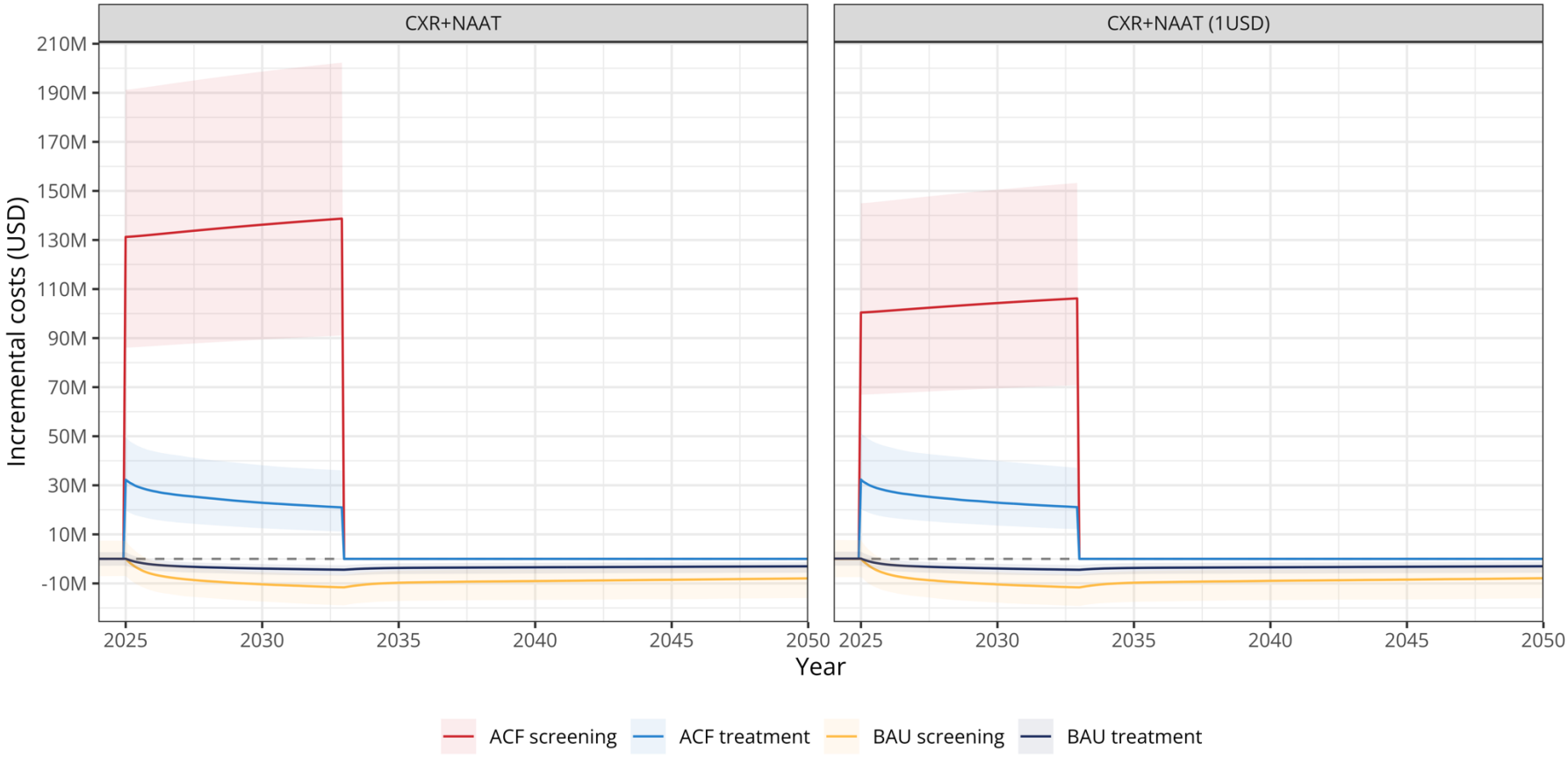
TB prevalence by each population-wide screening algorithm per threshold. Main analysis evaluates performance to reach TB prevalence of 50 per 100,000 people. Lines represent TB prevalence, and the shaded area shows the lower (2.5% quantile) and upper (97.5% quantile) bounds. Dashed lines represent TB prevalence thresholds (±10%). NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); CXR: Chest radiography with CAD software interpretation.

Figure S3. Proportional reduction of TB prevalence under NAAT-only approach and ACT3.



Proportional TB prevalence reduction under three annual rounds of NAAT-only algorithm compared to business-as-usual. Line represents proportional TB prevalence reduction per 100,000 people, and the shaded area shows the lower (2.5% quantile) and upper (97.5% quantile) bounds. The symbols and error bars represents TB prevalence proportional reduction as observed in the ACT3 trial [11].

Figure S4. Incremental costs under CXR+NAAT algorithm.



Incremental costs compared to the business-as-usual (BAU) counterfactual of population-wide screening interventions in Viet Nam using a CXR+NAAT algorithm to achieve a TB prevalence of 50 per 100,000 people. Incremental costs are shown by category, with ACF representing intervention-specific costs and BAU reflecting business-as-usual TB prevention and care costs. The main analysis assumed an Xpert MTB/RIF Ultra cartridge cost of 8 USD, while a sensitivity analysis explored a reduced cartridge cost of 1 USD. Lines represent incremental costs, and the shaded areas indicate the lower (2.5% quantile) and upper (97.5% quantile) bounds.

Supplementary Tables:

Table S1. Calibration targets.

Target	Year	Value [95%CI]	Source
TB prevalence per 100,000 people	2007	250 [202 – 310]	[12]
	2018	227 [177 – 290]	[12]
TB mortality rate per 100,000 people	2000	59.7 [37.3 - 87.7]	[6,8]
	2010	33.5 [22.8 - 45.7]	[6,8]
TB notification rate per 100,000 people	2010	79.4 [63.5 - 95.3]	[6,8]
	2020	73.2 [58.5 - 87.8]	[6,8]
Proportion asymptomatic TB	2007	0.70 [0.56 - 0.84]	[13]
	2018	0.66 [0.53 - 0.79]	[13]

Calibration targets, with brackets indicating 95% confidence intervals (95%CI), for TB epidemiology in Viet Nam were set for the adult population aged 15 years and older. TB prevalence refers specifically to infectious TB (i.e., asymptomatic and symptomatic), TB mortality is specific to deaths from symptomatic TB, TB notification represents the number of individuals with symptomatic TB initiating treatment through the business-as-usual approach, and the proportion of asymptomatic TB refers to the proportion of all infectious TB that is asymptomatic. Estimates for the TB prevalence used as calibration targets differ from those available in reference; since publication, an observed disparity in the proportional decline was corrected by the authors, and the estimates provided here reflect this correction.

Table S2. Model parameter description, ranges, and non-implausible points.

Parameters	Description	Ranges	Non-implausible ranges [95%UI]	Sources
beta (β)	Transmission coefficient	6.00 - 20.00	14.16 [8.82 - 19.29]	-
kappa (κ)	Relative transmission from asymptomatic TB	0.62 - 1.00	0.82 [0.64 - 0.98]	[13]
pi (π)	Relative risk of reinfection after recovery from unconfirmed TB	0.14 - 0.30	0.21 [0.15 - 0.29]	[14]
rho (ρ)	Relative risk of reinfection after treatment completion	2.14 - 4.27	3.15 [2.23 - 4.19]	[15]
infcle	Rate of clearance from infection per year	0.93 - 3.30	1.90 [1.09 - 2.94]	[1]
infunc	Rate of progression from infection to unconfirmed TB per year	0.04 - 0.23	0.16 [0.06 - 0.22]	[1]
infasy	Rate of progression from infection to asymptomatic TB per year	0.01 - 0.10	0.06 [0.01 - 0.10]	[1]
uncrec	Rate of recovery from unconfirmed TB per year	0.14 - 0.23	0.18 [0.14 - 0.22]	[1]
uncasy	Rate of progression from unconfirmed to asymptomatic TB per year	0.21 - 0.28	0.25 [0.21 - 0.28]	[1]
asyunc	Rate of recovery from asymptomatic to unconfirmed TB per year	1.24 - 2.03	1.66 [1.30 - 1.99]	[1]
asysym	Rate of progression from asymptomatic to symptomatic TB per year	0.56 - 0.94	0.88 [0.76 - 0.94]	[1]
symasy	Rate of recovery from symptomatic to asymptomatic TB per year	0.46 - 0.72	0.54 [0.47 - 0.68]	[1]
theta_ini (θ_t)	Rate of treatment initiation from symptomatic TB per year (initial)	0.00 - 0.57	0.46 [0.34 - 0.56]	-
theta_fin (θ_t)	Rate of treatment initiation from symptomatic TB per year (final)	0.57 - 0.77	0.71 [0.60 - 0.76]	[8]
delta (δ)	Rate of treatment completion per year	2.00	-	[16]
phi_ini (ϕ_t)	Rate of treatment failure per year (initial)	0.11 - 1.00	0.63 [0.21 - 0.97]	-
phi_fin (ϕ_t)	Rate of treatment failure per year (final)	0.07 - 0.11	0.09 [0.07 - 0.11]	[8]

mutb_ini ($\mu_{TB,t}$)	TB-specific mortality rate per year (initial)	0.28 - 0.38	0.34 [0.29 - 0.37]	[10]
mutb_fin ($\mu_{TB,t}$)	TB-specific mortality rate per year (final)	0.00 - 0.28	0.17 [0.07 - 0.27]	-
mu (μ)	Background mortality rate per year	0.014	-	-

Model parameters description for deterministic TB transmission model calibrated to TB epidemiology in Viet Nam. Ranges for priors and median value with corresponding 95% uncertainty intervals (95%UI) for non-implausible ranges (posteriors) are shown. When range is not shown, constant value was used. All parameters are expressed per year.

Table S3. Probability of a positive test per model state for each screening tool.

Test	State	Value (Range)	Description
Nucleic acid amplification test (NAAT, Xpert MTB/RIF Ultra)	Susceptible	0.006 (0.005 – 0.008)	(1 – specificity) for individuals in a community in Kampala, Uganda [17]
	Infected	0.006 (0.005 – 0.008)	(1 – specificity) for individuals in a community in Kampala, Uganda [17]
	Cleared	0.006 (0.005 – 0.008)	(1 – specificity) for individuals in a community in Kampala, Uganda [17]
	Recovered	0.040 (0.020 – 0.060)	(1 – specificity) for individuals screened positive for symptoms and/or CXR with a history of TB in the community [18]
	Unconfirmed TB	0.044 (0.026 – 0.070)	(1 – specificity) for pulmonary TB from individuals in primary care facilities and local hospitals [19]
	Asymptomatic TB	0.775 (0.676 – 0.856)	Sensitivity for smear-negative TB from individuals in primary care facilities and local hospitals [19]
	Symptomatic TB	0.909 (0.862 – 0.947)	Sensitivity for pulmonary TB from individuals in primary care facilities and local hospitals [19]
	Treated	0.040 (0.020 – 0.060)	(1 – specificity) for individuals screened positive for symptoms and/or CXR with a history of TB in the community [18]
Chest radiography with CAD software interpretation (CXR)	Susceptible	0.085 (0.069 – 0.134)	Median and interquartile range for the proportion of national TB prevalence survey participants with abnormal CXR, regardless of TB status [20]
	Infected	0.085 (0.069 – 0.134)	Median and interquartile range for the proportion of national TB prevalence survey participants with abnormal CXR, regardless of TB status [20]
	Cleared	0.085 (0.069 – 0.134)	Median and interquartile range for the proportion of national TB prevalence survey participants with abnormal CXR, regardless of TB status [20]
	Recovered	0.503 (0.481 – 0.524)	Proportion with abnormal CXR suggestive of TB among participants of national TB prevalence survey reporting TB history [21]
	Unconfirmed TB	0.677* (0.626 – 0.712)	Midpoint between the median and bounds of values for Recovered/Treated and Symptomatic TB [Assumption]
	Asymptomatic TB	0.677* (0.626 – 0.712)	Midpoint between the median and bounds of values for Recovered/Treated and Symptomatic TB [Assumption]
	Symptomatic TB	0.910 (0.900 – 0.920)	Sensitivity of CAD software for bacteriologically confirmed TB in screening use case [22]
	Treated	0.503 (0.481 – 0.524)	Proportion with abnormal CXR suggestive of TB among participants of national TB prevalence survey reporting TB history [21]

Nucleic acid amplification test (NAAT, Xpert MTB/RIF)	Susceptible	0.0022 (0.0016 – 0.0029)	(1 – specificity) for individuals in a community in selected villages in Ca Mau province, Viet Nam [23]
	Infected	0.0022 (0.0016 – 0.0029)	(1 – specificity) for individuals in a community in selected villages in Ca Mau province, Viet Nam [23]
	Cleared	0.0022 (0.0016 – 0.0029)	(1 – specificity) for individuals in a community in selected villages in Ca Mau province, Viet Nam [23]
	Recovered	0.026 (0.005 – 0.083)	(1 – specificity) for individuals with a history of TB in primary care facilities and local hospitals [19]
	Unconfirmed TB	0.016 (0.007 – 0.030)	(1 – specificity) for pulmonary TB from individuals in primary care facilities and local hospitals [19]
	Asymptomatic TB	0.606 (0.484 – 0.717)	Sensitivity for smear-negative TB from individuals in primary care facilities and local hospitals [19]
	Symptomatic TB	0.847 (0.786 – 0.899)	Sensitivity for pulmonary TB from individuals in primary care facilities and local hospitals [19]
	Treated	0.026 (0.005 – 0.083)	(1 – specificity) for individuals with a history of TB in primary care facilities and local hospitals [19]
Further investigation (informed by prolonged cough)	Susceptible	0.061 (0.047 – 0.074)	Median and interquartile range for the proportion of national TB prevalence survey participants reporting prolonged cough, regardless of CXR or TB status [20]
	Infected	0.061 (0.047 – 0.074)	Median and interquartile range for the proportion of national TB prevalence survey participants reporting prolonged cough, regardless of CXR or TB status [20]
	Cleared	0.061 (0.047 – 0.074)	Median and interquartile range for the proportion of national TB prevalence survey participants reporting prolonged cough, regardless of CXR or TB status [20]
	Recovered	0.131 (0.089 – 0.162)	Midpoint between the median and bounds of values for S/I/C and Unconfirmed TB [Assumption]
	Unconfirmed TB	0.201 (0.129 – 0.249)	Median and interquartile range for the proportion of national TB prevalence survey participants reporting prolonged cough with abnormal CXR, regardless of TB status [20]
	Asymptomatic TB	1.00	Assuming a strong clinical appraisal that is able to diagnose confirmed TB [Assumption]
	Symptomatic TB	1.00	Assuming a strong clinical appraisal that is able to diagnose confirmed TB [Assumption]
	Treated	0.566 (0.545 – 0.581)	Midpoint between the median and bounds of values for Recovered and Asymptomatic/Symptomatic TB [Assumption]

Probability of a positive test result for each screening diagnostic tool for each state in the model and were independently sampled from uniform distributions for each model run. Test positivity under further investigation refers to individuals who have tested positive based on a given screening algorithm. *Under a sensitivity analysis, evaluating revised CXR sensitivity for *Unconfirmed* and *Asymptomatic* TB, the value matches the one in *Recovered* and *Treated*. CAD: Computer-aided diagnosis; TB: Tuberculosis.

Table S4. Costing estimates for business-as-usual TB diagnosis and treatment.

Cost type	Cost per individual (US$)	Distribution	Notes
Diagnosis for DS-TB	264.0	Gamma distribution, standard deviation 20% of the mean	Considering NNT, CXR, bacteriological costs, and staff time costs
Diagnosis for DR-TB	1595.0	Gamma distribution, standard deviation 20% of the mean	Considering NNT, CXR, bacteriological costs, and staff time costs
Treatment for DS-TB	81.0	Gamma distribution, standard deviation 20% of the mean	Includes TB drugs, healthcare staff, bacterial monitoring, and overhead costs per treatment episode
Treatment for DR-TB	973.0	Gamma distribution, standard deviation 20% of the mean	Includes TB drugs, healthcare staff, bacterial monitoring, and overhead costs per treatment episode

Costing estimates per individual for business-as-usual TB diagnosis and treatment provided by the national TB programme in Viet Nam. Costs were independently sampled from gamma distributions as specified for each model run. CXR: Chest radiography; DR-TB: Drug-resistant TB; DS-TB: Drug-susceptible TB; NNT: Number needed to test; TB: Tuberculosis; US$: United States dollar.

Table S5. Costing estimates for population-wide screening algorithms.

Analysis	Algorithm	Cost per individual (US$)	Distribution
Main analysis	NAAT-only	8.0	Gamma distribution, standard deviation 20% of the mean
	CXR+NAAT	1.7	Gamma distribution, standard deviation 20% of the mean
	CXR-only	1.2	Gamma distribution, standard deviation 20% of the mean
Sensitivity analysis	NAAT-only (US$1 NAAT)	3.0	Gamma distribution, standard deviation 20% of the mean
	CXR+NAAT (US$1 NAAT)	1.3	Gamma distribution, standard deviation 20% of the mean

Costing estimates per individual for different population-wide algorithms. Estimates represent the average cost per individual screened, calculated from the total costs of six years of community-wide screening interventions, informed by the ACT3 trial and the ongoing ACT5 trial [11,24]. Costs account for several factors, including the number of screening days per year, human resource costs (e.g., technicians, field workers, laboratory staff, administrative staff, and supervisors), the proportion of the population participating, the proportion providing sputum samples, the number undergoing NAAT, consumables, setup of screening sites, and transportation. For the CXR+NAAT algorithm, costs also include the proportion of CXR deemed abnormal, requiring confirmatory NAAT testing. Unit costs were independently sampled from a gamma distribution. NAAT: Nucleic acid amplification test; CXR: Chest radiography; US$: United States dollar.

Table S6. Performance of population-wide screening interventions to reach TB prevalence threshold of 100 per 100,000 inhabitants.

Screening algorithm	BAU	NAAT		NAAT+CXR		CXR
Rounds required to reach threshold	Not reached	3 annual rounds		3 annual rounds		2 annual rounds
Cumulative TB incidence	2.25m (95%UI: 1.57-3.04)	1.39m (95%UI: 0.94-1.89)		1.52m (95%UI: 1.04-2.06)		0.79m (95%UI: 0.55-1.10)
Cumulative TB deaths	273k (95%UI:123-475)	160k (95%UI: 70-278)		177k (95%UI: 77-308)		94k (95%UI:41-163)
Cumulative DALYs	8.12m (95%UI: 5.85-10.83)	5.13m (95%UI: 3.60-6.82)		5.62m (95%UI: 4.04-7.37)		3.09m (95%UI: 2.21-4.17)
Cumulative TPs diagnosed through screening	N/A	369k (95%UI: 281-450)		313k (95%UI: 232-392)		988k (95%UI: 666-1,307)
Cumulative FPs diagnosed through screening	N/A	1,384k (95%UI: 1,033-1,834)		617k (95%UI: 360-983)		21,107k (95%UI: 16,340-25,722)
Unit price of NAAT	N/A	US$8	US$1	US$8	US$1	N/A
Cost of diagnosis/screening	363m (95%UI: 222-578)	1,343m (95%UI: 952-1,846)	641m (95%UI: 471-842)	639m (95%UI: 478-858)	548m (95%UI: 398-719)	311m (95%UI: 230-411)
Cost of treatment	138m (95%UI: 86-209)	235m (95%UI: 157-344)		176m (95%UI: 114-268)		1,806m (95%UI: 1,133-2,796)
Budget impact	505m (95%UI: 328-757)	1,583m (95%UI: 1,183-2,102)	878m (95%UI: 677-1,113)	822m (95%UI: 617-1,075)	722m (95%UI: 548-932)	2,118m (95%UI: 1,451-3,093)
Annual cost of front-loading	N/A	429m (95%UI: 297-586)	192m (95%UI: 139-255)	162m (95%UI: 113-219)	131m (95%UI: 93-183)	967m (95%UI: 646-1,466)
Annual cost savings	N/A	8.0m (95%UI: 1.9-15.8)		6.9m (95%UI: 0.3-14.8)		13.0m (95%UI: 7.1-21.8)
ICER compared with BAU (US$ per DALY averted)	N/A	354 (95%UI: 144-811)	123 (95%UI: 24-325)	123 (95%UI: 21-359)	84 (95%UI: 1-285)	318 (95%UI: 133-724)

Epidemiological performance and economic impact of population-wide screening interventions in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 100 per 100,000 people. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. Budget impact includes cumulative costs of screening/diagnosis and treatment for both BAU and the intervention algorithm up to 2050. The cost of front-loading refers to intervention-specific screening and treatment costs, presented as the annual average during the intervention period. Annual cost savings are defined as the difference in BAU-specific diagnosis and treatment costs between the intervention algorithm and the BAU counterfactual, averaged over the time horizon. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; FP: False positive; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; TP: True positive; UI: Uncertainty interval; US$: United States dollar.

Table S7. Performance of population-wide screening interventions to reach TB prevalence threshold of 20 per 100,000 inhabitants.

Screening algorithm	BAU	NAAT		NAAT+CXR		CXR
Rounds required to reach threshold	Not reached	11 annual rounds		12 annual rounds		4 annual rounds
Cumulative TB incidence	2.25m (95%UI: 1.57-3.04)	0.62m (95%UI: 0.42-0.85)		0.68m (95%UI: 0.47-0.93)		0.36m (95%UI: 0.26-0.49)
Cumulative TB deaths	273k (95%UI:123-475)	63k (95%UI: 26-107)		68k (95%UI: 29-113)		43k (95%UI:20-74)
Cumulative DALYs	8.12m (95%UI: 5.85-10.83)	2.92m (95%UI: 2.06-3.84)		3.25m (95%UI: 2.35-4.31)		1.77m (95%UI: 1.30-2.35)
Cumulative TPs diagnosed through screening	N/A	711k (95%UI: 520-907)		718k (95%UI: 504-946)		1,262k (95%UI: 852-1,676)
Cumulative FPs diagnosed through screening	N/A	5,276k (95%UI: 3,917-6,834)		3,022k (95%UI: 1,754-4,667)		42,402k (95%UI: 32,130-51,051)
Unit price of NAAT	N/A	US$8	US$1	US$8	US$1	N/A
Cost of diagnosis/screening	363m (95%UI: 222-578)	4,259m (95%UI: 2,782-6,223)	1,671m (95%UI: 1,097-2,380)	2,031m (95%UI: 1,375-2,873)	1,555m (95%UI: 1,061-2,243)	420m (95%UI: 293-577)
Cost of treatment	138m (95%UI: 86-209)	540m (95%UI: 336-827)		349m (95%UI: 215-562)		3,494m (95%UI: 2,148-5,477)
Budget impact	505m (95%UI: 328-757)	4,801m (95%UI: 3,301-6,780)	2,219m (95%UI:1,586-2,973)	2,368m (95%UI: 1,692-3,259)	1,929m (95%UI: 1,387-2,599)	3,913m (95%UI: 2,598-5,873)
Annual cost of front-loading	N/A	426m (95%UI: 290-605)	191m (95%UI: 136-259)	187m (95%UI: 131-260)	150m (95%UI: 106-207)	958m (95%UI: 634-1,447)
Annual cost savings	N/A	15.5m (95%UI: 9.0-24.9)		15.2m (95%UI: 8.8-24.7)		16.9m (95%UI: 10.6-26.6)
ICER compared with BAU (US$ per DALY averted)	N/A	825 (95%UI: 380-1,713)	328 (95%UI: 143-688)	381 (95%UI: 172-818)	291 (95%UI: 122-643)	537 (95%UI: 240-1,207)

Epidemiological performance and economic impact of population-wide screening interventions in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 20 per 100,000 people. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. Budget impact includes cumulative costs of screening/diagnosis and treatment for both BAU and the intervention algorithm up to 2050. The cost of front-loading refers to intervention-specific screening and treatment costs, presented as the annual average during the intervention period. Annual cost savings are defined as the difference in BAU-specific diagnosis and treatment costs between the intervention algorithm and the BAU counterfactual, averaged over the time horizon. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; FP: False positive; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; TP: True positive; UI: Uncertainty interval; US$: United States dollar.

Table S8. Performance of population-wide screening interventions with further investigation post-screening.

Screening algorithm	BAU	NAAT	CXR+NAAT	CXR
Rounds required to reach threshold	Not reached	6 annual rounds	8 annual rounds	3 annual rounds
Cumulative TB incidence	2.25m (95%UI: 1.57-3.04)	1.03m (95%UI: 0.68-1.41)	1.04m (95%UI: 0.69-1.43)	1.22m (95%UI: 0.83-1.67)
Cumulative TB deaths	273k (95%UI:123-475)	113k (95%UI: 47-194)	112k (95%UI: 46-196)	140k (95%UI: 62-248)
Cumulative DALYs	8.12m (95%UI: 5.85-10.83)	3.99m (95%UI: 2.77-5.31)	4.17m (95%UI: 2.89-5.56)	4.52m (95%UI: 3.22-6.06)
Cumulative TPs diagnosed through screening	N/A	490k (95%UI: 377-594)	489k (95%UI: 364-600)	514k (95%UI: 374-670)
Cumulative FPs diagnosed through screening	N/A	272k (95%UI: 182-410)	224k (95%UI: 127-383)	3,057k (95%UI: 2,236-4,051)
Unit price of NAAT	N/A	8USD	8USD	N/A
Cost of diagnosis/screening	363m (95%UI: 222-578)	2,399m (95%UI: 1,655-3,405)	1,243m (95%UI: 816-1,746)	478m (95%UI: 339-641)
Cost of treatment	138m (95%UI: 86-209)	137m (95%UI: 91-204)	134m (95%UI: 84-203)	369m (95%UI: 237-553)
Budget impact	505m (95%UI: 328-757)	2,540m (95%UI: 1,794-3,567)	1,377m (95%UI: 955-1,885)	921m (95%UI: 688-1,177)
Annual cost of front-loading	N/A	387m (95%UI: 262-555)	145m (95%UI: 95-209)	193m (95%UI: 139-262)
Annual cost savings	N/A	11.7m (95%UI: 5.8-20.3)	11.6m (95%UI: 5.9-20.2)	9.5m (95%UI: 3.8-18.0)
ICER compared with BAU (US$ per DALY averted)	N/A	489 (95%UI: 207-1,105)	219 (95%UI: 73-521)	113 (95%UI: 28-278)

Epidemiological performance and economic impact of population-wide screening interventions with further investigation post-screening in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 50 per 100,000 people. Further investigation was applied and costed exclusively for individuals who screened positive under their respective algorithm. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. Budget impact includes cumulative costs of screening/diagnosis and treatment for both BAU and the intervention algorithm up to 2050. The cost of front-loading refers to intervention-specific screening and treatment costs, presented as the annual average during the intervention period. Annual cost savings are defined as the difference in BAU-specific diagnosis and treatment costs between the intervention algorithm and the BAU counterfactual, averaged over the time horizon. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; FP: False positive; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; TP: True positive; UI: Uncertainty interval; US$: United States dollar.

Table S9. Performance of population-wide screening interventions with revised CXR sensitivity.

Screening algorithm	BAU	NAAT	CXR+NAAT	CXR
Rounds required to reach threshold	Not reached	6 annual rounds	9 annual rounds	3 annual rounds
Cumulative TB incidence	2.25m (95%UI: 1.57-3.04)	0.95m (95%UI: 0.63-1.31)	1.00m (95%UI: 0.67-1.35)	0.68m (95%UI: 0.47-0.93)
Cumulative TB deaths	273k (95%UI:123-475)	104k (95%UI: 44-184)	105k (95%UI: 45-185)	79k (95%UI: 34-139)
Cumulative DALYs	8.12m (95%UI: 5.85-10.83)	3.74m (95%UI: 2.64-4.99)	4.14m (95%UI: 2.91-5.52)	2.79m (95%UI: 2.00-3.74)
Cumulative TPs diagnosed through screening	N/A	555k (95%UI: 411-688)	544k (95%UI: 395-698)	985k (95%UI: 672-1,305)
Cumulative FPs diagnosed through screening	N/A	2,779k (95%UI: 2,059-3,696)	1,924k (95%UI: 1,122-3,013)	31,354k (95%UI: 24,199-38,227)
Unit price of NAAT	N/A	US$8	US$8	N/A
Cost of diagnosis/screening	363m (95%UI: 222-578)	2,428m (95%UI: 1,675-3,465)	1,350m (95%UI: 945-1,881)	374m (95%UI: 273-509)
Cost of treatment	138m (95%UI: 86-209)	336m (95%UI: 220-511)	272m (95%UI: 158-425)	2,570m (95%UI: 1,623-4,103)
Budget impact	505m (95%UI: 328-757)	2,766m (95%UI: 1,965-3,782)	1,639m (95%UI: 1,191-2,196)	2,967m (95%UI: 2,005-4,487)
Annual cost of front-loading	N/A	427m (95%UI: 299-599)	159m (95%UI: 110-219)	938m (95%UI: 623-1,448)
Annual cost savings	N/A	12.3m (95%UI: 6.5-21.4)	12.2m (95%UI: 5.9-21.0)	14.3m (95%UI: 8.1-23.2)
ICER compared with BAU (US$ per DALY averted)	N/A	516 (95%UI: 233-1,073)	283 (95%UI: 114-640)	456 (95%UI: 204-1,062)

Epidemiological performance and economic impact of population-wide screening interventions with revised CXR sensitivity for unconfirmed and asymptomatic TB in Viet Nam per algorithm when conducted to reach TB prevalence threshold of 50 per 100,000 people. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. Budget impact includes cumulative costs of screening/diagnosis and treatment for both BAU and the intervention algorithm up to 2050. The cost of front-loading refers to intervention-specific screening and treatment costs, presented as the annual average during the intervention period. Annual cost savings are defined as the difference in BAU-specific diagnosis and treatment costs between the intervention algorithm and the BAU counterfactual, averaged over the time horizon. BAU: Business-as-usual; CXR: Chest radiography; DALY: Disability-adjusted life year; FP: False positive; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (Xpert MTB/RIF Ultra); TB: Tuberculosis; TP: True positive; UI: Uncertainty interval; US$: United States dollar.

Table S10. Cost-effectiveness of population-wide screening interventions for TB.

Analysis type	Screening algorithm	DALYs averted compared to BAU	Additional costs (US$) compared to BAU	Incremental DALYs	Incremental costs (US$)	ICER (US$ per DALY averted)
Reducing the unit price of NAAT cartridges to US$1	CXR+NAAT	4.28m (95%UI: 2.93-6.16)	0.71b (95%UI: 0.35-1.11)	4.28m (95%UI: 2.93-6.16)	0.71b (95%UI: 0.35-1.11)	167 (95%UI: 57-380)
	NAAT	4.38m (95%UI: 2.97-6.19)	0.83b (95%UI: 0.44-1.27)	Removed due to extended dominance with respect to CXR-only		
	CXR	5.94m (95%UI: 4.18-7.97)	2.44b (95%UI: 1.41-3.88)	1.52m (95%UI: 0.79-2.37)	1.61b (95%UI: 0.51-3.06)	1,057 (95%UI: 642-1,291)
TB prevalence threshold of 100 per 100,000 people	CXR+NAAT	2.55m (95%UI: 1.53-3.92)	0.31b (95%UI: 0.08-0.55)	2.55m (95%UI: 1.53-3.92)	0.31b (95%UI: 0.08-0.55)	123 (95%UI: 21-359)
	NAAT	3.02m (95%UI: 1.93-4.47)	1.07b (95%UI: 0.64-1.57)	Removed due to extended dominance with respect to CXR-only		
	CXR	5.06m (95%UI: 3.56-6.86)	1.61b (95%UI: 0.91-2.58)	2.49m (95%UI: 1.57-3.54)	1.31b (95%UI: 0.59-2.25)	528 (95%UI: 376-636)
TB prevalence threshold of 20 per 100,000 people	CXR+NAAT	4.89m (95%UI: 3.34-6.92)	1.86b (95%UI: 1.19-2.73)	4.89m (95%UI: 3.34-6.92)	1.86b (95%UI: 1.19-2.73)	381 (95%UI: 172-818)
	NAAT	5.19m (95%UI: 3.65-7.35)	4.29b (95%UI: 2.79-6.26)	Removed due to simple dominance with respect to CXR-only		
	CXR	6.32m (95%UI: 4.49-8.66)	3.39b (95%UI: 2.08-5.43)	1.46m (95%UI: 0.81-2.31)	1.52b (95%UI: 0.12-3.62)	1,036 (95%UI: 148-1,567)
Performance of using Xpert MTB/RIF in a NAAT-only algorithm	NAAT (Xpert MTB/RIF)	4.29m (95%UI: 2.93-6.16)	2.96b (95%UI: 1.89-4.41)	Removed due to simple dominance with respect to CXR+NAAT		
	CXR+NAAT	4.29m (95%UI: 2.86-6.14)	0.97b (95%UI: 0.52-1.49)	4.29m (95%UI: 2.86-6.14)	0.97b (95%UI: 0.52-1.49)	225 (95%UI: 85-520)
	NAAT (Xpert MTB/RIF Ultra)	4.36m (95%UI: 3.09-6.23)	2.25b (95%UI: 1.45-3.31)	Removed due to extended dominance with respect to CXR-only		
	CXR	5.94m (95%UI: 4.18-7.97)	2.44b (95%UI: 1.41-3.88)	1.61m (95%UI: 0.86-2.56)	1.49b (95%UI: 0.34-2.87)	927 (95%UI: 393-1,124)

Performance of further investigation post-screening	CXR	3.59m (95%UI: 2.43-5.23)	0.41b (95%UI: 0.15-0.68)	3.59m (95%UI: 2.43-5.23)	0.41b (95%UI: 0.15-0.68)	113 (95%UI: 28-278)
	CXR+NAAT	3.96m (95%UI: 2.61-5.83)	0.87b (95%UI: 0.43-1.36)	0.37m (95%UI: 0.00-1.15)	0.46b (95%UI: 0.03-1.00)	1,293 (95%UI: 1,153-1,555)
	NAAT	4.14m (95%UI: 2.77-5.99)	2.03b (95%UI: 1.24-3.06)	0.16m (95%UI: 0.00-0.48)	1.16b (95%UI: 0.23-2.23)	6,183 (95%UI: 5,165-10,441)
Revised CXR sensitivity for unconfirmed and asymptomatic TB	CXR+NAAT	3.98m (95%UI: 2.64-5.73)	1.12b (95%UI: 0.65-1.69)	3.98m (95%UI: 2.64-5.73)	1.12b (95%UI: 0.65-1.69)	283 (95%UI: 113-640)
	NAAT	4.36m (95%UI: 3.09-6.23)	2.25b (95%UI: 1.45-3.31)	Removed due to extended dominance with respect to CXR-only		
	CXR	5.35m (95%UI: 3.77-7.33)	2.44b (95%UI: 1.49-4.00)	1.34m (95%UI: 0.62-2.16)	1.32b (95%UI: 0.22-2.95)	962 (95%UI: 750-1,447)

Cost-effectiveness sensitivity analyses of population-wide screening interventions in Viet Nam per algorithm. The values represent cumulative accrual over the 25-year time horizon, extending up to 2050. BAU: Business-as-usual; CXR: Chest radiography with computer-aided detection software interpretation; DALY: Disability-adjusted life year; ICER: Incremental cost-effectiveness ratio; NAAT: Nucleic acid amplification test (primarily Xpert MTB/RIF Ultra unless specified otherwise); TB: Tuberculosis; UI: Uncertainty interval; US$: United States dollar.

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6.3 Summary

In this chapter, I calibrated a natural history TB model to TB epidemiology in Viet Nam, to assess the impact and cost-effectiveness of annual rounds of various population-wide screening algorithms. All screening algorithms demonstrated a reduction in TB burden compared to business-as-usual between 2025 and 2050. While these interventions required substantial front-loaded investments, they were followed by persistent cost savings. Notably, the two-step approach combining CXR and NAAT proved to be particularly cost-effective. These findings underscore the potential of symptom-agnostic population-wide screening interventions as a pathway to rapidly reducing TB prevalence in high-burden settings, highlighting the need to integrate such strategies into existing TB prevention and care frameworks.

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Chapter 7: Discussion

This chapter provides the key findings and further discussion of the research projects presented in the previous chapters, highlighting their implications. Additionally, it outlines future recommendations and presents the overall conclusions of the thesis.

7.1 Key findings

The key findings of the thesis are as follows:

- The annual risk of infection (ARI) is severely underestimated when not accounting for immunoreactivity reversion in its calculation (*Chapter 3*).
- Globally, a sizeable number of individuals have a recent viable *Mycobacterium tuberculosis* (*Mtb*) infection and are at high risk of progression to disease (*Chapter 4*).
- Mass screening with chest radiography (CXR) can result in a reduction of tuberculosis (TB) burden by identifying and treating early disease (*Chapter 5*).
- Symptom-agnostic population-wide screening algorithms are a cost-effective intervention for rapidly reducing the TB burden, generating average cost savings immediately, despite their substantial front-loaded investment (*Chapter 6*).

7.2 Further discussion

Further discussion of each of the research projects (*Chapters 3–6*) is addressed below:

7.2.1 Chapter 3: Immunoreactivity reversion and the annual risk of infection

This chapter addresses *Objective #1* of the thesis by quantifying the impact of immunoreactivity test reversion upon the estimated ARI. Furthermore, this chapter is a key component to achieve the first aim of the thesis on estimating the global burden of viable *Mtb* infection.

I concluded that the estimated ARI is substantially underestimated when not accounting for immunoreactivity test reversion [1]. Immunoreactivity reversion does regularly occur and empirical data shows that reversion can be associated with age, degree of immunoreactivity, and time from presumed exposure, among others [2]. Thus, awareness of *Mtb* immunoreactivity test reversion is critical to correctly estimating and interpreting the ARI [1,3]. An excellent example comes from an adolescent cohort in Cape Town, where participants were tested with an interferon-gamma release assay (IGRA) at baseline and again after two years, with half of the cohort undergoing additional testing at intermediate

time points [4]. When IGRA positivity was examined using a longitudinal analysis that accounted for reversion, the resulting ARI was found to be twice as high as estimates derived from cross-sectional methods, which are traditionally used in immunoreactivity surveys [4].

Populations experiencing three times more *Mtb* transmission than previously estimated fundamentally alters our understanding of TB dynamics and response priorities [1]. Firstly, this imbalance emphasises the predominance of disease driven by recent infections, as progression to TB disease is most likely within the first two years after infection [5]. This highlights the importance of prioritising interventions targeting *Mtb* transmission, rather than focusing on preventing progression to disease from remote infections. TB prevention and care efforts rely on ARIs ranging between 1% and 2% [3]; yet they overlook the heightened risk associated with recent infections, which can result in misinformed national TB policies. Secondly, translating immunoreactivity prevalence directly into TB incidence and prevalence without considering their limitations and underlying assumptions risks misrepresenting the true burden of disease [6,7]. However, immunoreactivity trends can still offer valuable insights, especially since current surveillance primarily targets endpoints at the opposite extreme of the spectrum, such as symptomatic TB or death, which are associated with an unfixed and variable incubation period [8]. Shifting attention to earlier stages of the spectrum addresses critical gaps in current surveillance and is essential for recalibrating TB prevention and care strategies to better reflect *Mtb* transmission and disease dynamics.

While my findings highlight the pitfalls of directly interpreting immunoreactivity as *Mtb* infection burden, they do not diminish its potential utility in tracking trends [8]. Measures of the force of infection derived from repeat surveys can offer immediate and actionable insights into the performance of TB prevention and care interventions, bypassing the variability and delays inherent in tracking outcomes at the later stages of the spectrum [8,9]. When appropriately interpreted, these surveys provide a cost-effective alternative to TB prevalence surveys, offering critical insights into transmission risk at a fraction of the cost [8]. This highlights the need for reintroducing immunoreactivity surveys as a key tool for monitoring trends and informing interventions.

7.2.2 Chapter 4: Global burden of viable *Mycobacterium tuberculosis* infection

This chapter addresses *Objective #2* of the thesis by estimating viable *Mtb* infection burden, accounting for revised estimates of the ARI and self-clearance of infection. Notably, this

chapter was set to achieve the first aim of the thesis on estimating the global burden of viable *Mtb* infection.

I concluded that 156 million people were recently infected with viable *Mtb*, equating to 2.0% of the global population [10]. Because of the recency of infection, this population is at high risk of progression to disease, and thus would benefit from receiving TB preventive therapy (TPT) [10,11]. Given the limited empirical data on the proportion self-cleared after 10 years since infection, I estimated the total number infected with viable *Mtb* to be between 5% and 8% [10], based on assumptions informed by available evidence [12,13]. While this estimate is less intimidating than 'one quarter of the global population' [14], it is important to highlight that this is reflecting individuals with infection capable of progressing to disease in the absence of reinfection, rather than those that were ever exposed to *Mtb* [10]. More importantly, my estimates of recently infected with viable *Mtb* are two times higher than previously estimates of those ever exposed to *Mtb*, as indicated by immunoreactivity (2.0% v 0.8%) [10,14], highlighting again the shift in understanding the underestimation of the ARI and suggesting a rapid turnover of infections.

The significant difference between the global estimates of 'latent' TB infection and viable *Mtb* infection underscores the disparity between measured immunoreactivity and infection capable of progressing to disease [10,14]. This highlights the urgent need for a diagnostic test capable of detecting the presence of viable *Mtb* in individuals with established infection or those along the TB disease spectrum where conventional bacteriological diagnostic methods yield negative results. For the former, such a test would enable accurate targeting of individuals with current viable *Mtb* infection for TPT, rather than relying on an (often single) immunoreactive test of past exposure. For the latter, within the conceptual TB states, a specific test would be invaluable for diagnosing bacteriologically unconfirmed TB—states with evident macroscopic pathology but bacteriologically negative results [15,16]. Such a test could enhance the effectiveness of screening algorithms, particularly those employing CXR as an initial step. It would also pave the way for further research into specific, potentially shorter, drug regimens tailored for bacteriologically unconfirmed TB.

As explained in *Chapter 4*, the aim was to determine the 'real' burden of viable *Mtb* infection, establishing a medically actionable target—an estimated population that would benefit from TPT [10]. These revised estimates also raise the question of the resulting TB burden

generated from this reservoir, though considerations of the TB spectrum and its undulating pathways require further exploration to fit the puzzle [13]. Additionally, these estimates can support policymaking for TB vaccine candidates, as country- and age-specific estimates of infected populations can influence proposed coverage and efficacy targets depending on the vaccine profile.

7.2.3 Chapter 5: Tuberculosis screening in the Kolín study

This chapter addresses *Objective #3* of the thesis by re-evaluating the impact of a historical mass CXR screening programme in the Kolín district, Czechoslovakia. This chapter serves as a component to achieve the second aim of the thesis on evaluating the impact of population-wide screening interventions for TB.

The mass CXR screening campaign conducted in Kolín was historically considered an epidemiological failure, consolidating the lingering belief that such campaigns are not a cost-effective tool for interrupting transmission [17]. However, with my re-evaluation, I concluded otherwise; what was deemed a failure—namely, the detection of individuals with smear-negative TB—likely contributed to the early identification of individuals with TB (either already infectious or on the verge of becoming infectious), thereby potentially reducing background *Mtb* transmission and preventing future suffering [18]. Unlike the conventional approach of targeting only those with symptoms and sputum smear-positivity, early treatment interrupts transmission and contributes to reduce TB burden [19]. Historical TB literature represents a valuable yet underutilised resource for addressing contemporary scientific and policy questions, as its re-analysis can provide insights and efficiently answer contemporary challenges [20]. For example, a recent analysis of a similar campaign conducted in Glasgow in 1957 revealed a significant and sustained reduction in TB notifications in the following years [21]. A key contributor to this reduction was the detection of individuals with early, asymptomatic TB [21]. As with the Kolín study, the potential impact of improved housing and social conditions must also be considered when interpreting these results [18,21]. Nonetheless, based on contemporary evidence, only a symptom-agnostic approach seems to result in the desired outcome of a reduced TB burden [22,23].

7.2.4 Chapter 6: Population-wide screening for tuberculosis

This chapter addresses *Objective #4* of the thesis by calibrating a natural history model of the spectrum of TB disease to TB epidemiology in Viet Nam to assess the cost-effectiveness of

various population-wide screening algorithms. Notably, this chapter was set to achieve the second aim of the thesis on evaluating the potential impact, cost, and benefits of population-wide screening interventions for TB in a high-burden setting.

I concluded that population-wide screening could enact a substantial and cost-effective reduction of TB burden [24]. Using a model that reflected the spectrum of TB, I calibrated parameters to align with TB epidemiology in Viet Nam and the outcomes observed in the ACT3 trial [22,24]. An algorithm combining CXR with a confirmatory bacteriological test using Xpert MTB/RIF Ultra proved to be the most cost-effective compared to a business-as-usual approach [24]. This two-step screening strategy also resulted in a lower number of false positive diagnoses, given the combined accuracy of the tools used [24].

One of the main drivers behind the impact observed in the population-wide screening algorithms was the TB natural history model, which incorporated earlier TB states into intervention strategies, reflecting the current understanding of the disease spectrum [15,16,24]. TB prevalence surveys have consistently shown that around half of individuals diagnosed are not experiencing symptoms [25]. Although these individuals are not typically targeted by conventional symptom- and facility-based diagnostic approaches, they can contribute significantly to *Mtb* transmission [19,26]. Screening, particularly through CXR-based algorithms, also identified individuals with bacteriologically unconfirmed TB. While these individuals are not actively contributing to transmission, they represent a significant reservoir at risk of progressing to infectious disease [13]. Here, early treatment not only prevented future suffering for the individuals but also provided societal benefits by reducing potential transmission.

Ultimately, the effectiveness of the screening algorithms depended on the probability of a positive test result from the tools employed. Somewhat counterintuitively, a highly specific test may be preferred, as widespread implementation could otherwise result in many individuals being mistakenly placed on treatment due to false positive results [27]. However, this assumes that screening positivity directly leads to treatment without further evaluation, which is often not the case. For instance, in the ACT3 trial, individuals with a positive screen were asked to provide two additional spontaneously expectorated sputum samples for microscopy, culture, and drug-susceptibility testing [22]. They also attended a clinical assessment, which often included a CXR [22]. Based on the combined findings from these

assessments, the attending clinician determined whether to recommend TB treatment [22]. This additional post-screening evaluation step likely reduced the number of false positives and overtreatment, resulting in a more favourable ratio of true to false positives and lowering treatment costs, as suggested by the sensitivity analysis. Nevertheless, these interventions are not consistently reported or standardised, making it difficult to quantify their processes (e.g., determining specific 'test positivity' values and costs at each step) and incorporate them accurately into mathematical models

Furthermore, current pooled data on test positivity for individuals without TB are derived from clinical settings rather than the community, potentially underestimating the specificity of the test employed [28]. This leads to elevated estimated treatment costs, not only for individuals with TB but also for those without the disease who may be subjected to unnecessary treatment [27]. Moreover, treatment is not without risk, as individuals may experience side effects, incur additional costs, and face stigma associated with TB treatment [29–31].

The implementation of population-wide screening interventions is inherently tied to economic considerations. These interventions are expensive and require strong governmental commitment along with institutional or external funder support. Such funding demands in the medium-term could pose challenges. However, while the average front-loaded investment during the intervention years represents a significant burden for national TB programmes, economic benefits are quickly realised once the intervention concludes [24]. Advocating for TB eradication on economic grounds is compelling [32], as trends indicate that cost savings will persist alongside the long-lasting societal benefits of the intervention [24].

7.3 Strengths

Some overall strengths of the thesis are:

- The thesis incorporates a broad analysis of TB, addressing both the dynamic nature of *Mtb* infection and TB disease while fully acknowledging current shifts away from the binary paradigm. Consequently, the mathematical models used offer timely and novel insights into TB epidemiology, aligning with evolving perspectives on the disease.

- Models and parameters used were grounded in data, building upon recent work on the spectrum of TB [13,33]. When data was lacking, broad assumptions were made to fully explore the impact of parameter uncertainty on the overall results [10,24].

7.4 Limitations

Some overall limitations of the thesis are:

- Despite efforts to ground models in available data, gaps in empirical evidence required assumptions for parameters like self-clearance rates and test performance in community settings [10,24]. While sensitivity analyses helped address uncertainties, some key outcomes—such as estimates of viable *Mtb* infection burden and intervention cost-effectiveness—may need to be revisited as more robust data emerge. This limitation highlights the inherent challenges of modelling in areas where data are scarce, yet it underscores the importance of ongoing research to refine these estimates.
- TB along the spectrum of disease has complex pathways [13]. While the models incorporated the spectrum of TB, necessary simplifications were made to ensure tractability. This limits the ability to capture individual variability in factors like progression, regression rates, and test performance, potentially affecting the precision of findings for diverse populations. Despite these constraints, the broader insights provided by the models remain highly relevant for informing strategic TB prevention and care planning.
- The focus on Viet Nam for population-wide screening interventions limits the generalisability of findings to other high-burden countries with differing epidemiological and healthcare contexts. Intervention feasibility, cost-effectiveness, and outcomes may vary in other settings. While the findings provide a compelling case for Viet Nam, further calibration in diverse contexts is necessary to create a comprehensive investment case and inform global policy. This limitation is moderate, as Viet Nam serves as a valuable exemplar for high-burden countries, but broader applicability remains constrained.
- Modelling for population-wide screening assumed ideal conditions, which may not reflect real world implementation. Practical challenges such as logistical, social, and economic barriers—and changes in these factors over time—could influence the feasibility, sustainability, and effectiveness of the interventions. This limitation is significant, as it underscores the potential gap between theoretical projections and actual outcomes, emphasising the importance of validating findings through real-world data and pilot implementations to ensure practicality and scalability.

7.5 Future recommendations

The research projects embedded in this thesis have made substantial contributions to TB research, with each chapter offering a unique perspective and path forward to TB elimination. Future recommendations include:

7.5.1 Test for viable *Mycobacterium tuberculosis* infection

Immunoreactivity tests, while still useful in specific scenarios (e.g., recent conversion or known exposure), are insufficient to accurately identify viable *Mtb* infection. [11]. Future research should prioritise the development of diagnostic tools capable of identifying viable *Mtb* in individuals who are not actively expelling bacilli. These tools could include biomarkers specific to *Mtb* that indicate active biological processes, rather than relying solely on the direct detection of the bacteria or its DNA. Such a tool would be critical for identifying individuals who would benefit from TPT, as well as for diagnosing those with macroscopic evidence of lung disease when conventional bacteriological methods fail [15]. Ultimately, this test, apart from feasible, would need to be widely available and affordable, in order to complement existing TB prevention and care strategies.

7.5.2 Interpreting immunoreactivity tests

In lieu of the above, we can still effectively utilise the readily available *Mtb* immunoreactivity tests. Firstly, long-held assumptions about immunoreactivity should no longer guide clinical management [2]. For instance, a single positive immunoreactivity test does not necessarily indicate current infection or a lingering risk of disease progression; relying on this may cause unnecessary anxiety for individuals, as immunoreactivity is a poor predictor of long-term progression risk [2,34]. Further assessment and follow-up retesting are warranted to accurately determine risk. Similarly, a negative immunoreactivity test should not be interpreted as proof that exposure has never occurred, as reversion may have taken place. Instead, it should be viewed as a baseline, enabling recency of exposure to be evaluated in future tests if needed. In general, we must acknowledge that a single immunoreactivity test provides only a limited snapshot of what is a dynamic process [2]. Ideally, immunoreactivity testing should be incorporated into an integrated monitoring procedure for high-risk groups, particularly those at heightened risk of exposure to *Mtb* and progression to TB disease, where timely assessments of recent exposure can guide the provision of TPT [8].

7.5.3 Reintroducing immunoreactivity surveys

Immunoreactivity surveys can provide valuable insights into *Mtb* exposure at the population level. Re-introducing immunoreactivity surveys should be considered by the TB community as part of monitoring efforts towards TB eradication. In recent times, immunoreactivity surveys have been largely abandoned due to test limitations, operational challenges, and difficulties in interpreting results [8]. However, at a fraction of the cost of TB prevalence surveys, immunoreactivity surveys present a feasible alternative for resource-limited settings or regions with lower TB prevalence [8]. When conducted as repeat surveys, they can provide valuable insights into transmission trends, offering guidance for TB prevention and care strategies [9]. Evidence indicates a strong correlation between immunoreactivity trends and TB burden [22,35], making these surveys a relatively cost-effective option for TB surveillance in scenarios where prevalence surveys are not feasible. Additionally, immunoreactivity surveys can help categorise trends by age groups and risk factors, further enhancing their utility [8].

7.5.4 Expanding population-wide screening efforts

Historical evidence strongly supports symptom-agnostic population-wide screening interventions for TB [36], with contemporary findings from the ACT3 trial further highlighting their potential as an effective strategy for reducing the TB burden [22]. Scaling such interventions, especially in high-burden settings, should be a priority. While these efforts are resource-intensive, modelling suggests they yield significant impact on TB burden and cost savings in the years following implementation [24]. However, in low-resource settings, their feasibility depends on greater commitments from manufacturers to reduce costs and improve accessibility. Additionally, research should prioritise optimising screening algorithms to maximise both efficacy and cost-effectiveness.

7.5.5 Reassessing test positivity

The impact of a screening algorithm hinges on the performance of the test employed. In modelling, test positivity directly shapes outcomes, influencing the diagnosis of individuals with TB (linked to sensitivity) and significantly affecting overtreatment of those without TB (linked to specificity). However, most estimates are drawn from clinic-based studies [28], which often overestimate sensitivity and underestimate specificity relative to the test's likely performance in community settings. This discrepancy leads to an underestimation of the cost-effectiveness of mass screening efforts. Accurate capture of test performance in

community settings is essential for improving model predictions. Furthermore, test performance can vary depending on the TB state of the individual, meaning that reporting TB as a singular outcome limits the ability to accurately represent the complexity of the disease in models. Additionally, diagnostic accuracy is frequently assessed against the imperfect gold standard of culture from a single spontaneous sputum sample, whereas using multiple samples or induced sputum can significantly improve yield [37]. This has important implications when evaluating trace positivity in Xpert MTB/RIF Ultra assays, raising the question of whether such results truly represent false positives or reflect the limitations of single-sample culture, potentially yielding false negatives. More refined diagnostic methods may even detect TB years before it becomes microbiologically evident [38]. Acknowledging the limitations of this standard, particularly in detecting bacteriologically unconfirmed TB, is crucial for making meaningful adjustments in models. Additionally, further research is needed to develop and validate improved diagnostic standards that can more effectively identify individuals with TB, ensuring more accurate representation in both clinical practice and modelling efforts.

7.5.6 Reporting of post-screening procedures

As noted previously, screening positive does not directly lead to treatment initiation but requires additional steps beforehand [22]. However, while screening procedures are typically standardised and explicitly reported, post-screening assessments are often left to staff and resources beyond the observation of the trial. Although this is understandable, studies should strive to carefully document and quantify these processes to enable their integration into mathematical models for more precise evaluations of interventions. Based on sensitivity analysis results [24], incorporating these factors could significantly enhance the cost-effectiveness of population-wide screening strategies.

7.5.7 Enhancing modelling to guide interventions

Mathematical modelling has proven to be an invaluable tool for simulating interventions and their outcomes, providing critical support for policy decision-making and guiding TB prevention and care strategies. As George Box famously stated, "*all models are wrong, but some are useful*" [39], stressing the need for modellers to strive for maximum utility. Continued refinement of models to incorporate updated assumptions and data, including transmission dynamics across the TB spectrum, will further strengthen evidence-based decision-making.

7.6 Conclusions

While the global TB response remains far from achieving the *End TB Strategy* targets [40], recognising the dynamic nature of *Mtb* infection and the spectrum of TB disease is likely to propel progress. The evolving understanding of *Mtb* infection as a more active process, rather than a 'latent' one, already suggests that TPT strategies could be targeting a smaller population [41]. An accurate marker of viable *Mtb* infection would further aid this process, particularly given the likely rapid turnover of infections and self-clearance, with a larger group at high risk of progression to disease than previously believed [10,14]. This rapid turnover also underscores the need for interventions that reduce *Mtb* transmission. Population-wide screening using a symptom-agnostic approach can detect individuals with TB earlier in their disease pathway—a period with significant contribution to transmission [19]. These interventions, which have been employed in the past [36], are now supported by contemporary evidence [22]. However, curing someone of TB is sometimes not enough [42], and a sizeable population can present with ongoing challenges in the form of post-TB lung disease [43]. Furthermore, TB remains fundamentally a biosocial problem [44], requiring substantial efforts to address various social determinants of health in order to truly achieve a world free of TB.

7.7 References

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