Modelling the South African tuberculosis epidemic: the effect of HIV, sex differences, and the impact of interventions

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Thesis presented for the degree of

Doctor of Philosophy

in the Division of Epidemiology & Biostatistics,

School of Public Health and Family Medicine,

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Date of submission: 30 August 2022

Declaration

I, Mmamapudi Kubjane, declare that the work included in this thesis is my original work, except where acknowledgments specify otherwise. Neither whole work of this thesis, nor any part of it has been, or will be submitted for another degree in this or another University.

Signature: Signed by candidate Date: 30 August 2022

Inclusion of publications

This thesis includes published manuscripts as per the general provision 6.7 in the General Rules for the degree of Doctor of Philosophy (PhD) of the University of Cape Town. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the publications below in my PhD thesis. My co-authors have also agreed that I may include the publications.

1. Kubjane M, Osman M, Boulle A, Johnson LF. The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: A mathematical modelling analysis. [*published online ahead of print, 2022 Jul 21]. Int J Infect Dis*. 2022; S1201-9712(22)00438-6].

2. Kubjane M, Cornell M, Osman M, Boulle A, Johnson LF. Drivers of sex differences in the South African adult tuberculosis incidence and mortality, 1990-2019. [*Submitted to Scientific Reports*]. (Preprint link, DOI:10.21203/rs.3.rs-1908771/v1)

The contribution of all other authors is stated in each of the respective manuscripts. My overall contribution was study conceptualisation, writing parts of code for the mathematical model developed, reviewing the literature; extracting data from publicly available sources; data analysis, data visualisation and interpretation of results, writing the first drafts for each manuscript and addressing feedback and comments from co-authors.

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Acknowledgements

I would like to thank my primary supervisor Leigh Johnson for his patient guidance and the critical and insightful feedback he always provided throughout the many years of working with him. I am also very grateful for the opportunity to learn and work on adding TB dynamics to an already large and complex mathematical model (the Thembisa HIV model) – this took a lot of time, so I appreciate the time and energy you invested. In the process, I have also acquired a lot of valuable technical skills, which will be helpful throughout my career. To Andrew Boulle, thank you for providing critical inputs and feedback, and supporting the work.

I would like to thank all co-authors of the manuscripts that addressed the objectives of this PhD research. I valued your time, input, and different perspectives. I also thank Morna Cornell, who has played a mentoring role in the early stages of my PhD.

Huge thanks to my family and friends for their understanding, kindness and continued support. And lastly, a special loving memory of my late mom Makwane Kubjane who remains my inspiration.

Funding

I would like to thank the funding support and research training opportunities I have received from the Fogarty HIV-Associated Tuberculosis Training Program Fellowship (Fogarty International Center of the National Institutes of Health, award number: D43 TW010559). I thank the support of the Bill and Melinda Gates Foundation for funding my conference attendances (award number: 019496). I would also like to acknowledge the PhD funding I received from the International epidemiology Databases to Evaluate AIDS (National Institutes of Health, award number: UO1AI069924) and the South African Department of Science and Technology/National Research Foundation Centre of Excellence in Epidemiological Modelling and Analysis.

Abstract

The South African tuberculosis (TB) epidemic is driven mainly by HIV, and the TB disease burden is greater in males than females. Additional factors that drive the epidemic include undiagnosed and untreated TB, contributing to transmission; and highly prevalent TB risk factors such as alcohol misuse, smoking, diabetes, and undernutrition, which increase the risk of progression to TB disease. These factors are distributed differently by sex and likely explain the observed sex disparities in TB. The South African TB control programme has implemented multiple interventions, including directly observed therapy strategy (DOTS), antiretroviral therapy (ART), intensified screening activities, the provision of isoniazid preventative therapy (IPT) and the implementation of Xpert MTB/RIF as a first-line diagnostic tool. However, few analyses have quantified the historical impact of HIV and the combined impact of TB interventions on the South African TB epidemic at a national level. In addition, factors that influence sex disparities in the South African TB burden have not been explored thoroughly. Also, it remains uncertain whether, with existing interventions, it would be feasible for South Africa to meet the End TB targets to reduce TB incidence and mortality by 80% and 90% respectively (relative to 2015 levels) by 2030.

This thesis aims to address the abovementioned gaps in knowledge and provide insights into understanding the population-level TB dynamics, using a mathematical model. The first objective is to quantify TB incidence and mortality due to HIV and assess the impact of interventions mentioned above on TB incidence and mortality between 1990 and 2019. The second objective is to explore the extent to which the following factors contribute to sex differences in TB: HIV, ART uptake, smoking, alcohol abuse, undernutrition, diabetes, health-seeking patterns, social contact rates and TB treatment discontinuation. The third objective is to project the future impact of increasing screening, improving linkage to TB care and retention, increasing preventative therapy, and reducing ART interruptions.

An age- and sex-stratified dynamic tuberculosis transmission model for South Africa was developed. To dynamically model the effect of HIV and ART on TB incidence and mortality, the TB model was integrated into the Thembisa model, a previously-developed HIV and demographic model. In addition, age- and sex-specific relative risks were applied to rates of progression to TB disease to capture age and sex differences in tuberculosis incidence. The model also included a diagnostic pathway representing health-seeking patterns and the sensitivity and specificity of the diagnostic algorithm. A Bayesian approach was used to

calibrate the model to the numbers of people starting treatment from the electronic tuberculosis register, deaths from the vital register, microbiological tests, and the national tuberculosis prevalence survey.

The model estimated rapid increases in TB incidence and mortality in the mid-to-late 1990s, influenced by HIV. Between 1990 and 2019, approximately eight million people developed tuberculosis, and two million died from TB; HIV accounted for at least half and two-thirds of the TB incidence and mortality, respectively. The TB epidemic peaked in the mid-to-late 2000s, followed by declines until 2019. The ART program and TB screening efforts, which were expanded in the mid-2000s, contributed the most to reductions in TB incidence and mortality, while other interventions had minor impacts. Due to the heavier HIV burden in women than men, women experienced greater HIV-associated TB incidence and mortality than men. However, because of the higher ART uptake among women than men, women experienced greater relative reductions in TB incidence and mortality over the period 2005–2019. Consequently, the higher TB burden among men has been sustained; the estimated male-to-female ratios of TB incidence and mortality in 2019 were 1.7 and 1.65, respectively. Additional factors explaining the excess TB in men are smoking, alcohol abuse and delays in health-seeking patterns. Sex differences in undernutrition, social contact patterns, and treatment discontinuation had minimal effect on TB sex disparities.

Projections of the model to 2030, considering the effects of COVID-19-related disruptions to TB care, suggest that increasing TB screening would be the most impactful among all interventions explored. However, the model also suggests that the 2030 End TB milestone is unlikely to be met by scaling up existing interventions. Other interventions that need to be explored include targeted universal TB testing and other diagnostic tests such as digital chest x-rays, urine Lipoarabinomannan, and biomarkers to identify individuals at risk of TB disease.

Accelerating progress toward TB incidence and mortality reductions will require developing affordable and efficient rapid diagnostic tools to identify potential and active TB cases. Research and innovation efforts towards finding a vaccine effective in preventing TB disease are also critical. In addition, it is essential to improve the uptake of TB preventative therapy in HIV-positive individuals and perhaps further expand provision to other TB risk groups. The higher burden of TB in males highlights the need for men to be targeted for routine screening to ensure earlier diagnosis and improved management and retention in TB and HIV

care. Additionally, broader interventions are needed to reduce TB risk factors such as alcohol consumption and tobacco smoking.

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AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BCG	Bacillus Calmette Guérin
BMI	Body mass index
CI	Confidence interval
CORTIS	Correlate of Risk Targeted Intervention Study
COVID	Coronavirus disease
DOTS	Directly Observed Therapy Short course
DHIS	District Health Information System
DoH	Department of health
HR	Hazard Ratio
HbA1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
3HP	Isoniazid-rifapentine for 12 weeks
IHME	Institute for Health Metrics and Evaluation
ILTFU	Initial loss to follow-up
IGRA	Interferon-gamma assays
IPT	Isoniazid preventative therapy
IQR	Inter-quartile range
LAM	Lipoarabinomannan
LTBI	Latent tuberculosis infection
MDG	Millennium development goals
MDR	Multi-drug resistant
M.tb	*Mycobacterium tuberculosis*
M:F	Male to female ratio
NICD	National institute for communicable diseases
OR	Odds ratio
PAF	Population attributable fraction
P:N	Prevalence-to-notification

RR	Relative risk
SADHS	South African Demographic Health Survey
SANHANES-1	South African National Health and Nutrition Examination Survey
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SATVI	South African Tuberculosis Vaccine Initiative
SDG	Sustainable development goals
STI	Sexually transmitted infection
TB	Tuberculosis
TPT	Tuberculosis preventative therapy
TST	Tuberculin skin test
WHO	World Health Organization
ZAMSTAR	Zambia, South Africa Tuberculosis and AIDS Reduction

Chapter 1. Introduction

1.1. Global burden of tuberculosis

Tuberculosis (TB), caused by *Mycobacterium tuberculosis (M.tb)*, contributes significantly to the global disease burden (1). According to the World Health Organisation (WHO), in 2020, approximately 9.9 million (range: 8.9–11.1 million) people developed TB disease, and 1.3 million (range:1.2–2.5 million) died due to TB (1). The burden of TB is distributed differently by age and sex, and adult males (aged ≥ 15 years) carry a heavier burden (56%), while adult females carry approximately 33%, and children (aged <15 years) almost 11% of the burden of TB (1). The pooled estimate of the male-to-female (M:F) ratio for TB prevalence based on 56 prevalence surveys conducted in 24 countries is 2.2 (95% confidence interval (CI) 1.9–2.5) (2); and the surveys further show that compared to females, males have greater delays in TB diagnosis and treatment initiation (2).

The burden of TB also varies significantly across the six WHO geographic regions. The region with the highest number of new people falling ill with TB disease is South East Asia (43%), followed by the African (25%) and the Western Pacific (18%) regions (1). Drug-resistant TB is also remains a health challenge; the prevalence of drug-resistance is around 3–4% in newly treated TB cases and 18–21% in previously-treated TB case (3). Countries that carry the most significant burden of resistant TB globally are India (27%), China (14%) and the Russian Federation (9%) (3).

Multiple factors contribute to the high burden of TB. Human immunodeficiency virus (HIV) is the strongest individual-level and population-level TB risk factor, increasing the risk of developing TB disease and worsening treatment outcomes (4–6). In southern Africa, HIV is the primary driver of TB, with at least half of the people with TB disease are HIV-positive (3). Other important determinants of TB that contribute significantly to the global burden of TB include undernutrition, alcohol abuse, tobacco smoking and diabetes (3,7). The WHO estimated the population attributable fractions (PAF) of the abovementioned risk factors to be 8.1% for alcohol abuse, 3.1% for diabetes, 7.6% for HIV, 7.1% for smoking, and 19% for undernutrition (1). Furthermore, these risk factors are distributed differently by sex and likely drive the existing sex differences in the burden of TB. The Global Burden of Disease Study (2019) estimated the fraction of global tuberculosis deaths due to alcohol abuse, smoking,

and diabetes to be 4.3, 6.2, and 1.2 times higher among males than among females, respectively (7).

Global efforts against TB have included the establishment of strategies such as the WHO End TB Strategy (8) and high-level meetings (9) where TB policy leaders commit to implement and invest in measures required to meet targets to reduce the TB burden and mortality substantially. Since the discovery of effective anti-TB drugs, TB control efforts have been mainly biomedical, focusing on developing novel regimens and diagnostic technologies (10). Although these control efforts have led to substantial reductions in the burden of TB, these declines have been slow. Between 2015 and 2020, the number of people with TB and TB deaths dropped by 11% and 9.2%, respectively (1). These reductions were short of the WHO End TB Strategy 2020 milestones which aimed to reduce TB incidence and mortality by 20% and 35% over 2015-2020 (1,11).

The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes COVID-19, has brought more challenges and caused global TB control efforts to regress (1,12). Worldwide, the COVID-19 pandemic led to over-burdened health care systems, and COVID-19-related interventions restricting people's movement have caused disruptions to TB care-seeking patterns (3,13). Data from many settings showed that people's health facility attendance rates dropped in the first four months of the pandemic compared to attendance patterns for the same period in previous years (14,15). Consequently, globally TB notifications dropped by approximately 18% between 2019 and 2020 (1). Altogether, these COVID-19-related disruptions slowed down the declines in TB incidence and caused mortality rates to increase by 5.6% between 2019 and 2020 (1,16).

The End TB Strategy 2030 milestones aim to reduce the global TB incidence by 80% and global TB mortality by 90% by 2030 in comparison to 2015 levels (11). Given the existing challenges in TB control, it remains uncertain whether the targets will be met.

1.2. South African burden of tuberculosis

In 2020, the WHO estimated that approximately 328 000 (range: 230 000–444 000) South Africans developed TB disease and of these, 71% were HIV-positive (1). The prevalence of TB in South Africa is also higher in males than females, with an estimated M:F TB prevalence ratio of 1.62, and a much higher TB prevalence in the 35-44 years and 65+ age

groups (17). The number of TB deaths in 2020 were estimated at 61 000 (range: 49 000–82 000) (1); and more males die of TB than females (18).

South Africa has the largest HIV epidemic globally, with approximately 8 million people living with HIV (19) – the main driver of TB in the country. In addition to HIV, another major factor which increases the burden of TB is under-diagnosis of individuals with TB disease, which drives TB transmission and mortality (2,20). Recurrence of TB disease is also a problem among individuals with a history of previous TB treatment (21,22). Additionally, there are other highly prevalent TB risk factors such as undernutrition, alcohol misuse, tobacco smoking, and diabetes (3,7). The 2019 GBD study estimated that in HIV-negative individuals, compared to females, males have higher TB mortality PAFs for smoking (21% vs 5%) and alcohol (41% vs 16%); however the TB mortality PAFs for diabetes were higher in females (11%) than males (10%) (7).

South Africa has made strides to control the TB epidemic. Some of the major TB control efforts include intensified case finding and infection control (23), implementing new diagnostic tools such as Gene Xpert MTB/RIF and Xpert Ultra as first line diagnostic tools, the provision of TB preventive therapy, and antiretroviral therapy (ART) for HIV-positive individuals (23,24). However, despite observing falling TB trends due to some of these interventions, South Africa is still ranked among the 20 high TB burden countries (25). Additionally, like most countries, South Africa's TB control also experienced significant setbacks due to the COVID-19 pandemic, and it is uncertain whether the End TB targets remain feasible (26,27).

1.3. Problem statement and rationale

Tuberculosis remains a significant public health challenge in South Africa, and its main determinants are well documented. However, very few analyses that capture South African demographic details (i.e., age and sex) have quantified the contribution of these factors that drive the TB epidemic. In addition, while multiple TB interventions have been implemented, there have not been any systematic analyses to quantify how these interventions have contributed to reducing TB incidence and mortality at a national level. Dynamic mathematical models are valuable tools that can be used to understand the population-level dynamics of TB and assess the past and future impact of interventions. There is, therefore, a need for national-level mathematical models that are calibrated to South African data that can

be used to systematically evaluate the impact of risk factors and interventions on TB incidence and mortality.

1.4. Aim and objectives

The aim of this PhD is to develop a dynamic transmission model of TB and HIV for South African adults (15 years and older). The model will be used to address the three specific objectives of this PhD:

1. To describe the South African TB epidemic trends between 1990 and 2019, quantify TB incidence and mortality due to HIV, and assess the impact of programmatic interventions – increased screening, directly observed therapy, Xpert MTB/RIF, isoniazid preventative therapy and ART – on TB incidence and mortality between 1990 and 2019
2. To explore the extent to which the following factors contribute to sex differences in TB incidence and mortality: HIV, ART uptake, smoking, alcohol abuse, undernutrition, diabetes, health-seeking patterns, social contact rates and TB treatment discontinuation.
3. To estimate the future impact on TB incidence and mortality, of increasing screening, improving linkage to TB care and retention, increasing preventative therapy, and reducing ART interruptions.

1.5. Data sources

This study relied on publicly available data, which were obtained from published reports, epidemiological studies, or extracted from registers. Below is a summary of data that were used to calibrate the model and their sources (Table 1-1). The full description of how these data were obtained and cleaned, and how they were used, is provided in Chapter 3.

Table 1-1: Summary of calibration data and their sources

Data description	Strata	Sources
National tuberculosis prevalence data	Age, sex, year: 2018	South African Department of Health
Number of people screened and positive diagnoses	Years: 2004–2019	National Institute for communicable diseases; Nanoo *et al.* (24)
Number of people who initiate treatment and treatment outcomes	Age, sex, years: 2004–2016, HIV status	Electronic tuberculosis register (28)
Number of tuberculosis deaths	Age, sex, years: 1997–2016	Statistics South Africa vital register

1.6. Organisation of thesis

This first **Chapter 1** has described the status of the global and South African tuberculosis epidemics; it has also described the thesis rationale, aims and objectives. **Chapter 2** is a literature review that provides a broad context for this thesis by summarising literature on TB, the simplified natural history of TB, the commonly described TB determinants, and an overview of TB HIV mathematical models. The review also describes the evolution of the global and South African TB control strategies. **Chapter 3** provides a detailed description of the methodological approach, and the data sources and assumptions that were used to develop the TB-HIV model which forms part of this PhD. This thesis also presents our model estimates for the 'baseline' scenario and compares these to estimates from WHO and Institute for Health Metrics and Evaluation (IHME).

Chapter 4 describes the South African TB epidemiological trends between 1990–2019; assesses TB incidence and mortality attributable to the HIV epidemic; and assesses the impact of various interventions on TB incidence and mortality. Given the observed sex disparities in the burden of TB, **Chapter 5** explores how sex differences in TB could be explained by social mixing patterns, diabetes, tobacco smoking, alcohol misuse, undernutrition, health-seeking and poor retention in TB care. Lastly, **Chapter 6** evaluates the potential impact of scaling up existing interventions, focusing on 1) improving steps in the care cascade (increasing microbiological testing rates, reducing pre-treatment loss to follow-up, improving TB treatment outcomes); 2) improved provision of ART and IPT for people living with HIV, and 3) the provision of preventative therapy for previously treated individuals. This chapter also assesses the potential for South Africa to meet the End TB

goals. Finally, **Chapter 7** summarises and discusses the results of the analyses of this thesis, and outlines areas for further research.

Chapter 2. Literature review

This chapter aims to review and discuss the existing literature on the development of TB and its determinants, control policies, and TB-HIV mathematical models. The chapter is in two parts. The first part (A) gives an overview of the simplified TB natural history; it describes the evolution of TB control strategies, the distribution of TB by age and sex, and the effects of selected risk factors. The second part (B) gives an overview of existing TB-HIV mathematical models and methodological approaches used. In each section, some of the research gaps identified are discussed.

2.1. Part A: The natural history and control of tuberculosis

The four main aspects that are described in this first of the literature review are: 1) the development stages of TB, 2) the evolution of TB control strategies; 3) the distribution of TB by age and sex; and lastly, 4) the role of selected TB risk factors namely diabetes, undernutrition, tobacco smoking and alcohol abuse.

2.1.1. The transmission and development of tuberculosis

The primary mode of TB transmission is by the release of bacilli into the air through talking, or coughing, or sneezing by an infectious individual, or by breathing (29). The classic symptoms of pulmonary TB include fever, night sweats, coughing for a long period, and excessive unintentional weight loss (30,31). Tuberculosis commonly affects the lungs (pulmonary TB); however, it can also affect other parts of the body (extrapulmonary TB).

The natural history of TB is complex, and it is not a discrete process with distinct states as classically described (32). However, for simplicity and for the sake of laying the foundation to describe the disease, its determinants, and measures to control it, we can look at its development in three discrete stages. These stages are i) exposure to *M.tb* bacilli in the air, ii) latent TB infection (LTBI) following inhalation of aerosols containing bacilli, and iii) development of active TB disease. These three states will be expanded further later in Chapter 3 when describing the TB natural history structure for the compartmental mathematical model developed in this thesis.

i. *Exposure*

The degree of exposure to *M.tb* can be measured in terms of duration and proximity to aerosols containing bacilli. Exposure risk depends on the frequency of contacts between susceptible and infectious individuals with active TB disease over a given period (i.e. contact rate) (33). Environmental conditions that can increase the likelihood of exposure to *M.tb* include overcrowded living conditions and inadequate ventilation (34,35). Household studies have shown a positive association between the risk of infection with *M.tb* and household density or crowding (36,37). The exposure risk is increased through limited airflow, sharing breathed air, and increased contact with infectious individuals. Additionally, social behaviours such as alcohol drinking are associated with close contacts between individuals (38,39); thus, this may contribute to TB transmission.

Undiagnosed and untreated active TB in the population is another factor contributing to TB transmission through increasing exposure to *M.tb*. Many resource-limited settings have a high prevalence of undiagnosed and untreated active TB (40–42). Studies from these settings also show that there are usually delays between the onset of TB symptoms and those detected and eventually treated (43–46). Reasons for high undiagnosed and untreated TB include socioeconomic factors such as low education and poor access (geographical or sociopsychological barriers) (47). Another important source of undiagnosed and untreated TB are asymptomatic TB (48,49).Other reasons are the inadequate capacity of health systems to detect TB early, to treat and manage TB patients until they are cured (43–46). As a result, poor diagnosis and treatment of TB may explain a large proportion of transmission in these resource-limited settings.

The primary mode of acquiring TB infection is through the inhalation of aerosol containing *M.tb* from an infectious individual with pulmonary TB, usually released through coughing, shouting or sneezing (34). These *M.tb*-containing particles can remain suspended in the air for minutes to hours (50). Successful infection depends on the infectiousness of the source individual with active TB; and infectiousness can be measured by the number of bacilli contained in the droplets released into the air and the virulence of the bacteria. Several empirical studies and literature reviews (33,51,52) have suggested that smear-positive pulmonary TB individuals are more infectious than smear-negative individuals. For example, a study using DNA fingerprints assessed the link between recently infected individuals and the sources of infection. This analysis showed that smear-negative individuals were 0.22

(95% CI 0.16-0.32) times as likely to transmit TB as smear-positive patients (53). The immune status of the infectious individual also determines their infectiousness. For example, immune-suppressive conditions such as HIV infection are associated with reduced infectiousness, decreased bacillary load and reduced cavitary disease (54).

ii. *Latent tuberculosis infection*

Following inhalation of aerosols containing bacilli, for simplicity, two scenarios are possible. In the first case, bacteria may be cleared before infection occurs through innate immune mechanisms. These mechanisms involve mucociliary clearance in the upper respiratory tract, and the individual may not have immunological signatures of infection (34,55). In the second case, successful *M.tb* infection results and through a combination of innate and adaptive immune responses to *M.tb*, it is then detectable by immunoreactivity to TB tests (34,55). In this second case, the individual is considered to have acquired a latent TB infection (LTBI) unless or until clinical symptoms are detected (55,56).

The main tests used to identify LTBI are the tuberculin skin test (TST) and interferon-gamma assays (IGRA), which mainly indicate immunoreactivity to TB (57). As a result, if a person tests positive, their positive result does not reflect their risk of developing TB disease but rather indicates that they have, at some point in time been exposed to *M.tb* (58). Some limitations with these tests include low specificity of the TST, and it is often unable to differentiate actual infection from Bacillus Calmette Guérin (BCG) vaccination (54). As a result, using this test may lead to false-positive TST results and hence overestimate LTBI prevalence in settings with high BCG coverage. The IGRA test overcomes the limitation of low specificity in BCG vaccinated individuals (54). However, both the IGRA and TST tests have limited sensitivity in immune-suppressed individuals (i.e., people living with HIV) (54).

Using a mathematical model and assumptions based on TST, Houben and colleagues estimated the global prevalence of LTBI to be 23.0% (95% uncertainty interval: 20.4%–26.4%) (59). Cohen *et al*. also estimated the global LTBI prevalence by using a meta-analysis of LTBI prevalence studies from varying geographical settings and specified the use of IGRA and TST (60). The estimated LTBI prevalence was 24.8% (95% CI: 19.7–30.0%) based on IGRA and 21.2% (95% CI: 17.9–24.4%) based on TST (60). Altogether, scientific evidence suggests that one-fourth or 1.7 billion people of the global population is estimated to have LTBI (59,60).

The presence of LTBI is thought to confer partial immunity against reinfection; however, the extent of this protection is contentious. A meta-analysis of studies, most of which used historical data before large-scale TB preventative therapy, estimated that individuals with LTBI had a 0.79 (95% CI 0.70–0.86; I-squared=0.7) reduction in the risk of fast progressive TB after reinfection than those without LTBI (61). The effect of HIV and how ART modifies this partial immunity is not well-understood.

iii. *Development of active tuberculosis disease*

Following infection, individuals develop active or clinically detectable TB disease, generally in two ways. In the first case, approximately 5% of immunocompetent individuals develop active TB within two years of becoming infected, commonly referred to as *fast or rapid progression* to TB disease (62,63). In the second case, the onset of clinical symptoms occurs much later, sometimes even a couple of decades later; this is commonly referred to as *endogenous reactivation* (64,65). For individuals with LTBI, the risk of developing active TB disease (reactivation) varies with time since exposure to infection, on average it is estimated at 10–20 per 100 000 individuals per year (63,66).

Although the risk of reactivation is low, multiple risk factors can increase the risk of developing TB disease through immune suppression. These risk factors include smoking, alcohol abuse (67–69) and clinical conditions such as HIV, diabetes (70,71), silicosis (35,72), immune-compromising treatments, malignancies (34), and undernutrition (73). The relative importance of these risk factors and their contribution to the burden of TB depends on their prevalence in the respective populations.

The standard modes to detect active pulmonary TB disease, particularly before 2011, were sputum smear microscopy and sputum culture. Smear microscopy is convenient but limited by its low sensitivity. While sputum culture is the gold standard diagnostic tool for TB, it is associated with a long turnaround period (about 2-6 weeks) (34). In recent years (from 2011), Xpert MTB/RIF test is the recommended diagnostic used globally and in South Africa. This test provides rapid detection of TB and can also determine if TB is resistant to rifampicin, one of the most commonly used TB drugs (34).

Detection of extrapulmonary TB is usually performed at secondary or tertiary hospitals using TB blood culture, tissue cultures, histological or cytological examination. Individuals with extrapulmonary TB are usually less infectious unless the site of disease is on their respiratory

tracks, or if in addition to extrapulmonary TB, they also have pulmonary TB disease (74). The symptoms for extrapulmonary TB, although non-specific, may include unintended weight loss, nights sweats and fever; other symptoms depend on the extrapulmonary TB body site affected or type (75). The common types of sites of extrapulmonary TB include the larynx, pleura, kidneys, bones and joints, lymph nodes or brain (74). Extrapulmonary TB is estimated to represent 16% of incident individuals globally; this proportion ranges 8% between 24% (3,74).

Besides recovery due to treatment, studies from the pre-antibiotic era have suggested that a certain proportion of active TB patients recovered naturally without treatment (also called spontaneous recovery) (76). Tiemersma *et al*.'s review of studies conducted during the pre-chemotherapy era estimated case fatality rates of 0.7 and 0.2 among untreated smear-positive and smear-negative active TB individuals, respectively, and the estimated mean duration of untreated TB disease was 3.33 years (76). Based on this meta-analysis, it could be shown that the average natural recovery rates are 0.212 and 0.091 per annum for untreated smear-positive and smear-negative active TB individuals, respectively (76).

2.1.2. Tuberculosis by age and sex

Age and sex are the most basic demographic characteristics and individual-level determinants of health. Thus, like other diseases, the burden of TB and mortality have age and sex patterns that are essential to understanding the TB epidemiology.

i. *Age*

The age patterns from TB notification rates data show a peak in children aged 0–4 years, followed by lower TB rates in the 5–10 years age group. However, during the adolescent age groups (15–19 years), there is an increase leading to a second peak in the 20–24 years age group, and then sometimes a third peak in the 45–49 years age categories (77–80). These observed age differences, particularly the TB rates in individual between ages of 5 and 14 years, are not well understood (81,82).

Plausible explanations for the age differences in TB include differences in immune response to infection and exposure to TB risk factors. Childhood (<15 years) TB infections are most likely due to exposure of susceptible children to adults with active TB (83), and the increased

risk of TB disease is suggested to be due to fast progression in children (80,84). Among young adults (20–24 years) and the middle age groups (45–49 years), the pattern can be explained by a combination of factors, including reactivation of LTBI, reinfection and rapid progression to TB disease due to the presence of immune-suppressive chronic conditions such as HIV and diabetes; or exposure to TB risk factors such as alcohol abuse and tobacco smoking. It could also be due to the high prevalence of untreated active TB individuals and social mixing between these age groups (83,85).

ii. *Sex*

With respect to sex, males carry a higher TB burden than females. The estimated male-to-female ratio of incident TB by WHO regions ranges between 1.3 in the Eastern Mediterranean Region and 2.1 in the European and West Pacific regions (3). Sex disparities in TB may be due to genuine sex-related epidemiological differences or systematic differences in reporting between males and females (2). However, TB prevalence surveys, which are meant to reflect the actual TB burden and reduce biases that may arise due to differences in reporting or healthcare-seeking behaviours, have confirmed this pattern of a higher TB prevalence in males (2).

There is substantial evidence showing that sex disparities are due to epidemiological differences, which may be biological, socio-behavioural, and socioeconomic risk factors (35,86,87). The mechanism by which these factors increase the burden of TB is through directly or indirectly influencing the risk of a) exposure to *M.tb*, b) acquiring LTBI or c) developing active disease. Biological hypotheses suggest that certain female sex hormones may play a role in providing protection against the susceptibility to infection and the development of TB disease (86,87). It has also been observed that males and females have different behaviours that may expose them to TB. For instance, compared to females, males tend to be more likely to smoke tobacco and drink alcohol excessively (88,89). These risk factors increase the risk of developing TB by suppressing cell-mediated immunity (90,91) and explain a considerable amount of the TB burden at the population level (92,93).

Furthermore, smoking and alcohol drinking are associated with social mixing patterns that facilitate TB transmission (69). Social contact patterns tend to be age- and sex-assortative; compared to women, men have more social contacts with other men, which increases their risk of TB acquisition (83,85). Undiagnosed and untreated TB also contributes to the burden

of TB by increasing exposure to *Mtb* and driving TB transmission. Horton *et al*. estimated the M:F ratio of prevalence-to-notification ratio (P:N) at 1.55 (95% CI 1.25–1.91) (2), suggesting that females may access TB care earlier than males. It could also be that males are not well-served by health care facilities, and as a result, leads to the higher burden of undiagnosed TB than in females.

Additionally, compared with women, men who eventually access TB care are more likely to be lost to follow-up and experience poor outcomes, including treatment failure and death (38,93). Socioeconomic reasons that may explain these include higher rates of employment in men and associated difficulties in adhering to treatment (particularly in the context of directly observed treatment). Men are also more likely to take on occupations such as mining which is are associated with exposure to silica and other industrial pollutants, which increase the risk of developing TB (72).

2.1.3. Tuberculosis risk factors – HIV, diabetes, smoking, undernutrition, and alcohol

Multiple TB risk factors exist; their significance to TB morbidity and mortality depends on the strength of their relative effect on TB disease or mortality and their prevalence in the population. For this PhD thesis, in addition to HIV, focus is on four TB risk factors that are potentially contributing significantly to increasing the population-level risk of TB globally and in the South African context. These risk factors include diabetes (indicated by glycated haemoglobin levels (HbA1c) >6.5%), undernutrition (or body mass index (BMI) <18 kg/m^2), tobacco smoking and alcohol abuse (defined as drinking at least 40g alcohol per day).

i. *HIV*

Strong evidence suggests that HIV has an effect on increasing progression to TB disease following recent infection (or reinfection). Studies conducted among prisoners and patients in hospitals have shown that a higher proportion of HIV-positive individuals were more likely to have incident TB due to recent transmission (94,95). Among HIV-positive individuals, TB disease risk following infection is much higher among those with low CD4 counts (i.e. 17.5 per 100 patient-years for CD4 <200 cells/µl compared to 3.6 per 100 patient-years for CD4 >350 cells/µl) (96).

Antiretroviral therapy modifies the effect of HIV on TB and is an important factor in the epidemiology of TB in this current large-scale ART era. The benefits of ART include

restoration of immunity, increases in CD4 count and reduction in the risk of developing active TB (4,97). A meta-analysis comparing individuals on ART and those not on ART showed that ART reduces TB incidence and further highlighted that initiating ART at higher CD4 counts has additional benefits (97). Another meta-analysis showed that an increase in 100 cells/µl of CD4 count is associated with a 30% reduction in TB risk (incidence rate ratio (IRR) 0.70, 95% CI 0.53–0.86) (98).

HIV also increases the risk of TB mortality (99,100), and CD4 count is an independent predictor of TB mortality before and during ART (99,101–103). The study by Kaplan *et al.* showed that a 50 cells/ml increase in CD4 count was protective against TB mortality (adjusted hazard ratio (HR) 0.82, 95% CI 0.35–0.42) (103). Several other studies have shown the protective effect of ART against TB mortality (104,105).

In South Africa, the adult HIV prevalence was 10.8% (95% CI 9.9–11.8%) and 14.0% (95% CI 13.1–15.0%) in 2002 and 2017, respectively. A higher prevalence was found among women (17%) than men (10.6%) in 2017. The estimated number of people on ART in 2017 was 4 401 872 (62.3%, 95% CI 59.2–65.2%) (19). ART became widely available in the public sector from 2004 (106), and its impact on mortality became evident after 2005 (107,108).

ii. ***Poorly controlled diabetes (HbA1c > 6.5%)***

Diabetes is an immune suppressive condition that increases susceptibility to developing TB disease (RR3.59, 95% CI 2.25–5.73) (70). Diabetes is also associated with adverse TB outcomes such as death and treatment failure and relapse (reactivation) of disease after treatment (109). On average, females have a higher prevalence of diabetes; however, they are less likely to be undiagnosed than men (110). Therefore, men might be more likely to have poorly controlled diabetes. In 2016, the South African Demographic Health Survey (SADHS) reported the prevalence of diabetes (HbA1c >6.5%) in adults? at 13% for females and 8% for males (89).

iii. ***Undernutrition***

Undernutrition, commonly defined by low BMI (<18 kg/m²), is associated with an increased risk of developing TB disease due to micro-and macro-nutrient deficiencies, which negatively impact immunity (111). Lönnroth *et al.*'s meta-analysis demonstrated an inverse relationship

between BMI and TB incidence within the range: 18 kg/m²–30.0 kg/m² range (73). The study showed that the risk of TB increased by 13.8% (95% CI 13.4–14.2) for each unit decrease in body mass index (73). Undernutrition in adults is common, particularly among men (73). In South Africa, the prevalence of underweight in males and females is 13.1% and 4%, respectively (112).

iv. *Tobacco smoking*

Tobacco smoking is associated with a wide range of diseases, including TB. Various epidemiological studies have shown the effect of tobacco smoking on developing active TB and TB death (113–115). In addition, chronic exposure to tobacco and smoke impairs pulmonary macrophages, which play an essential early defence mechanism against TB (116). It has, however, been shown that the adverse effect of smoking on the immune system reduces when an individual ceases to smoke (116). This suggests that the effect of smoking depends on whether an individual is currently exposed to smoking. There is also a dose-response pattern in exposure to smoking and TB risk – the risk of developing active TB increases with an increase in a daily dose of cigarettes and an increased duration of smoking (114). In South Africa, tobacco smoking is more common among males (37%) than females (8%) (89).

v. *Alcohol abuse*

Heavy alcohol drinking impairs the immune system and increases an individual's susceptibility to active TB infection and the reactivation of latent disease (68). The amount of pure alcohol in a single drink of alcohol is usually estimated at 10ml or 8g (though definitions of a ‘standard drink’ differ across settings). Risky alcohol consumption or alcohol use disorder is usually defined as drinking at least 40g of alcohol per day / or on one occasion (117). This can also be defined as consuming at least five alcoholic drinks on one occasion.

Lönnroth *et al.*'s meta-analysis estimated pooled relative risk across all studies that used a cut-off exposure level set at 40 g; the pooled relative risk was 2.94 (95% CI: 1.89–4.59) (69). In this study, alcohol abuse was defined as drinking at least 40g of alcohol per day (69). A more recent meta-analysis estimated a 35% increased relative risk of tuberculosis for alcohol users than non-alcohol users (RR1.35, 95% CI: 1.09–1.68) (118). In the 2016 SADHS, risky alcohol drinking was defined as consuming at least five drinks on at least one occasion in the past 30 days. From this survey, 28% of males and 5% of females reported risky drinking (89).

These risk factors (i.–v.) above have established effects on increasing the progression to active TB disease and given their high prevalence in South Africa; they potentially contribute to active TB incidence.

2.1.4. The evolution of global tuberculosis control efforts, progress, and challenges

This section describes the evolution of global and South African TB control strategies. Knowledge of the changes in TB control strategies is important in understanding and explaining some of the observed trends in the TB epidemic and predicting the future course of the epidemic.

i. *Earlier tuberculosis control policies: 1800–1981*

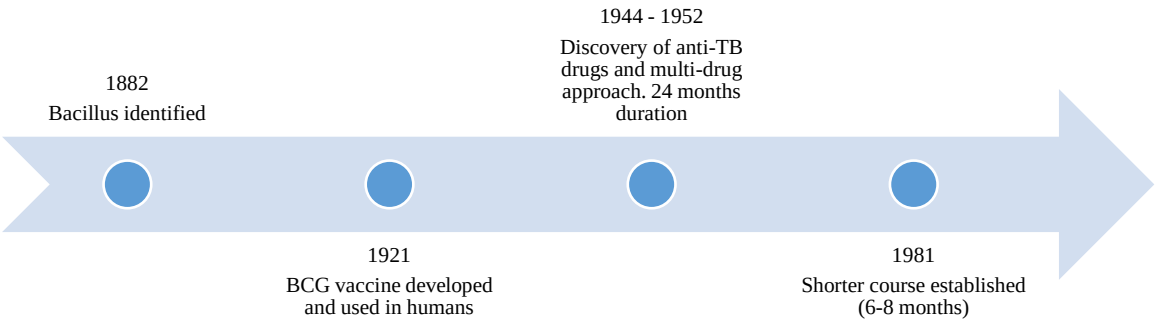
Although the discovery of the bacillus tubercle, the causative agent for *Mtb*, was made in 1882 by Robert Kock, TB existed long before (119). Additionally, evidence suggests that even before the availability of a TB vaccine and effective chemotherapy, TB notification rates were already declining during the 19th century (120). These declining trends were observed in industrialised countries; for example, in Europe, there was a constant decline in TB notifications from the 19th century until the mid-1980s (121).

There are varying hypotheses regarding what may have led to the declining TB trends even before effective chemotherapy. Some scientists hypothesised that the declining TB trends were due to reduced virulence of *Mtb* over time and possibly natural selection towards resisting TB disease in humans (120). There was insufficient evidence to prove this hypothesis, however. Other hypotheses were that the decline was due to economic development and sanatoria to isolate infectious patients in communities (33,120). This hypothesis was supported by the observed relationship between improved socioeconomic conditions and reduced TB disease. For instance, economic development is associated with improved nutrition, which reduces susceptibility to developing TB disease (33,120). Furthermore, improved socioeconomic status is associated with better housing and living conditions (i.e., lower density), leading to reduced risk of exposure and infection. Also, the isolation of infectious individuals in sanatoria broke the transmission chain in communities, possibly contributed to reducing TB infection rates (33,120).

Tuberculosis control efforts advanced from the 1920s to the 1980s, starting with the development of the *Mycobacterium Bovis* Bacillus Calmette-Guérin (BCG) vaccine and its

first administration in humans (Figure 2-1) (122). Today BCG remains the only licenced TB vaccine; its efficacy is highly variable across geographic regions, but it is most effective against severe forms of TB in children (122).

Figure 2-1: Early TB control policies: 1800–1981



BCG = Bacillus Calmette–Guérin. TB = Tuberculosis.

Another significant advancement in TB control was the development of anti-TB drugs. Rifampicin was one of the first effective TB treatment drugs developed in 1944 (122). Subsequently, other anti-TB drugs – isoniazid, ethambutol, and pyrazinamide – were developed. The approach of multi-drug combination treatment began during this period, and the treatment duration was 24 months. In 1980, a shorter treatment course of 6-8 months was established with the combination of drugs being isoniazid, rifampicin, ethambutol and pyrazinamide (122). Most of these drugs are still at the core of the present day TB curative programs globally.

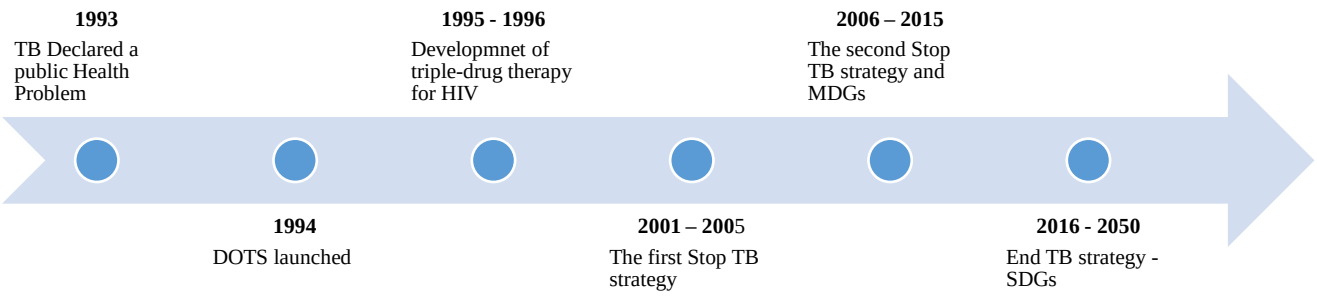
Altogether, the preventative effect of BCG and TB chemotherapy probably contributed substantially to TB control efforts and the decline in notified TB rates and mortality until the late 1980s.

ii. *The emergence of HIV and the spike in TB notifications (1980s–2000s)*

Although HIV existed before the 1980s, it was between 1983 and 1984 that it was discovered as the causative agent for AIDS (Figure 2-2) (123). A breakthrough in antiretroviral therapy drug discovery occurred between 1995-1996 when triple-drug therapy was developed (123). The late 1980s and 1990s were marked by an increase in TB incidence, with a tremendous

increase observed in sub-Saharan Africa. For example, it was reported that between 1985 and 1991, the annual incidence of TB individuals increased by three-fold in Zambia and two-fold in Malawi (124). HIV/AIDS, which emerged around this period, and inadequate health systems to promptly detect and treat TB individuals were suggested to explain this rise in TB morbidity (120,124). As a result, these sharp increases in TB and HIV globally drew interest from organised global bodies to respond to these epidemics.

Figure 2-2: Some of the significant shifts in global tuberculosis control strategies: 1990 – present



DOTS = Directly observed treatment short course; MDG = Millennium Development goals; TB = Tuberculosis; SDG = Sustainable Development Goals.

iii. *Directly Observed Therapy Strategy Era (1994–2000)*

In 1991, the World Health Assembly recognised TB as a significant public health problem (125). Later in 1994, the Directly Observed Treatment Short Course (DOTS) strategy was launched (125). The main aim of the DOTS strategy was to ensure effective TB control by detecting infected individuals and treating them to reduce transmission (125). In addition, two global targets were set for 2000. First, the target was to detect at least 70% of infectious TB individuals; second, it was to cure 85% of those individuals (125). Under this DOTS strategy, there was an emphasis for healthcare workers to directly monitor patients to ensure that they swallow the TB drugs over the 6-8 months treatment course (125,126). In contrast, under self-administration treatment (SAT), patients would be administered prescribed TB treatment drugs without direct supervision by healthcare workers (126).

Detection of patients during the DOTS era was mainly passive, and the first-line diagnostic tool used was smear-microscopy (125). In most resource-limited settings, detection and treatment were prioritised for smear-positive patients for efficiency and cost-effectiveness (125). The strategy also recommended that countries have monitoring and evaluation of programme activities (125). Alongside the DOTS strategy, vaccination with BCG was still recommended, mainly to prevent severe forms of TB in children (125).

Despite the broad implementation of DOTS, its limitations were evident in resource-limited settings. Not all countries had the capacity to expand their DOTS strategy; there were also inadequate TB surveillance and monitoring systems in place (127). As a result, it was impossible to evaluate progress towards these targets in these settings. Furthermore, although DOT reduces default rates, it had no major effect on reducing other treatment outcomes such as relapse, treatment failure, or acquiring drug resistance compared to SAT (128). In addition to these limiting factors, there were other arising public health challenges, including the rapid growth of the HIV epidemic and the emergence of multidrug-resistant (MDR) TB (127).

iv. *Stop TB Strategy and the Millennium Development Goals era (2001–2015)*

First Global Plan to Stop TB (2001–2005): In 2001, the DOTS strategy was revised and integrated into the "Stop TB Strategy". This revised strategy aimed to expand DOTS further and address the rising TB associated with HIV and MDR-TB (127). The Stop TB Strategy also sought to support health systems and highlighted the importance of enhancing research and development of new TB diagnostics, drugs and vaccines (127). In addition, issues resulting from TB associated with HIV were addressed by integrating TB and HIV care services. For instance, patients with TB were offered HIV testing and antiretroviral treatment (if HIV-positive and eligible according to the guidelines then) (127). Also, HIV-positive patients were prioritised for intensive TB screening, and early TB detection and TB preventative therapy was recommended (if eligible) (127).

Second Global Plan to Stop TB (2006–2015): The Global Plan to Stop TB was modified again and launched as the second Stop TB Strategy to accelerate progress to meet the TB-related Millennium Development Goals (MDGs) (127). The specific TB-related MDG targets were to detect >70% of new sputum smear-positive TB individuals and cure > 85% of these individuals; to achieve declining trends for TB incidence by 2015, and to halve active TB

prevalence and death rates by 2015 compared with their levels in 1990 (127). The ultimate goal was to reduce TB incidence to less than one new case per million by 2050 (127).

In this revised strategy, the prevention and treatment of TB in HIV-positive individuals were prioritised. The WHO recommended the implementation of "the Three Is" – Isoniazid preventive treatment, intensified case finding for active TB, and TB Infection Control – for HIV-positive individuals (129). Over time, guidelines for providing antiretroviral treatment (ART) to TB patients living with HIV evolved, with early ART initiation being emphasised (129).

Efforts to improve the detection of individuals with TB were made by expanding access and use of diagnostic tools, including smear microscopy and culture testing. From 2010, the use of GeneXpert MTB/RIF and the Genotype MTBDR Line Probe Assays were recommended (130). Compared to smear microscopy, GeneXpert MTB/RIF was particularly an improvement as it provided improved sensitivity and specificity, allowed the detection of Rifampicin resistance, and had a quicker processing time for results (~two hours compared to ~48 hours for smear microscopy) (75,130). The detection and effective treatment of active TB individuals through these efforts was estimated to have saved approximately 43 million lives between 2000 and 2014 (131).

The year 2015 marked the end of the MDG era (2000–2015) and a transition to the Sustainable Development Goals (SDG) era. The MDG target to reverse active TB incidence was achieved by all the six WHO regions (131). The estimated decline in TB incidence from the year 2000 was 1.5% per annum on average. However, the target for halving TB mortality rates by 2015 relative to 1990 was only achieved by four of the six WHO Regions (exceptions being the European and African regions) (131). Similarly, the target to halve active TB prevalence rates was not attained by all WHO regions (exceptions being the European, African, and Eastern Mediterranean regions).

v. *Moving from the Millennium Development Goals to the Sustainable Development Goals and End TB strategy (2016–2050)*

From 2016, the Stop TB Strategy transitioned to the End TB Strategy. The aim of the End TB strategy shifted focus from TB control to elimination (11). Elimination, in this context, is defined as less than one TB case per million population, and the elimination target has been set for 2050 (11). The intermediate targets for the 2050 elimination goal were specified in

alignment with the SDGs and were set to be reached by 2035. The three main intermediate targets are 1) to reduce TB deaths by 95% compared to 2015 levels; 2) to reduce the TB incidence rate by 90% (<10 TB individuals per 100000 population), and 3) to also ensure that no families of active TB patients would suffer financially due to the costs of TB care (11).

The End TB strategy also highlights the necessity of a multisectoral approach and addresses broader TB determinants. The strategy furthermore encourages political commitment and securing funding for TB programs. As a result, more commitments to accelerate progress towards attaining the SDG were made at the first United Nations High-Level Meeting on TB in 2018 (9). Some of the special considerations include prioritising LTBI detection and treatment with preventative therapy. Another consideration is recognising that people exposed to TB risk factors such as diabetes, undernutrition and alcohol disorders; people living in informal settlements; and miners as key and vulnerable populations need to be targeted for TB interventions (i.e., detection and management) (132).

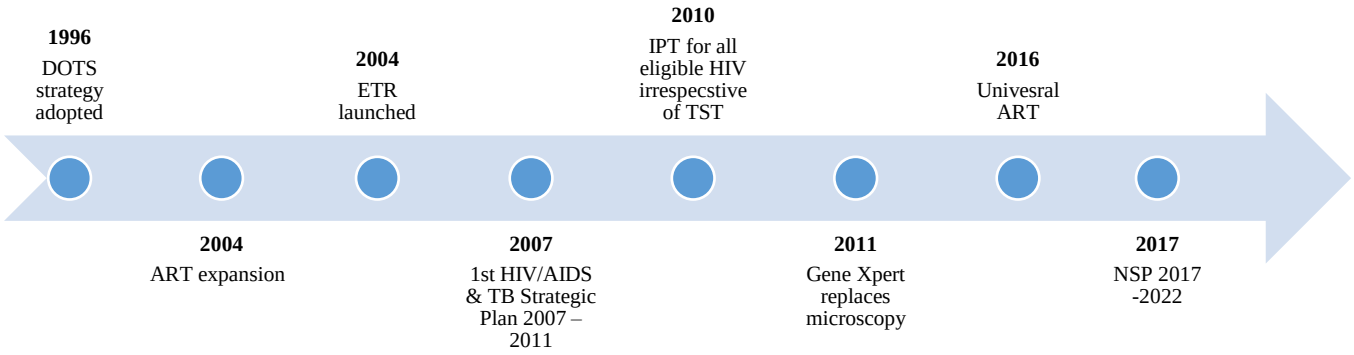
As far as diagnostics are concerned, the post-2015 strategy highlighted the importance of laboratory strengthening for countries to perform large scale rapid and accurate drug sensitive/resistant TB testing. As a result, Gene Xpert MTB/RIF was expanded in most countries as a first-line diagnostic. However, the sensitivity Gene Xpert MTB/RIF was still suboptimal in immunosuppressed individuals such as HIV-positive individuals (3). Subsequently, newer assays such as Xpert MTB/RIF Ultra, offering improved sensitivity in these populations, were developed (3). In 2018 the WHO further recommended the use of the urine lateral flow lipoarabinomannan (LAM) for HIV-positive individuals who have very low CD4 counts and are severely ill (131). Although the sensitivity of this test is still low (~42%), it is beneficial for the patients who cannot produce sputum samples to be tested (133).

While BCG is currently the only licenced vaccine, there are about nine registered vaccines in Phase IIb and Phase III clinical trials (3). The M72/AS01$_E$ vaccine (134), revaccination with BCG in adolescents (135) and the MTBVAC which uses a live attenuated mycobacterium (136), are some of the promising candidate vaccines on the development pipeline. For instance, the M72/AS01$_E$ was shown to have 50% (90% CI 12.0–71.0%)-efficacy against *Mtb.* infection over a three-year follow-up, and is yet to be tested for effectiveness in broader population groups (134).

vi. *Tuberculosis control efforts in South Africa*

The DOTS strategy was adopted in 1996 through the South African TB treatment programme and became widely implemented in 2002 (125). BCG had been part of the country's immunisation programme at relatively high coverage (~84%) (137). In 2002, the WHO's "3Is" policy of IPT intensified case finding, and infection control was adopted (23). Additionally, the electronic tuberculosis register (ETR.Net) was launched in 2004 to ensure quality monitoring of the epidemic (125). This system provides surveillance data on notified drug-susceptible TB individuals who have initiated treatment and is a valuable data source for tracking the epidemic.

Figure 2-3: Some of the significant events in controlling the tuberculosis epidemic in South Africa



DOTS = Directly observed treatment short course; HIV = human immunodeficiency virus; ART = Antiretroviral therapy; AIDS = acquired immunodeficiency syndrome; ETR = electronic tuberculosis register; IPT = isoniazid preventative therapy; NSP = national strategic plan.

The emergence and subsequent rapid growth of the HIV epidemic during the early 1990s impeded TB control efforts and drove the rapid increase of TB notifications rates in South Africa (4–6). From the mid-2000s, more efforts were made to integrate TB and HIV care services, emphasising preventing and detecting TB in HIV-positive individuals. To ensure more national response to HIV, TB and other public health issues, in 2007 South Africa launched the National Strategic Plan (NSP) for HIV, TB, and Sexually transmitted infections which details a five-year plan to achieve specific targets and track the progress towards tackling these persisting public health problems (138). Antiretroviral therapy was made widely available in the public sector from 2004 (106). Over time ART guidelines have also evolved, allowing patients to start treatment earlier in the course of their infection, and a

significant shift was the adoption of a policy of universal ART eligibility (in 2016), which allows the provision of ART to all HIV-positive individuals.

Although IPT had always been recommended for high-risk populations (i.e., HIV-positive individuals), there had been ambiguity around TST requirements and concerns about IPT leading to drug resistance. In 2010, the guidelines were made less strict, recommending IPT for all eligible individuals irrespective of their TST test result (139). In 2011, the country introduced GeneXpert MTB/RIF to replace smear microscopy (23) to improve TB detection.

Overall, the control efforts by the South African TB program contributed to declining TB incidence rates indicated by an analysis showing a decline in microbiological confirmed TB notifications from 848 (95% CI 845–850) per 100 000 population in 2008 to 774 (95% CI 771–776) per 100 000 population in 2012 (24). Tuberculosis mortality has also been on a declining trend (18). However, despite these improvements, South Africa still has high TB mortality and morbidity. The country did not meet the 2015 MDG goals to halve TB mortality and prevalence relative to 1990. The major reason for South Africa not meeting the MDG target may be the emergence of the HIV epidemic in the 1990s and the delays in the rollout of ART during the 2000s (140). As noted, other TB risk factors potentially contribute to the population-level TB risk. To meet the end TB goals, more impactful interventions that address these problems are required.

The latest South African NSP (2017–2022) has adopted the 90-90-90 targets of the Stop TB Partnership Global Plan to end TB (138). These targets aim to ensure that: 90% of all people who need TB treatment are diagnosed and receive appropriate therapy as required; 90% of people in vulnerable populations are diagnosed and receive appropriate therapy, and that treatment success is attained for at least 90% of all people diagnosed with TB (132,138). In this context, vulnerable populations for TB include people who are HIV-positive, household contacts of patients with active TB, health care workers, prisoners, pregnant women, children ≤ 5 years, people who have diabetes, people living in informal settlements and miners (138). The NSP aims to ensure that these populations are targeted for interventions and given social and economic support (138).

2.1.5. Summary of the literature review (Part A)

In summary, multifactorial determinants of TB exist and primarily increase the risks of exposure to *M.tb*, acquiring LTBI, and progressing to active TB disease. Tuberculosis control strategies have evolved over time with earlier strategies focusing on finding infectious TB individuals, isolating them, and providing them with curative treatment. There have also been advances in technologies to improve diagnosis. However, with the emergence of HIV and drug-resistant TB, it has become clear that biomedical and curative approaches alone are insufficient to control TB.

South Africa has also made notable improvements and achieved some milestones in controlling TB. However, undiagnosed, and untreated TB contributes to transmission, and TB risk factors – HIV, diabetes, undernutrition, alcohol abuse and tobacco smoking – contribute to high TB incidence. Furthermore, there are apparent differences in the distribution of these risk factors by sex, and they may thus explain the higher TB burden in males than females.

This review gave an overview of the broad development stages of TB, global and South African TB control strategies. These aspects of the TB natural history and controls strategies will be reflected in mathematical models reviewed in Part B.

2.2. Part B: Mathematical models of tuberculosis

Part B of the literature review aims to provide a context of existing TB dynamic transmission mathematical models which also include HIV effects. More specifically, the main aspects discussed are:

i.) Modelling the tuberculosis natural history and the effects of human immunodeficiency virus and antiretroviral therapy.
ii.) Modelling tuberculosis treatment and treatment outcomes.
iii.) Modelling tuberculosis transmission.
iv.) Modelling the impact of additional tuberculosis controls strategies:
- Diagnostic strategies
- Tuberculosis treatment-related strategies
- Antiretroviral therapy
- Isoniazid preventative therapy

- Vaccines

v.) Comparisons of independent mathematical TB-HIV models.

vi.) Calibration approaches.

vii.) South African-specific tuberculosis modelling studies.

viii.) Summary of literature and gaps.

This literature review seeks to search and identify modelling studies most relevant to this PhD's research question. It must be noted that this was not a systematic review of TB modelling studies. A search was conducted in PubMed using the following terms: ((dynamic OR transmission) AND (mathematical model)) AND (tuberculosis OR TB)) AND ((human immunodeficiency virus OR HIV)). The literature search was restricted to studies written in English, those conducted in humans, no start date restriction, but included those published by 31 April 2022. The PubMed search resulted in 398 articles. Additionally, reference lists of published literature reviews (141,142) were used to identify studies. When screening the articles, only studies based on dynamic transmission models were included – that is, mathematical modelling studies that explicitly modelled the risk of TB infection such that it depends on prevalent TB in the population (i.e., changes over time). Furthermore, the search was restricted to studies that included HIV and its effect on TB. After exclusions, 54 dynamical TB-HIV mathematical modelling studies were included in this literature review.

2.2.1. Overview of reviewed mathematical modelling studies

Table 2-1 summarises the dynamical TB-HIV models in the review. The summary includes the authors, the year in which the studies were published, the modelled countries, the main research questions addressed, the modelling frameworks used, and the interventions implemented. The summary also shows whether the models have been calibrated and the data sources used in calibration. Lastly, the table summarises the various modelling studies' structures: TB natural history, HIV-related structures (i.e., CD4 count, ART status, duration on ART) and the demographic characteristics considered (i.e., age and sex).

i. *Settings/countries modelled*

Most studies modelled Sub-Saharan African countries, including South Africa, Zimbabwe, Kenya, Uganda, Botswana, Gabon, Ghana, Tanzania, Botswana, Lesotho, Malawi, Swaziland, and Zambia. A few other studies modelled selected populations in the United

States of America (143,144) and Asian populations (145,146), and some were not intended to represent specific populations (147,148). While the Southeast Asian and Sub-Saharan African regions carry the highest burden of TB globally (3), their TB epidemics are driven by different factors. As a result, the predominant representation of Sub-Saharan African countries in most of these TB-HIV modelling studies reviewed here most likely reflects the high burden of TB-HIV in the region compared to other regions (149).

Table 2-1: Summary of transmission dynamic mathematical modelling studies of TB and HIV

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
1	Massad E (150); 1993	South Africa	To give a theoretical framework for studying the interaction between TB and HIV.	Compartmental, deterministic	NA	NA	NA	TB HIV
2	Dye C (151); 1998	WHO regions: Sub-Saharan Africa, Americas, Eastern The Mediterranean, Europe (Eastern and Western), Southeast Asia, Western Pacific).	To explore the potential impact of the DOTS strategy	Compartmental, deterministic	Improved case finding and cure	Validated using WHO TB incidence and mortality data; UNAIDS HIV prevalence data	Age structured: Children (<15 years old) and adult population (>15 years old).	TB: sputum-smear positive, sputum-smear negative or extrapulmonary. HIV
3	Porco T (152) ; 2001	United States of America	To project the impact of HIV on increasing the likelihood and the expected severity of TB outbreaks.	Compartmental. Stochastic / Markov	NA	NA	NA	TB HIV
4	Murray M (144); 2002	Sudan, United States of America, Algeria, Netherlands	To investigate social and demographic determinants of TB cluster distributions.	Individual-based model. Stochastic	BCG vaccination, case finding, standard treatment, Isoniazid preventative therapy.	Calibrated to LTBI prevalence and TB incidence data from WHO.	Age structured: 3 age categories: 0-10; 11-20; >20 years	TB, HIV
5	Raimundo SM (153); 2002	Brazil, Sao Paulo State. Prisons.	To describe TB transmission dynamics of AIDS and TB in a closed population (prisons) to see how the diseases impact each other.	Compartmental, deterministic	NA	Fitted to Sao Paulo female prisons TB and HIV data	NA	TB, HIV

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
6	Currie C (154); 2003	South Africa, Kenya, Uganda	To assess and compare the health benefits of TB treatment versus TB prevention and HIV treatment	Compartmental, deterministic. HIV modelled statically.	HAART, IPT, improving TB treatment (improved cure rates).	Bayesian approach. Used TB and HIV data from WHO.	Adult population: 15-49 years	TB, HIV
7	Schinazi RB (145); 2003	Theoretical. Suggested for South-East Asia	To explore whether HIV can invade a population that already has high levels of TB.	Compartmental, deterministic	NA	NA	NA	TB: smear-positive or smear-negative. HIV
8	Guwatudde D (155); 2004	Uganda	To assess the impact of isoniazid preventative therapy on the prevalence of TB and TB-associated mortality.	Compartmental, deterministic. HIV infection at a constant rate.	Preventative therapy for HIV-positive individuals with LTBI.	NA	NA	TB, HIV
9	Williams B (146); 2005	India	To evaluate the impact of the HIV epidemic and the Revised National TB Control Program on TB in India, 1990-2015.	Compartmental, deterministic	DOTS	Fitted to ANC data using maximum likelihood.	Adult population: > 15 years	TB: smear-positive or smear-negative. HIV: ART; CD4
10	Naresh R (156); 2005	Theoretical. No specific country	To study parameters involved in the spread of TB.	Compartmental, deterministic	NA	NA	NA	TB, HIV
11	Cohen T (157); 2006	Sub-Saharan Africa. High TB and HIV burden settings	To demonstrate the impact of various IPT policies targeted at HIV-positive individuals with TB disease, in settings with increasing TB and HIV epidemics, and their effect on the emergence of drug-resistant TB.	Compartmental, deterministic	IPT for LTBI in HIV–TB coinfected and ART	Calibrated to UNAIDS and WHO TB data for high TB and HIV burden settings.	NA	TB, MDR HIV, ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
12	Dowdy D (158); 2006	Hypothetical population, high HIV setting	To assess the impact of improved TB diagnostic approaches for TB control in populations with a HIV high prevalence	Compartmental, deterministic	Molecular testing, mycobacterial culture testing, targeting active case finding to HIV-positive individuals; HAART	NA	Adult population	TB: smear-positive or smear-negative. HIV, ART
13	Hughes G (159); 2006	Zimbabwe	To explore strategies for controlling TB transmission by more efficient TB case detection.	Individual-based model, Stochastic. HIV modelled statically	Active case finding	Calibrated to household survey data. Validated by comparing model outputs with Zimbabwe TB incidence data.	Age structured: Age (children and adults). Sex structured.	TB: infectious and non-infectious HIV
14	Salomon JA; (160) 2006	South-East Asia region: India, Indonesia, Bangladesh, Myanmar, Thailand	To assess the potential health benefits of reducing the TB treatment duration	Compartmental, deterministic.	DOTS scale up (higher detection rates and cure rates), reducing treatment duration to two months.	WHO TB incidence and mortality data	NA	TB: smear-positive or smear-negative. HIV
15	Bacaer N (142); 2008	Masiphumelele, Cape Town, South Africa	To assess the impact of HIV and TB control measures on TB in the Masiphumelele community.	Compartmental, deterministic	Condom promotion, increased TB detection, isoniazid preventive therapy, ART	Fitted to TB prevalence and HIV prevalence data.	NA	TB, HIV
16	Dowdy D (161); 2008	South Africa	To evaluate the potential impact of improved TB diagnosis (expanded culture and drug sensitivity testing).	Compartmental, deterministic	Increasing access to culture and drug susceptibility testing	WHO TB incidence, prevalence, and mortality estimates	NA	TB HIV, ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
17	Sánchez MS (162); 2008	Kenya	To determine the impact on the TB burden, of shortening TB treatment course alone, or combined with improved detection and cure of individuals with active TB.	Compartmental, deterministic	Shortened treatment duration (2 months) alone or in combination with advanced detection and DOTS treatment	WHO TB incidence and mortality (1980-2004)	NA	TB HIV
18	Basu S (163) ; 2009	Botswana	To evaluate the benefits and risks of IPT delivered through ART clinics.	Compartmental, deterministic	IPT and ART	Mentioned "face validity": compared model TB and HIV incidence; INH-resistant TB prevalence data	NA	TB INH-resistant TB HIV, ART
19	Dowdy D (164); 2009	Hypothetical, representative of WHO African Region	To assess whether keeping high rates of TB detection could sustain annual declines of 5–10% in TB incidence over long periods.	Compartmental, deterministic	Expansion (rapid and gradual) of annual case detection rates.	Validation by comparing model estimates to 2005 WHO TB incidence and mortality data	NA	TB: smear-positive or smear-negative HIV
20	Naresh R (148); 2009	NA	To assess how TB affects the spread of HIV in a population that is growing.	Compartmental, deterministic	NA	NA	NA	TB HIV
21	Sánchez MS (165); 2009	Kenya	To determine what explains the discrepant TB and HIV trends in Kenya	Compartmental, deterministic	NA	Calibrated to TB and HIV data (1980-2004)	NA	TB HIV

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
22	Williams BG (166); 2010	Gabon, Ghana, Tanzania, Botswana, Lesotho, Malawi, South Africa, Swaziland, Zambia	To investigate ART's short-term and long-term impacts on TB incidence, if HIV testing occurs regularly (yearly).	Compartmental, deterministic	ART	Fitted model to WHO TB incidence and UNAIDS HIV prevalence data (1980-1997)	NA	TB HIV: HIV, ART, CD4
23	Basu S (147); 2011	No specific population/country was modelled. Theoretical.	Tested the hypothesis that institutional amplifiers (i.e., prisons, hospitals, mines) increase the transmission rate.	Compartmental, deterministic	Reducing the per-person duration of exposure to an institutional amplifier, the number of persons exposed, and the at-risk group's case detection and treatment rates.	NA	NA	TB, HIV
24	Mellor GR (167); 2011	Zimbabwe	To assess the effectiveness of targeted case-finding strategies for TB in a high HIV prevalence setting.	Individual-based model, Stochastic. HIV modelled statically.	Contact-tracing strategies with case-finding targeted at high-risk groups.	Used WHO TB incidence and UNAIDS HIV prevalence data.	Age structured, assigned individual age.	TB: active TB (infectious / non-infectious) HIV
25	Mills LH (168); 2011	Modelled to approximate Botswana in 1990	Assess how clustering of contacts in communities with high TB incidence may affect the rates of reinfection with TB and how clustering modifies the impact of IPT.	Individual-based model, Stochastic	IPT	*Not described clearly.	NA	TB: fast and slow LTBI. HIV.

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
26	Menzies NA (169); 2012	Botswana, Lesotho, Namibia, South Africa, Swaziland	To estimate the potential health and economic consequences of MTB/RIF Xpert implementation.	Compartmental, deterministic an economic evaluation	The rollout of Xpert as a first-line diagnostic. DOTS treatment and ART	Bayesian approach. Used WHO TB incidence and prevalence data and UNAIDS HIV prevalence data.	Adults, 15+ years	TB: smear-positive or smear-negative; DOTS and non-DOTS treatment. Treatment history: treatment naïve and treatment-experienced. MDR/XDR HIV; CD4 count; ART
27	Houben M. G. J (170); 2014	HIV-positive, TST-positive participants from three clinical trials were conducted in Kenya, Uganda, and South Africa.	To show that IPT does not cure *Mtb* infection in most HIV-positive individuals.	Compartmental, deterministic	IPT	Least squares. Fitted to controlled trial Nairobi (Kenya) and Kampala (Uganda); non-placebo-controlled trial Soweto (South Africa).	NA	TB. HIV; CD4 count; ART
28	Pretorius C (171); 2014	South Africa	To quantify the impact of expanding access to ART on TB.	Comparison of three independent models: Individual-based, deterministic and a multivariate regression (noting that this is not a dynamical model)	Improving the provision of pre-ART and ART services, and increasing the threshold CD4 for ART initiation	Three models calibrated to South African HIV–TB data: WHO data for TB incidence and mortality estimates and the UNAIDS for HIV prevalence.	Adults, 15+ years	TB. HIV, CD4 counts, ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
29	Chindelevitch L (172); 2015	South Africa	To assess the impact of improving TB programmes: coverage, diagnosis, and treatment effectiveness and expanded ART use through broadened eligibility.	Compartmental, deterministic	TB programme coverage, diagnosis (Xpert) and treatment effectiveness broadened ART eligibility.	Bayesian calibration approach. WHO TB incidence data.	NA	TB. smear-positive or smear-negative; DOTS and non-DOTS treatment. 28Treatment history: treatment naïve and treatment-experienced. MDR/XDR HIV; CD4 count; ART
30	Knight GM (173); 2015	South Africa	To assess the impact of a hypothetical shortened TB regimen.	Individual-based model and Economic evaluation	Shortening treatment; 4-month regimen	Nelder-Mead simplex algorithm. WHO TB prevalence and incidence data; UNAIDS HIV prevalence and ART coverage data.	Age structured adult population.	TB. smear-positive or smear-negative; DOTS and non-DOTS treatment. MDR/XDR HIV; CD4 count; ART
31	Knight GM (174); 2015	South Africa	To assess if the NSP targets could be met if scale-up of control strategies was implemented in 2014.	Individual-based model, Stochastic	Increasing ART eligibility, providing IPT, Improved TB case finding and case management.	Nelder-Mead simplex algorithm. WHO TB prevalence and incidence; UNAIDS HIV prevalence and ART coverage data.	Age structured adult population.	TB. smear-positive or smear-negative; DOTS and non-DOTS treatment. MDR/XDR HIV; CD4 count; ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
32	Vynnycky E (175); 2015	South Africa miner population	Exploring factors that contribute to the lack of population-level impact of IPT.	Compartmental, deterministic	1) reduced initial loss to follow-up and treatment delay, 2) Xpert used as the initial test for new miners, 3) increased ART coverage (80%) for all HIV-positive miners and 4) IPT provision for all ART recipients.	Bayesian melding to Thibela TB randomised clinical trial data	Age structured: 4 age strata: <30, 30–39, 40–49, and ≥50 years	TB: smear-positive or smear-negative. LTBI not on IPT/ on IPT; Reinfected not on IPT/ on IPT. HIV
33	Gilbert JA (176); 2015	South African, rural KwaZulu-Natal	To assess the effectiveness of combining TB and HIV interventions in rural South Africa for more than ten years.	Compartmental, deterministic	1) GeneXpert screening test for MDR-TB; 2) treatment decentralization; 3) improved first-line TB treatment cure rate; 4) IPT, 5) ART expansion, 6) community-based integrated TB/HIV intensified case finding.	Calibrated to WHO TB prevalence and incidence data; HIV prevalence from the Actuarial Society of South Africa.	NA	TB: smear-positive or smear-negative. Slow and fast LTBI. MDR/XDR HIV; CD4 count; ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
34	Houben RMGJ (177); 2016	South Africa, Ghana	An accessible TB model that can produce country-specific TB burden estimates and allows policymakers in various countries to use the model decision making.	Deterministic compartmental	Increased Case Detection (non-MDR), improved treatment success, detection, linkage to care, provision of IPT to HIV-positive and HIV-negative persons, increased ART coverage, HIV testing, active case finding among household members and IPT for child household contacts.	Manually fitted to WHO TB notification data.	Age structured: Children (<15 years old) and adult population (>15 years old).	TB. smear-positive or smear-negative. Treatment history: treatment naïve and treatment-experienced. MDR/XDR HIV; CD4 count; ART
35	Blaser N (77); 2016	South Africa, Cape Town community	To study factors that drive age patterns of TB incidence	Individual-based model	NA	Fitted to Cape Town TB notification data	Age structured: 5-year age categories.	TB; HIV; ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
36	Gilbert JA (178); 2016	South Africa, rural Kwa Zulu Natal	Evaluate the costs and health benefits of implementing interventions to improve TB and HIV screening and linking to care.	Compartmental, deterministic with an economic evaluation	TB & HIV detection. GeneXpert screening test for MDR-TB, MDR-TB treatment decentralisation, improved drug sensitive TB treatment cure rates, IPT, ART expansion, and community-based integrated case-finding	Calibrated to WHO TB prevalence and incidence data; HIV prevalence from the Actuarial Society of South Africa.	Adult population: 15-64 years	TB: smear-positive or smear-negative. Slow and fast LTBI. MDR/XDR HIV; CD4 count; ART
37	Sumner T (179); 2016	South Africa, Khayelitsha	To determine the risk of infection and proportion of individuals cured by IPT.	Compartmental, deterministic	IPT combined with ART	Bayesian approach. Fitted to trial data and LTBI prevalence from Wood *et al.* study	Adult population	TB: smear-positive or smear-negative. MDR/XDR HIV; CD4 count; ART
38	Houben RMGJ (180); 2016	China, India, South Africa	To evaluate if the post-2015 End TB goals can be met in high TB burden countries.	Comparison of 11 TB transmission models: 2 Individual-based models and nine compartmental	Improving prevention, case finding and diagnosis, and treatment	All models were calibrated to country-specific TB and HIV data.	Varying. <15 and 15+ years. Only one study included sex stratification.	Varying across models: late/early LTBI; access to TB care; TB treatment history; MDR. HIV: ART; CD4

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
39	Menzies NA (181); 2016	China, India, South Africa	To evaluate resource requirements and cost-effectiveness of control policies to attain the post-2015 End TB strategy goals.	Comparison of 11 TB transmission models: 2 Individual-based models and nine compartmental	Improving prevention, case finding and diagnosis, and treatment	All models were calibrated to country-specific TB and HIV data.	Varying. <15 and 15+ years. Only one study included sex stratification.	Varying across models: late/early LTBI; access to TB care; TB treatment history; MDR. HIV: ART; CD4
40	Williams BG (182); 2017	South Africa	To assess the potential impact and associated costs of universal ART and HIV expanded prevention.	Compartmental, deterministic and an economic evaluation	ART to every HIV-positive individual irrespective of their CD4 cell count	Fitted to the prevalence of HIV and ART from UNAIDS and WHO tuberculosis notification rates	Adult population: 15+ years	TB HIV: HIV, ART, CD4
41	Shrestha S (183); 2017	South Africa, mining population	To quantify the likely impact of targeting miners with vaccines.	Individual-based, transmission model	Two vaccination campaigns in 20 years to miners and labour-sending communities.	Age- and sex-specific HIV prevalence and ART coverage data.	Age and sex structured	TB: Vaccinated HIV: HIV, ART, CD4

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
42	Marx F (184); 2018	South Africa, Cape Town community	To estimate the potential population-level effect of interventions targeted to individuals with a history TB treatment completion.	Compartmental, stochastic	Yearly targeted active case finding in persons with a history of TB treatment completion, and lifelong secondary IPT.	Bayesian calibration approach. Data: TB treatment registers; Western Cape data on HIV prevalence	Age structured: two categories for children (0-14 years); adults +15 years	TB: complete and incomplete; TB treatment naïve and treatment-experienced. HIV, ART, CD4
43	McCreesh N (185); 2018	South Africa, Cape Town	To assess the contribution of different social contact patterns: 1) household; 2) individuals outside the household repeatedly contacted with daily-monthly frequency; 3) non-repeated) to TB transmission.	Individual-based, transmission model	NA	Used WHO TB incidence and mortality data, electronic TB treatment register, and UNAIDS HIV prevalence data.	Age structured: two categories for children (0-14 years); adults +15 years	TB: smear-positive or smear-negative. HIV; CD4 count; ART
44	Rhines AS (186); 2018	South Africa	To evaluate the impact of IPT in adolescents.	Compartmental, deterministic	IPT targeted at adolescents	To WHO TB incidence, prevalence, and mortality data and UNAIDS HIV prevalence data	Age-structured: children, adolescents, and adults	LTBI not treated with IPT; LTBI treated with IPT; active TB (false negative). HIV; CD4 count; ART

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
45	Kendall EA (187); 2019	South Africa, Cape Town	To determine the population-level impact of the provision of the 12-month IPT regimen to HIV-positive individuals on ART.	Compartmental, deterministic	12-month IPT and ART	Bayesian approach. To TB-HIV epidemic data in Khayelitsha: TB notifications, TB prevalence, TB-associated mortality, MDR prevalence, HIV prevalence, proportion initiating ART.	NA	LTBI (remote and recent). HIV; CD4 count; ART
46	Sumner T (188); 2019	South Africa	To assess the impact of case-finding interventions on TB incidence, taking into account resource constraints.	Compartmental, deterministic	Xpert as a first-line test, adherence to Xpert-negative guidelines, cough-based screening, and symptom screening	Bayesian Calibration. To WHO TB notification, incidence, and mortality data; the number of TB screens from NDOH reports.	Age structured: 5-year age categories	TB. smear-positive or smear-negative. HIV; CD4 count; ART
47	Sumner T (189); 2019	South Africa	To estimate the potential impact of using the mRNA expression signature (COR) to target preventative therapy among HIV-negative individuals.	Compartmental, deterministic	mRNA expression signature COR-targeted preventative therapy for HIV-negative individuals, compared to IGRA	Bayesian Calibration Approach. Used WHO notification data	Age structured: 5-year age categories.	TB. Smear +/- Post-3HP (those treated with 3HP). HIV;

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
48	Hippner P (190); 2019	South Africa. 3 provinces: Limpopo, KwaZulu-Natal, Western Cape	To project the impact of meeting the 90-90-90 targets of the Stop TB Partnership Global Plan on the TB burden.	Compartmental, deterministic	Screening, linking to care, improving treatment success	Manually fitted to TB notifications (ETR), TB incidence (WHO), and screening data.	Age structured: Children (<15 years old) and adult population (>15 years old).	TB. Smear +/- Treatment history: treatment naïve and treatment-experienced. MDR/XDR HIV; CD4 count; ART
49	Ricks S (191); 2020	South Africa	To assess the potential impact on TB incidence and mortality of 1) LAM tests amongst those receiving HIV care, and 2) using LAM tests in patients irrespective of HIV status.	Compartmental, deterministic	LAM testing	Adaptive Bayesian Markov Chain Monte Carlo. To WHO data for estimates of TB incidence and mortality. Thembisa model and UNAIDS for HIV prevalence.	Adults, 15+ years	TB. HIV status, CD4 counts, ART. Further distinguished HIV-infected individuals by whether they are hospital inpatients or outpatients or if in routine care.
50	Marx F (192); 2020	South Africa, Cape Town community.	To evaluate the cost and health implications of post-treatment follow-up and secondary IPT.	Compartmental and an economic evaluation	Yearly active case finding in all individuals with a history of TB and who had completed TB treatment, and lifelong secondary IPT	Bayesian calibration approach. Data: Tuberculosis treatment register database; Western Cape data on HIV prevalence	Age: children (0-14 years); adults +15 years	TB: complete and incomplete; TB treatment naïve and treatment-experienced. HIV, ART, CD4

#	First Author. Year	Country	Research question addressed	Modelling framework	Interventions	Calibration or fitting to data or validation	Age and sex structure	Any other additional TB and HIV structures included
51	Harris R (193); 2020	South Africa, India, China.	To estimate the long-term impact of hypothetical TB vaccines with different features (prevent infection/disease) in South Africa, India and China.	Compartmental, deterministic	Regular early adolescent vaccination; ten-yearly large-scale campaigns to adults over between 2025 and 2050.	Bayesian approach. Used WHO TB incidence, prevalence, and mortality data.	Age structured: 0-14; 15-65; 65+	For South Africa, included HIV strata: HIV+ and HIV- Vaccinated; unvaccinated
52	Sumner T (194); 2021	CORTIS-HR study population – South Africa.	To project the future impact of using a blood transcriptomic biomarker (RISK11) to target preventive therapy to HIV-positive individuals.	Compartmental, deterministic	3HP	Bayesian calibration approach. Fitted to the incidence of TB infection in CORTIS-HR cohort	NA	On ART, no IPT; ART naïve, no IPT.
53	Jo Y (195); 2021	California, Florida, New York, Texas	To assess the cost and health benefits of testing and treatment of LTBI targeted at individuals who are: non–US natives, have diabetes, HIV-positive, homeless, or imprisoned.	Individual-based model (Shrestha *et al.* (183)	3HP under various TTT scenarios.	Fitted age- and sex-specific prevalence of HIV and ART coverage (2011) to the HIV model.	Age and sex structured	HIV, ART, CD4
54	Harris R (196) ; 2022	South Africa, India	To estimate the potential health impact and cost-effectiveness of routine adolescent M72/AS01$_E$-like vaccine in South Africa and India.	Compartmental, deterministic (193) and cost-effectiveness.	M72/AS01$_E$-like vaccine (to prevent TB disease; before or after infection with *Mtb*) to different age groups: 50% to 18 year-olds, 80% to15 year-olds, and 80% to 10 year-olds.	Bayesian approach. Used WHO TB incidence, prevalence, and mortality data.	Age structured: 0-14; 15-65; 65+	For South Africa, included HIV strata: HIV+ and HIV- Vaccinated; unvaccinated

AIDS = acquired immunodeficiency syndrome; Antenatal Care = ANC; ART = antiretroviral therapy; CORTIS-HR = Correlates of Risk of TB Disease in High-Risk Populations. DOTS = directly observed short course; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; 3HP = rifapentine plus isoniazid for three months; IPT = isoniazid preventative therapy; LAM = Lipoarabinomannan; LTBI = latent tuberculosis infection; NA = not applied; NDOH = National Department of Health; NSP = National Strategic Plan; TB = Tuberculosis; TTT = Targeted testing and treatment. Smear +/- = smear positive and smear negative; WHO = World Health Organization; MDR=multidrug-resistant. UNAIDS = Joint United Nations Programme on HIV and AIDS. * Mentioned parameters being obtained from fitted to HIV and TB epidemic data but not described. Mills 2011.

ii. *Research questions addressed by modelling studies*

The questions addressed by the different TB and HIV modelling studies can be put broadly into four categories. First were studies that sought to understand various disease dynamics such as HIV and TB coinfection (150,153); or to explore environmental factors (i.e. prisons/health care facilities) (147,197) and host-related characteristics that drive transmission (185). Others explored factors that explain observed age patterns in the distribution of TB incidence (77). Some used molecular epidemiology to explore clusters of *Mtb* strains that drive transmission in the population (144). Second were studies that sought to evaluate various interventions and predict their impact. Interventions in these studies included TB treatment-related improvements such as shortening treatment duration and increasing coverage of DOTS (146,198); a combination of interventions such as the provision of ART and IPT (142,155,157,163,174,179,199,200); improving detection and diagnostic tools; other specific interventions for selected groups other than HIV-positive individuals targeted adolescents, individuals with a previous history of TB treatment (184), miners and prisoners, and individuals at risk of developing TB disease identified by biomarkers (189,194).

Third, other studies explored the potential impact of the existing candidate and hypothetical TB vaccines (183,193,196). Fourth were studies that sought to compare independent mathematical models to explore what might explain the differences in conclusions for models that address the same questions (171,180). Fifth, were modelling studies which included economic evaluations to link the health benefits of implementing various interventions with costs and cost-effectiveness (169,178,181,182,192,195,201).

iii. *Modelling frameworks*

The main distinguishing characteristics of TB models (and infectious disease models in general) are the modelled population's aggregation level. These models can first be classified as individual-based or compartmental models. Second, the models can either be classified as stochastic or deterministic, depending on whether they include or exclude random variation in the outcomes. In individual-based models, individuals in the population are simulated as separate units and assigned characteristics, allowing for heterogeneity. In compartmental models, individuals with the same characteristics are grouped, and events are calculated at an aggregate level (across groups) rather than individually. Stochastic models allow for random chance, such that for each simulation, there is variation in outcomes. On the other hand, with

deterministic models, there is a fixed relationship between input parameters and expected outputs calculated – i.e. for the same input parameters and initial conditions, we would expect the same outcome (202).

Among the reviewed studies here, 41/54 used a compartmental modelling approach; and 10/54 used an individual-based model. Three studies included in this review used and compared multiple independent mathematical models (using different frameworks) to answer the same research questions (171,180,181).

Earlier TB and HIV models used simple compartmental model structures to understand disease dynamics and the impact of interventions (145,156). However, compartmental models have been extended to include more complexity in recent years. For example, in addition to the common TB structures, some models have included age strata (177,184) and included more details in HIV progression states such as CD4 count and ART status (166,169,177,188). These compartmental models have been beneficial in answering multiple TB research and policy questions.

On the other hand, individual-based models allow the representation of individual characteristics important in determining TB disease. For example, they can make it easier to include demographic variables such as age and sex and model household or social contacts that drive transmission in the community (77,144,174,183). Individual-based models have also been implemented in studies that use molecular epidemiology. In these studies, various molecular techniques estimate the fraction of new active TB cases due to recent transmission, exogenous reinfection or endogenous reactivation (203–208).

Although additional details (i.e., more compartments and demographic structures) may make models more realistic, its challenges include computational intensity and insufficient data to parameterise such complex models. Thus, some of the factors determining the choice of a modelling framework include the research questions modellers wish to address, the level of detail in the available data to parameterise such models, and computational capacity.

iv. *Demographic factors modelled – sex and age*

Age is a basic individual-level determinant of health. Models including age categories can help explain the age distribution of TB disease. Among the reviewed studies, 18 explicitly stated to have included age structures (77,144,151,159,167,173–175,183). Of these studies

that included age structures, eight were individual-based models, and the others were compartmental models (175,177,184,186,189,190,192,209). It was unclear how or what age-specific assumptions were in some studies; however, several studies specified the age-specific assumptions. Few studies assigned individual ages (159,167,183); others included two broad age categories for children (<15 years old) and adult population (>15 years old) (151,159,177,184,185,190,192); and several other studies included more than three age categories (i.e. 5-year age categories among adults; 0-10; 11-20; >20 etc) (77,144,175,189,209).

Several studies assumed age-specific parameters for fast progression to TB disease following initial infection and reactivation. In most of these studies, children and adolescents are generally assumed to have a greater likelihood of progression to TB disease compared to adults (77,144,151,154,167,173,174,177,183,188,189). More specifically, Blaser *et al*. used an individual-based model to extend the work of Vynnycky and Fine (80) to determine the main factors driving the age patterns of developing TB disease in a context of high HIV (77). In the study, TB disease progression rates, TB treatment outcomes (i.e., failure), background population mortality rates, and HIV incidence rates were parameterised by age strata (77). The study also incorporated age-structured social mixing patterns for transmission (210). Their results suggested that partial immunity (due to initial latent TB infection) against subsequent infections and fast progression of TB in previously treated TB patients explain the observed TB age distribution (77).

Despite substantial evidence showing sex disparities in TB (a higher burden in men (2)), few modelling analyses include sex stratification; furthermore, limited studies explore factors that drive these observed sex differences. Of the few models that included sex structures in this review, no specific hypotheses regarding the drivers of sex differences in TB epidemiology were tested (167,183). Using an individual-based model, Shrestha *et al*. included age- and sex-specific rates of rapid progression to active TB and reactivation to capture differences in TB incidence (183). The age- and sex-specific rates were estimated by fitting the model to data. However, the factors responsible for these age and sex differences in progression to active TB were not explored.

2.2.2. Modelling the tuberculosis natural history, HIV and ART effects

Due to the limited data and difficulty identifying LTBI in HIV-positive individuals, most TB-HIV models do not make explicit assumptions regarding how HIV influences the likelihood of acquiring LTBI. Instead, most of the reviewed modelling studies apply the individual-level relative effects of HIV to rates of progression to TB disease, as suggested by empirical data (95,96,211).

i. *Progression to active tuberculosis – fast progression and reactivation*

The rates of LTBI fast progression and reactivation to active TB disease are commonly based on historical studies. Most mathematical models assume the rate of progression to be a decreasing function of time since infection. Higher risks of progression are assumed usually within the first two years of infection, representing fast progression. The common assumption is that a particular proportion, usually between 0.005 and 0.25, would progress to TB disease within two years of TB infection (65). After that, the annual reactivation rates are commonly allowed to vary between 0.000848 and 0.0134 (65). Most of these modelling studies (151,161,169,177,184,188–190,192) base their assumptions about fast progression and reactivation on previous modelling studies, particularly those by Vynnycky and Fine (1997) and Dye *et al.* (80,151).

From the dynamical TB transmission models reviewed, HIV was incorporated in two ways. In the first and most common approach, HIV incidence is assumed to be constant in some studies; in the second approach, HIV incidence is based on external data sources (i.e. UNAIDS estimates) (154,155,160,163). In addition to modelling TB progression dynamically in all other studies, these models also represent HIV progression at varying degrees of complexity. Some models were simplified and only included HIV-positive and HIV-negative states; others added ART status if considered in the model. In more recent models (151,164,169,184–187,192), the HIV-positive states are further divided into different CD4 count categories and duration since ART initiation (166,177,209,212) (shown in the last column of Table 2-1).

Evidence shows that the effect of HIV on developing TB disease or mortality depends on the level of immune suppression (95,96,211). Modelling studies commonly use CD4 count as a marker of immune competency or suppression. For instance, most studies use the category of

low CD4 counts (i.e., <200 cells/mm^3) to represent the most immune-suppressed individuals, who have an elevated risk of TB disease and death; high CD4 count (i.e., 699–1244 cells/mm^3) marks healthy individuals (213). As ART restores immunity, CD4 count as model variable can also be used to indicate the effect of ART on developing TB disease or mortality. Additionally, including CD4 count as a parameter has been helpful for models to incorporate the ART initiation guidelines based on specified CD4 count threshold (214). The inclusion of CD4 count also allows models to explore the likely impact of ART policies based on different CD4 thresholds. However, it is noted that currently, the WHO guidelines recommend for HIV-positive individuals to initiate ART regardless of CD4 count (76).

ii. *Partial immunity due to latent tuberculosis infection*

Evidence suggests that the presence of LTBI confers partial immunity against reinfection (61). It is, however, not clear if this protection is against reinfection or progression after reinfection. An earlier modelling study by Sutherland *et al.* estimated the protection due to LTBI infection to be 63% among males and 81% among females (84). Another modelling study by Vynnycky and Fine estimated this partial protection to be 0.16 for adolescents (15 years of age) and 0.41 for adults (>20 years of age) (80). Another a study, a meta-analysis comparing TB incidence among paired cohorts of individuals with and without LTBI estimated the pooled protection due to LTBI to be 79% (61). All these studies (61,80,84) did not incorporate the effects of HIV.

To set assumptions regarding this protection due to LTBI in HIV-negative individuals, most existing TB modelling studies (151,161,169,177,184,188–190,192,193) assume values between 25% and 81%. In most modelling studies, this protection is defined as a reduction in the risk of developing TB disease following infection in those with prior infection compared to those without prior infection (80). Then the assumed protection is then applied to the rates of progression to TB disease following reinfection; and the studies mentioned earlier are commonly cited (61,80,84).

Given the limited empirical data on the effect of HIV on partial protection due to prior infection, most modelling studies assume low or no protection for HIV-positive individuals. For example, Menzies *et al*. in their study, assumed a 25% (range: 14–39%) protection against developing TB disease among HIV-positive individuals with CD4 counts ≤350 cells/mm^3(169).

iii. *Infectiousness*

To capture the level of infectiousness individuals have, some TB models use smear status, whereas active TB individuals are classified as smear-positive and smear-negative (164,169,177,188). In these studies, it is assumed that smear-negative individuals are 0.22 times as likely to transmit compared to smear-positive individuals estimated by Behr *et al*. (1999) (53). The literature suggests that HIV-positive individuals have a lower likelihood of smear-positivity (215–217); most modelling studies assume the proportion of smear-positive to be 20–40% among HIV-positive and 30–60% among HIV-negative individuals (164,169,177,188).

iv. *Natural recovery*

Most TB models use meta-analytic estimates of untreated TB mortality and disease duration to approximate the average natural recovery rates at 0.091 and 0.242 per annum for untreated smear-positive and smear-negative active TB cases, respectively (76). However, there is uncertainty around the effect of HIV and ART on these parameters, and most mathematical modelling studies make arbitrary assumptions about these effects. For instance, some modelling studies have assumed annual natural recovery rates of 0.2 for HIV-negative persons, and 0.1 for HIV-positive persons not on ART, with CD4 counts >350 cells/mm^3; and assume that there would be no natural recovery for those with CD4 counts less than 350 cells/mm^3 (169,184,186,199).

v. *Tuberculosis mortality*

Most modelling studies use estimates from the meta-analysis of studies on untreated TB mortality for untreated TB mortality (83). The rates of untreated TB mortality were 0.212 and 0.061 per annum for smear-positive and smear-negative active TB individuals, respectively (76). There is a lack of data on the effect of some important variables such as sex, age, HIV, ART in untreated TB; as such, most TB modelling studies rely on empirical studies conducted on treated TB individuals. The effect of HIV and ART in most studies is assumed by allowing different rates of mortality which depend on ART status and CD4 count categories (151,164,169,184–187,192). Most of these modelling studies cite the empirical studies that have evaluated HIV-positive individuals' survival during ART (99,102,105,218).

vi. ***Post-tuberculosis treatment completion and tuberculosis recurrence***

In most modelling studies, once individuals complete their treatment, they are returned to the latent TB state and remain at risk of reinfection or relapse (implicitly assumed to be the same as reactivation in treatment naïve patients). However, in other studies (164,169,177,184,190,192), there is an additional compartment to distinguish between treatment naïve and treatment-experienced individuals. The reasons for distinguishing the states include capturing the differential risks of recurrent TB disease (164,184,192), modelling the likelihood of developing MDR TB (177,190), and allowing diagnostics algorithms that require confirmatory tests depending on individuals' TB treatment history (169). In these studies, the effect of HIV on TB recurrence was not explicitly modelled (164,184,192).

2.2.3. Modelling tuberculosis transmission dynamics

The transmission process involves a set of parameters, including an individual's susceptibility, the infectiousness of the person with active TB disease, and the degree of exposure, usually measured in terms of proximity, frequency, and duration of exposure (33).

There is variation in how different modelling studies simulate this process of transmission. Some studies simplified the process, including a single transmission parameter, to represent the probability of transmission if an individual comes into contact with an infectious individual (169,177,186,199,209). Other details included age- and sex-stratified social mixing and contact rates (77,174,185,193). Because the transmission parameter is difficult to measure empirically, most studies estimate the parameter by calibrating the model to observed TB data.

A few models have been implemented to explore the contribution of social contacts (185) and environmental settings (79,147,219) to transmission. For example, McCreesh *et al.* studied various social contact patterns and *Mtb* transmission using an individual-based model (185). These social contacts were 1) household; 2) repeated, defined as individuals outside the household repeatedly contacted with daily-monthly frequency; and 3) non-repeated (185). In addition, several other modelling studies have been used to assess transmission in various settings where the risk of TB infection is increased. These high-transmission settings are also referred to as institutional amplifiers (79,147,219) - which are spaces such as prisons, hospital

wards and mines. For example, Basu and colleagues conducted an analysis that showed that having a large population exposed to or having a high duration of exposure to institutional amplifiers worsened TB incidence even if detection and treatment rates were high (147).

Overall, these studies suggest that most TB transmission occurs in communal/congregate settings, from a small proportion of individuals who are likely highly infectious to a wide range of people they come into contact with (185,205). They also highlight that identifying and treating cases earlier in environmental conditions conducive to TB transmission is essential.

2.2.4. Modelling tuberculosis control strategies

i. *Diagnostic strategies*

One of the goals of diagnostic strategies and tools is to detect active TB cases early and initiate treatment to reduce the pool of undiagnosed and untreated TB in the population that contributes to transmission. Lin *et al*. illustrated a framework that captures the complex feedback between diagnostic strategies, demands on the health system and the impact on the TB transmission dynamics (220). Modelling a detailed diagnostic pathway is advantageous as it may allow models to capture the effect of untreated TB cases on TB transmission and estimate the number of true and false positives. More importantly, this would allow a better reflection of TB case-finding activities and the implementation of new diagnostic tools on TB incidence and mortality. However, these models may be complex, and often there is limited data to parameterise every step of the diagnostic pathway.

Most of the earlier models have used a simplified approach with the transitions between active TB and recovery represented by a single parameter for detection (142,151,221). In contrast, others have considered capturing the complexity of the diagnostic process (164,169,177,188,190). For instance, Menzies *et al*. and Sumner *et al.* incorporated a relatively detailed diagnostic algorithm by including the sensitivity and specificity of their assumed diagnostic algorithm, as well as follow-up tests (169,188). In their study, Sumner *et al.* incorporated resource constraints. The various interventions included Xpert MTB/RIF, adherence to Xpert MTB/RIF-negative guidelines, cough-based screening and symptom screening (209). This analysis suggested that for symptom screening to be impactful in reducing TB incidence, significant increases in resources are required (209). This study also

highlighted that it is essential for models to consider resource constraints when modelling the case-finding activities.

Including a detailed diagnostic process can also allow models to compare and assess the impact of implementing different diagnostic tools. In most countries, Xpert MTB/RIF was implemented from 2011 onward following WHO recommendations; before 2011, smear microscopy and culture testing were commonly used (131). Models can compare, under the implementation of smear microscopy and Xpert MTB/RIF, their ability to detect drug susceptibility; the numbers of microbiological diagnoses and their ability to detect actual active TB disease and true negative in the population; the level of loss to follow-up before treatment initiation and the level of empirical diagnosis. The importance of accounting for empirical treatment has been highlighted, and it is suggested that without considering the levels of empirical treatment, modelling studies are more likely to overestimate the effect of Xpert MTB/RIF on TB outcomes (169,222–224).

Several mathematical modelling studies have been conducted to estimate the anticipated benefits of employing Xpert MTB/RIF and replacing smear microscopy (169,188,190,225). Compared to microscopy, most studies anticipated substantial health benefits from GeneXpert implementation (169,226). Although in the initial analysis, Menzies *et al*. (169) did not account for the effect of the diagnostic tools on the levels of empirical treatment. They subsequently conducted a re-analysis and accounted for empirical treatment and the sensitivity and specificity of diagnostic algorithms (227). The revised analysis found a reduction in the benefits – 70% less disability-adjusted life years averted due to the use of Xpert MTB/RIF (227).

Modelling studies assessing the impact of active case finding have been implemented to target specific groups and use specific diagnostic tools. For example, other studies looked at the potential impact of improving diagnostic sensitivity (158) and providing expanded culture and drug sensitivity testing (161), combining TB and HIV interventions with community-based integrated intensified case finding (178). Others used individual-based models to assess the impact of intensive case finding by targeting household members of TB patients to be tested for TB (159,167). These studies suggest that active case-finding is particularly efficient at when targeted at HIV-positive individuals.

There have been innovations in diagnostic tools in recent years, and some modelling studies have sought to evaluate their potential impact on TB incidence or mortality. For example, Rick *et al*. modelled the impact of urine lipoarabinomannan flow (LAM) in HIV-positive individuals as per 2019 WHO guidelines (191). Their results suggested that LAM tests could substantially reduce TB deaths amongst people living with HIV who are severely ill (191). However, cost-effectiveness studies must assess the affordability and feasibility of implementing such an intervention in the broader population (191).

Sumner and colleagues have explored the impact of implementing biomarkers-targeted preventative therapy (189,194). In the first study, they estimated the potential impact on the South African TB incidence, of the mRNA expression signature (Correlate of Risk (COR)) – with improved specificity – to target preventative therapy to HIV-negative adults at risk of TB (189). This biomarker was compared to the interferon-gamma release assay (IGRA). The study suggested that targeting preventative therapy through tests such as COR may be more efficient than IGRA, and could lead to more reductions in TB incidence in HIV-negative individuals (189). The other analysis estimated the effect of repeat transcriptomic screening followed by the three months isoniazid-rifapentine (3HP) preventive therapy course in comparison to universal preventive therapy provided to HIV-positive individuals (188). The study showed that biomarker-targeted preventive therapy might be more effective than universal preventative treatment in HIV-positive individuals, although it would require repeat screening (188). These studies show that biomarkers may be beneficial and efficient alternatives for identifying individuals at risk of TB disease and targeting them with preventative interventions.

ii. *Tuberculosis treatment-related strategies*

Most mathematical models in the early 2000s modelled the DOTS strategies, reflecting the recommended global strategies. In these studies, DOTS was commonly operationalised by increasing case rates of detection and successful treatment (146,151). For example, Williams *et al*. assessed the impact of the Revised National TB Control Program DOTS (an expansion of the DOTS program) on TB in India (146). Other studies focus on the impact of shortening TB treatment duration (162,173). Overall, these studies suggested that improving the quality of TB treatment (i.e. high success rates) and reducing treatment duration can lead to enormous benefits; however, they also highlighted that HIV would undermine the impacts

(146,151,162,173). Another important suggestion was that shortening treatment would reduce costs incurred by patients (173)

iii. *Antiretroviral therapy*

The provision of ART for the HIV-positive population has become a critical intervention for TB care and prevention. As such, mathematical models have increasingly been used to assess the population-level impact of ART on TB incidence and mortality. For example, Williams *et al*. studied ART's short- and long-term impacts on TB incidence in nine African countries: Gabon, Ghana, Tanzania, Botswana, Lesotho, Malawi, South Africa, Swaziland, and Zambia (166). Other studies that modelled ART's potential impact on TB showed that ART, particularly when initiated earlier, would lead to substantial declines in TB incidence and mortality (166,212).

From the mid-2000s, global control strategies recommended that TB control strategies be integrated with HIV control efforts (i.e., TB screening and the provision of ART and IPT for HIV-positive individuals). As a result, increasingly, other modelling studies assessed intervention combinations, where ART was included as a component of the policy strategies, along with others (142,154,157,158,169,171,172,174,176–178,180). An earlier modelling study by Currie *et al.* assessed the impact of combined interventions (applied to South Africa, Kenya, and Uganda). The study concluded that improving TB detection and cure effectively reduces TB incidence and that ART would have a more substantial impact only when there is high coverage and adherence (154). Chindelevitch *et al*. examined the epidemiological impact of improving the TB-specific interventions in South Africa by increasing their coverage, detection, and treatment success, and the impact of increased ART access through broadening eligibility (172). The study suggested that TB-specific interventions would lead to most TB incidence and mortality reductions. However, with ART expansion, there would be even more significant reductions. These studies have been critical in providing evidence to support and advocate for integrated TB and HIV control efforts and early ART initiation.

iv. *Isoniazid preventive therapy*

Following the recommendations to combine IPT and ART to reduce TB risk in people living with HIV, more modelling studies have projected the likely impact of ART and IPT combined (142,155,157,163,174,179,199,200). An earlier modelling study by Guwatudde *et al*. suggested that IPT provision for the HIV-positive population will have a small impact in

Sub-Saharan Africa (155). Another study on IPT in HIV-positive individuals concluded that although IPT may reduce mortality, there was a potential to increase drug-resistant TB (157). However, a Bostwana-based study suggested that the contribution of IPT to increases in resistant TB was unlikely to surpass its overall impact on reducing the burden of TB (163).

Another analysis by Knight *et al*. assessed the potential impact of different intervention portfolios; one portfolio included long-duration IPT and ART for all people living with HIV regardless of CD4 count (174). In this study (34), they assumed a 36-months duration of IPT; they assumed those on IPT had a 63% reduction in the risk of developing TB disease through reactivation or reinfection. The coverage of IPT was assumed to be 10% at baseline (174). Kendall *et al*. explored the broader, community-level benefits of providing IPT for 12 months to 85% of patients initiating ART in Khayelitsha (199). The model was specifically designed to represent the Khayelitsha setting and a clinical trial study (228). The effect of IPT was estimated in the model as the relative rates of developing TB for those receiving IPT compared to those not receiving IPT; and were estimated at 0.54 during IPT and 0.76 after IPT (228). Overall, these studies suggested that IPT combined with ART reduces TB incidence and has an additional benefit on reducing TB transmission.

Other modelling studies have focused on targeting IPT to various population groups. These groups include previously treated TB cases (184,192), adolescents (186) and miners (175). For example, Rhines *et al*. suggested that providing IPT to adolescents could substantially benefit adolescents and have spillover benefits for the adult population (186). In this study, they assumed latently infected individuals would recover due to IPT at a rate of 0.47 per annum (229). In addition, IPT was assumed to reduce the reactivation rate of LTBI. For both HIV-positive and HIV-negative individuals, the rate of reactivation was assumed to be 0.0001 per annum (for individuals not on IPT, the reactivation rate is assumed to be 0.005 in HIV-negative individuals). Another IPT-related parameter included coverage and was implemented in sensitivity analysis scenarios set at 5%, 50% and 90%. Similarly, the rates of dropping out of IPT treatment and stopping IPT treatment were tested under sensitivity analysis (not based on empirical studies) (186).

Marx *et al*. showed that active case finding and targeting IPT to individuals who have completed TB treatment has potential to reduce TB morbidity and mortality (184). The authors (184) assumed IPT to reduce the risk of reactivation and the risk of progression to disease following reinfection (230,231). Vynnycky *et al*. explored factors that contributed to

the lack of the population-level impact of IPT in mineworkers (175). Their findings suggested it was because IPT only cured a small proportion of LTBI, especially in those who were also HIV-positive (175). Another modelling analysis also suggested that IPT is unlikely to cure LTBI in TST positive and HIV-positive individuals who are not on ART (232).

Overall, the studies on IPT highlight that targeting specific high-risk populations may be more feasible. However, despite its effectiveness in preventing TB disease and advocacy efforts, IPT coverage remains very low (107,108). In addition, there are limited empirical data regarding the levels of uptake (233,234), duration and completion of IPT. As a result, most modelling studies set hypothetical levels of IPT coverage, IPT initiation, and completion parameters; and most of these parameters are varied in sensitivity analyses.

v. *Vaccines*

In light of recent vaccine developments such as the BCG revaccination (the H4:IC31 vaccine) against *M.tb* infection (135) and M72/AS01$_E$ against bacteriologically-confirmed TB disease (134), a few models explored the potential impact of vaccines in different target populations. Harries *et al* estimated the impact of a vaccine that had 70% efficacy against TB disease over ten years, and compared it to a scenario with no vaccine in China, South Africa, and India (193). The study suggested that vaccines that prevent TB disease in *M.tb* infected individuals would yield the most significant impact (193). In another analysis, Harries *et al* suggested that implementing a M72/AS01$_E$-like vaccine to 50% of 18 year-olds may be more cost-effective than vaccinating 80% of 10 year-olds (196).

Shrestha *et al*. evaluated the impact of a hypothetical vaccine which had 60% efficacy over a period of ten years (183). In the study, they also compared the impact of a vaccine strategy targeted at miners and another strategy which targets all peopleresiding in a mining community (183). The study suggested that targeting high-risk demographics (miners) would enhances the feasibility of implementing potential vaccines strategies and impact on transmission (183).

2.2.5. Comparisons of independent mathematical TB-HIV models

Although different modelling studies usually agree with the general results suggesting that ART expansion would reduce TB incidence, there is sometimes variation in the extent to

which these declines occur. To understand some of these model differences, Pretorius *et al*. (171) and Houben *et al.* (180) conducted analyses to compare independent models addressing the same question. Pretorius *et al.* have compared three models – individual-based (PopART), deterministic (Menzies, 2014) and multivariate regression (Goals) – to assess the impact of broadening ART on TB outcomes in South Africa (171). Houben *et al*.'s analysis compared 11 models applied to India, China, and South Africa. The models were used to project the impact of a combination of interventions and assess the post-2015 End TB strategy (180). The modelled interventions were mainly focused on improving TB prevention, case finding and diagnosis and treatment (180).

In all these comparative analysis studies, all models agreed that ART expansion (171) or implementing combinations of interventions (180) would substantially reduce TB incidence and mortality. However, in the Pretorius *et al*. analysis, there were slight differences regarding the extent of reductions and what caused them. For example, one model (Menzies) showed a significant reduction in TB incidence (compared to Goals and PopART) and attributed it to CD4 eligibility expansion (171). Conversely, the other models (Goals and PopART) attributed most of the reduced TB incidence to increased ART coverage rather than CD4 eligibility (171). In the analysis by Houben *et al.*, the models projected that the post-2015 End TB strategy milestones of 50% reduction in TB incidence and 75% reduction in TB mortality seemed feasible for South Africa. However, for China and India, the milestones were projected not to be achievable (180). These differences were due to varying epidemiological contexts and the interventions implemented by national TB programmes (180).

Altogether, these two studies (171,180) above highlight the critical drivers of model differences: the country contexts and the underlying assumptions regarding the interventions implemented. Therefore, such comparative modelling studies are essential and can increase the robustness of mathematical model findings.

2.2.6. Calibration approaches

Calibration of mathematical models is mainly performed to ensure that model outputs are consistent with observed data and estimate uncertainty around specific input parameters and model outputs. Estimating the uncertainty around model outputs is helpful because it gives policymakers and scientists an idea of the credibility of conclusions based on the model

results (235). The calibration process involves the use of observed data (also referred to as target statistics) such as prevalence and mortality, algorithms to identify the best-fitting parameters, and measurement to determine how well the model fits the observed data (goodness of fit of the model) (236).

The goodness of fit values can measure the consistency of model estimates with real-world data. In the modelling studies that described their calibration process, some used the least squared difference between observed data and model outputs to measure the goodness of fit (232). Other studies, particularly those that implemented a Bayesian calibration approach, used the likelihood function to measure the goodness of fit (154,169,172,179,184,199,237). The likelihood function, in this case, represents the likelihood of observing a particular target statistic, assuming it follows a specified distribution.

A lot is still unknown regarding various TB natural history parameters, such as rates of transmission, natural recovery and partial immunity due to latent TB infection, and the effect of HIV on these parameters. Most models, therefore, estimate these parameters in the calibration process. In addition, the best-fitting parameters are often estimated by various calibration algorithms that help identify the set of parameter combinations that would yield the best-fitting likelihood. For models which have specified these algorithms, the methods used include Nelder-Mead (174,175), sampling importance sampling resampling (154,169,172,183) and Latin Hypercube Sampling (163,183). Finally, other studies calibrated manually by adjusting the input parameter values, running the model, and visually assessing how well the model estimates are close to the observed data (190,225).

The formal calibration process is complex and computationally intensive, especially when many model compartments, parameters, and target statistics are involved. However, when described systematically and good model fits are shown, it may ensure model credibility and reproducibility (238). On the other hand, a manual calibration may be more straightforward and allow modellers to understand critical parameters in their models. However, this manual calibration process may not be as efficient when the model is complex.

Most modelling studies have relied on the WHO TB and the UNAIDS HIV burden estimates as calibration targets statistics rather than actual data from surveys, TB notification systems or vital registers. While the estimates from the WHO and UNAIDS may be credible, it should be noted that they are themselves model outputs with some level of uncertainty around them

(239). As a result, this may lead to models implicitly using other models' assumptions, so results need to be interpreted carefully.

2.2.7. South African-specific tuberculosis modelling studies

Of the studies included in this review, at least 60% (33/54) represented the South African population and the TB epidemic. Among these South African based studies, most focused on modelling the epidemic at a national level (161,166,169–173,177,179,181,182,186,188,193,196,198). The majority of these national-level models were compartmental. Also, only a few of them included detailed demographic structures such as age (i.e., children (<15 years old) and adult population (15+ years old)) (177,188–190), and few (183) included sex stratification.

Most of the national-level models were interventional and developed to project the impact of proposed policy strategies. For instance, Knight *et al*. assessed whether South Africa would meet targets set in the South African 2012–2016 NSP by scaling up existing TB control interventions at the time (174), and Houben *et al.* assessed the potential for South Africa to attain the post-2015 End TB Strategy targets (180). The interventions modelled in these studies included ART, IPT, and improved TB case management. The consensus from these studies was that the aggressive scale-up of any single intervention would reduce TB incidence and mortality; however, it would not be sufficient to achieve the 2012–2016 NSP or post-2015 End TB strategy targets in South Africa (174,180).

Other South African modelling studies have focused on smaller peri-urban communities in the Western Cape (77,142,179,184,185,192,199), rural communities in KwaZulu Natal (176,178) and mining communities (175,183). These studies assessed the impact of combinations of interventions (TB case-finding, ART and IPT). However, only one study analysed the impact on TB incidence and mortality of achieving the 90-90-90 TB targets in three South African provinces – KwaZulu Natal, Western Cape, and Limpopo (190). The authors suggested that the impacts of interventions (active case finding, linkage to care, treatment success) varied mainly due to differences in the coverage levels of the interventions in the different provinces (190). For instance, the study suggested that to achieve the 90% target of screening in Limpopo, an increase of 29% in screening coverage levels would be needed, whereas for the Western Cape TB screening would need to increase nine by times (190).

Although much TB modelling work has been done for South Africa, most were led by technical experts or modellers from institutions outside South Africa (i.e., predominantly the United Kingdom and the United States of America). For example, in the comparative analysis of 11 models, by Houben *et al*., all modelling groups were from institutions outside of South Africa (180). This lack of locally developed and locally-led TB models may be due to a lack of capacity (240), resources or incentives for conducting such projects at a national level.

While most studies rely on the WHO TB incidence and mortality estimates for setting calibration targets, some have used South African-specific data, such as the electronic TB treatment register and the number of microbiological tests performed (77,177,184,190,192,209). The vital registry TB mortality data is also available but very few studies have relied on it. The challenges with using the vital registry data may be incomplete reporting or misclassification of causes of death; however, South Africa's system has improved and has relatively high levels of completeness (241).

2.2.8. Summary of the literature review (Part B)

The literature review showed that while many transmission dynamic modelling studies have focused on projecting the future impact of various interventions, none have retrospectively evaluated how the different evolving TB control policies have impacted TB incidence and mortality. Also, although the individual-level effect of HIV on TB incidence and mortality is established, the population-level impact HIV has had on TB and mortality has not been quantified. Furthermore, most of the reviewed modelling studies lacked demographic detail such as age and sex and the assessment of factors that drive age or sex disparities in TB. Additionally, most existing South African TB did not use South African-specific data for calibration, relying instead on WHO estimates. Another gap with existing models was the lack of locally developed models and the lack of long-term model involvement in policy formulation and evaluation.

This literature review was limited in that it was not exhaustive and systematic. In addition, the choice of restricting reviewed studies to those that explicitly modelled TB and HIV was limiting as there are other important modelling studies which focusses on non-HIV factors such as age, sex, environmental drivers of transmission, TB risk factors.

Chapter 3 describes a mathematical model South Africa which addresses some of these gaps in the literature. In Chapter 4 the model will be used to evaluate the past impact of HIV and interventions on TB incidence and mortality. Chapter 5 will explore factors that drive the sex disparities in the burden of TB. Lastly, Chapter 6 will estimates the future impact of scaling up existing interventions on the South African TB incidence and mortality and assesses the potential to attain the 2030 End TB milestones.

Chapter 3. Model development and calibration results

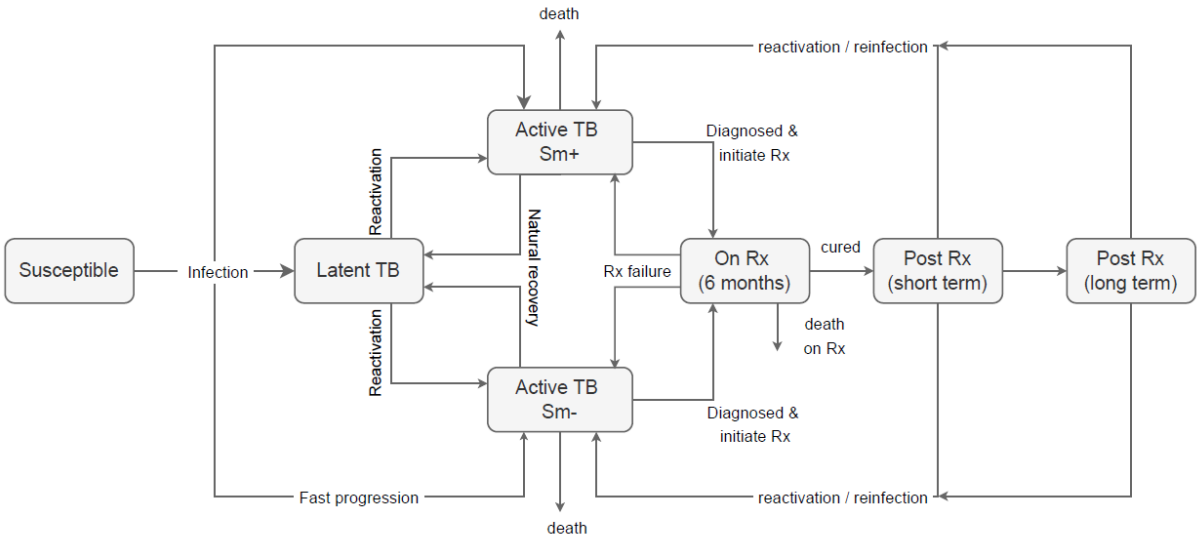
This chapter aims to describe the methodological approach used to develop and parameterise the TB-HIV model for this PhD and presents the results of the model calibration.

Contributions: Leigh F Johnson and Mmamapudi Kubjane wrote the code for the mathematical model, implemented in C++.

3.1. Overview

We developed an age- and sex-structured deterministic compartmental model of the TB and HIV epidemics for the South African adult population (ages 15 years and older). The core TB states were modelled following conventions used by previous modelling studies (80,242,243). We considered the following epidemiological states: susceptible, latent tuberculosis infection (LTBI), active TB smear-positive, active TB smear-negative, receiving treatment, and two post-TB treatment states – recent (six months after treatment) and long-term (more than six months after treatment), as shown in Figure 3-1.

Figure 3-1: The tuberculosis natural history model structure



TB = tuberculosis. Rx = treatment. Sm+ = smear-positive. Sm- = smear negative. Non-TB mortality transitions are not shown in the figure, but are the same for all states.

Although the model produces estimates for individuals with 15 years and older, it simulates TB transmission and the natural history from age 10 years. We assume a fixed proportion of children are latently infected with TB on reaching age 10. The prevalence of LTBI is based on an age-dependent function described in **section 3.2**, and the LTBI prevalence at the age of ten years is $F_{ltbi}(10) = 0.47$, which is where we then start simulating the potential for disease progression and transmission.

The TB transmission process and associated parameters are described in **section 3.4.** Following infection, individuals progress to TB disease through fast progression or remain infected with latent TB and may develop TB disease through reactivation or reinfection (described in **section 3.5**). Individuals with LTBI have partial immunity, which affords them a reduced risk of fast progression to TB disease following reinfection. Individuals with TB disease were further categorised by smear status – smear-positive or smear-negative. In these TB disease states, individuals may die or recover naturally and return to the LTBI state.

Active TB individuals can also be linked to TB care, which depends on attending a health facility, being screened, being diagnosed (empirically or microbiologically), and ultimately initiating treatment; the TB diagnosis and treatment initiation process are explained in **section 3.6**. Complete treatment is assumed to last an average of six months. Those on treatment can experience the following outcomes: a) cure; b) failure, after which they will return to the active TB states; c) discontinuation of treatment, of which a proportion will return to TB disease state and the remainder to the recovered state; and d) death. These treatment outcomes are further described in **section 3.7**. Following treatment completion, we consider two post-TB treatment states that depend on the time since treatment cure/completion, which account for recurrent TB episodes through reinfection and relapse (described in **section 3.8**).

To incorporate the effect of HIV and ART, the TB model was integrated into the Thembisa HIV model (244). The Thembisa HIV model is both a demographic and epidemiological model which simulates the South African population profile, as well as the burden of HIV dynamically from 1985. The demographic model assumptions in Thembisa, including population profiles, fertility, non-HIV mortality and migration are set the same as those in the Actuarial Society of South Africa (ASSA) 2008 model and are consistent with South African Census (245), vital registration data (246) and the National burden of disease study (247). A Bayesian approach was used to calibrate the Thembisa HIV model to several data sources including the HIV prevalence levels in national antenatal clinic surveys and national

household surveys, recorded numbers of deaths, reported numbers of ART patients, numbers of HIV tests performed; HIV prevalence in individuals tested for HIV; proportions of adults ever tested for HIV (from the Human Sciences Research Council surveys in 2005, 2008, 2012 and 2017 and the 2016 Demographic and Health Survey (DHS)) (244).

The TB model is nested within the HIV model. The HIV model makes assumptions about non-HIV mortality rates (in the HIV-negative population) and excess mortality in the HIV-positive population (which varies in relation to HIV disease stage, age, sex and treatment status). These mortality rates implicitly include TB mortality, and are used to adjust the population size by age and sex. In the TB sub-model we do not attempt to change the population size but rather calculate the number of deaths that would be due to TB if TB was the only cause of death. This means the change in population size is determined only by the HIV and non-HIV mortality assumptions, and not by the TB mortality assumptions.

Both the TB model and the HIV models are dynamic. However, the models are not calibrated at the same time. For the purpose of calibrating the TB model, the HIV parameters are held constant at the posterior means estimated in the previous calibration; this is reasonable given that the margins of uncertainty around the HIV estimates are relatively narrow. The estimates of TB deaths include HIV as a contributing or underlying cause of death (i.e., HIV underlying cause AND TB is either first, second, third, or fourth contributing cause of death).

In the model, the simulated South African population is updated every month and the sum of all the populations in the modelled TB states sum to the South African adult population that year. Additionally, at the end of each month the TB populations are summed up and ensured that they match the South African HIV-positive and HIV-negative population.

The structure of the HIV model is given in Figure 3-2, and a detailed description of the HIV model (Thembisa 4.3) has been published (248). Briefly, in this model, HIV-positive sub-populations are stratified by HIV testing history, CD4 count and antiretroviral treatment duration. For those diagnosed with HIV, there is an indicator for ART initiation, and the CD4 count levels are used to represent the HIV stage or baseline CD4 at which individuals initiated ART. For those not on ART yet, the CD4 compartment represents their CD4 count at that given point (*current CD4*). For those on ART, the duration that they have been on ART treatment is also tracked, and for each duration compartment an average CD4 count is calculated, which depends on the baseline CD4 count (248). The descriptions of how HIV

and ART affect the TB natural history (**section 3.5**); and health-seeking patterns (**section 3.6**) are provided in the respective sections.

Additionally, in the model, we have incorporated the effect of isoniazid preventative therapy (described in **section 3.9**). We have also explored the effect of selected TB risk factors on TB incidence in **section 3.10**, as these are particularly relevant in representing sex differences in TB incidence. **Section 3.11** describes the approach and data sources we used to calibrate the model. In **section 3.12,** the model calibration results are presented. Lastly, **section 3.13** compares the Thembisa TB/HIV model estimates to those produced by the World Health Organisation (WHO) and the Institute for Health Metrics and Evaluation (IHME).

Figure 3-2: The Thembisa HIV model structure

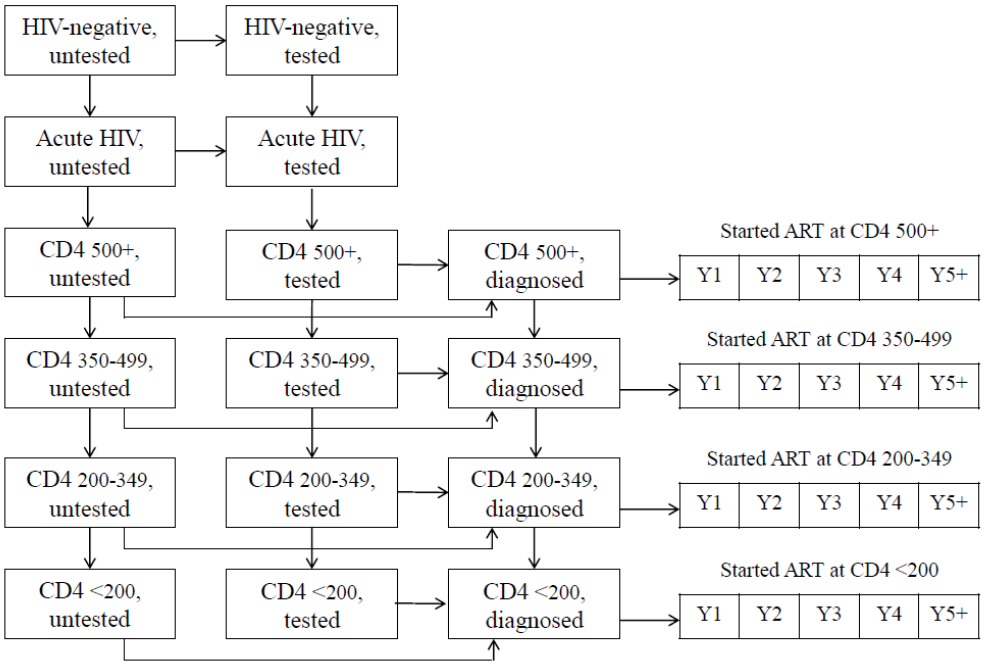


Figure from Johnson & Dorrington (248)

In the Thembisa HIV model, an average CD4 count in HIV-positive individuals who are not on ART is assumed for each of four CD4 stages, and is given in the first column in Table 3-1 below. CD4 counts in HIV-positive individuals receiving ART are dependent on the baseline CD4 count when they initiated ART and the number of years they have been receiving ART. These are shown in Table 3-1 below, and have been described and derived previously (249).

For the purpose of setting later assumptions about the effect of HIV on TB, it is necessary to assume an average CD4 count in the HIV-negative population. We set the average CD4 count in the HIV-negative population at 1000 cells/μl, based on Williams *et al*., who reported a range of CD4 levels between 699 and 1244 cells/μl (213). We assumed CD4 counts in patients on ART do not rise above 1000.

Table 3-1: Changes in average CD4 count after ART initiation

Years since ART initiation						
	Not on ART	1	2	3	4	+5
Baseline CD4 <200	100	297	383	426	486	512
Baseline CD4 200-349	275	450	539	600	703	770
Baseline CD4 350-499	425	564	658	738	882	987
Baseline CD4 500+	610	705	805	909	1000	1000

Source: Johnson & Dorrington (249)

3.2. Initial conditions

This section describes the assumptions we made about the proportion of the population with LTBI and active TB at the start of the simulation in 1985. All these initial assumptions are made for an HIV-negative population because HIV prevalence was very low in 1985.

3.2.1. Latent tuberculosis infection

In the model, we set the initial LTBI prevalence in the HIV-negative population using data from the CORTIS study (250). In this study, the QuantiFERON-TB Gold Interferon Gamma Release Assay (IGRA) assays were used to detect LTBI (Table 3-2) (250). However, we note that the relatively low sensitivity of IGRAs implies a high likelihood of missing true LTBI. Therefore, to approximate the proportion of true LTBI individuals given these imperfect diagnostic tools and the lack of a standard gold test for latent infection, we adjust the given prevalence using the sensitivity and specificity of QuantiFERON-TB Gold.

Table 3-2: Latent tuberculosis prevalence in HIV-negative individuals

Age Group	N	Unadjusted IGRA+ prevalence p_1	Adjusted prevalence p_2
15-24	1249	703 (56.3)	70.7
25-34	1062	748 (70.4)	89.7
35-44	379	271 (71.5)	91.2
45+	223	164 (73.5)	93.9
Total	2913	1886 (64.7)	86.4

Source: CORTIS study (250). https://www.clinicaltrials.gov/ct2/show/NCT02735590

We suppose the unadjusted LTBI prevalence, as measured by IGRA (Table 3-2), can be expressed as

$$p_1 = p_2 Se + (1 - p_2)(1 - Sp),$$

where p_2 is the adjusted (true) LTBI prevalence, and Se and Sp are the sensitivity and specificity of QuantiFERON-TB Gold, respectively. The assumed sensitivity and specificity of QuantiFERON-TB Gold were 0.78 and 0.96 respectively (251). Then we have

$$p_2 = (p_1 - (1 - Sp))/(Se + Sp - 1).$$

We fitted an exponential function to the adjusted prevalence p_2, and thus the prevalence of LTBI can be given by the expression dependent on age: $F_{ltbi}(age) = 0.98(1 - e^{-0.066age})$.

Limitations associated with using these IGRA-based data include a greater likelihood to underestimate the proportion of true IGRA-positives because of the low sensitivity of the tool. Another limitation of using these IGRA-based data to initiate the LTBI profiles in the model is that these are recent data and are possibly not a true reflection of LTBI prevalence in 1985. Nonetheless, we justify this with the fact that the proportions were from an HIV-negative population (and hence may represent the era where HIV prevalence was very low in South Africa) (250). Also, the study was conducted across multiple sites in South Africa and thus giving a better representation of the country's LTBI prevalence. In comparison, other existing earlier data on LTBI prevalence were conducted in smaller and specific population group (i.e., adolescents, gold miners, health care workers) (252–256) making them less representative nationally. Additionally, most of these earlier studies relied on TST, which has poor specificity, especially given the fact that South Africa is a country with high BCG vaccination coverage.

3.2.2. Initial active tuberculosis profiles

There are also limited data on the prevalence of active TB earlier than 1990. The available TB burden data from reports only dates from the early 2000s. We used WHO estimates to initialise the prevalence of TB in our model. The TB prevalence in 1990 was estimated to be 490 per 100 000 (257). The initial TB prevalence was set in 1985 in an HIV-negative population. We used a Cape Town-based population-based study that assessed the 2009 age-

specific TB notification rates (TB incidence) stratified by HIV status (78) to set the assumed relative levels of TB prevalence by age.

As with most routinely collected data, the notification data used to estimate the proportion of active TB cases are likely to be incomplete or affected by misclassification of TB status or duplication of individuals. Also, these data only represent one geographical setting - Western Cape. However, to initiate the model, we do not expect these initial assumptions to affect model outputs significantly.

As the literature suggests, males carry a higher burden of TB compared to females. The male to female ratio of the TB burden ranges between 1.5 and 2.1 across different geographical regions (2,25,86). In the model, we set the initial prevalence of TB by age and sex, represented by the proportions in Table 3-3.

These were computed using the following data: 1) the estimated 1990 South African TB prevalence by the WHO (257), 2) the Cape Town TB prevalence in an HIV-negative population (78) and 3) the ratio of male to female TB prevalence (258). For the age groups 15–75 years, we assume the prevalence (%) of active TB in males to be 50% higher than that in females (258). We assume that the overall prevalence $\bar{p} = 0.5\ (p_0 + p_1)$, where p_0 is the prevalence in males and p_1 is the prevalence in females. We then have $p_0 = 1.5 \times \bar{p}/(0.5 \times (1 + 1.5))$ and $p_1 = \bar{p}/(0.5 \times (1 + 1.5))$.

Table 3-3: Initial prevalence of tuberculosis by age and sex in an HIV-negative population

Age	HIV negative Population, a)	Number of active TB cases, b)	The proportion of active TB, c)	Proportion of TB in males, p_0	Proportion of TB in females, p_1
15–19	301447	988	0.004	0.005	0.003
20–24	306210	1693	0.007	0.008	0.006
25–29	287160	1381	0.006	0.007	0.005
30–34	251725	1015	0.005	0.006	0.004
35–39	224038	1042	0.006	0.007	0.005
40–45	179524	1053	0.007	0.009	0.006
45–49	171395	1076	0.008	0.009	0.006
50–54	156238	829	0.007	0.008	0.005
55–59	126738	571	0.006	0.007	0.005
60–64	104718	315	0.004	0.005	0.003
65–69	77231	195	0.003	0.004	0.003
70–74	52120	72	0.002	0.002	0.001
75+	62485	97	0.002	0.002	0.002
Total	3241508	12508	0.005	0.006	0.004

a) and b) are based on the Wood *et al.* study (78).

c = b/a × (0.0049÷0.0039)=$\bar{p}$; 0.0049 is the 1990 WHO prevalence of TB (257); and 0.0039 (= 12508/32 241 508) is the average TB prevalence from the Wood *et al.*, study (78). $p_0 = \frac{3\bar{p}}{2.5}$, $p_1 = \frac{2\bar{p}}{2.5}$.

3.2.3. The initial proportion of individuals previously treated for active tuberculosis

The initial proportions of individuals previously treated for active TB were based on self-reported data on prior TB diagnosis from the South African Demographic and Health Survey 1998 (SADHS) (259). The initial prevalence is specified by age and sex as reported in the SADHS (Table 3-4).

Table 3-4: Initial prevalence (%) of previous tuberculosis

Age category	Males	Females
15-25	0.8	1.1
25-34	2.1	1.8
35-44	4.1	2.0
45-54	5.2	2.6
55-64	4.1	2.2
65 and older	4.4	3.1
Overall	2.9	2.0

3.3. Estimating the proportion of new active tuberculosis cases that are smear-positive

Our model requires assumptions about the proportion of incident TB cases that are smear-positive, but most studies report the proportion of newly diagnosed/treated TB cases that are smear-positive. We expect the proportion of treated active TB cases that are smear-positive to be higher than the proportion of incident TB cases that are smear-positive due to the delays in TB diagnosis being greater for smear-negative TB than for smear-positive TB.

We used the Gupta *et al*. study to set the proportions of incident TB cases that are smear-positive, by HIV status (260). The study assessed how HIV and CD4 count affected TB disease site, smear status and overall laboratory confirmation of TB cases. The study was based on the 2009 electronic TB register for Cape Town. From this study, the proportion of HIV-negative individuals with known smear status who were smear-positive was 0.523; among HIV-positive individuals, the proportion was 0.326. The proportion of HIV-negative individuals with no laboratory confirmation for TB diagnosis was 0.374 (260). Given these data, we set the prior mean for the proportion of smear-positive individuals at 0.52. We further supposed an upper limit of 0.84 (=0.523/(1 – 0.374)), where 0.374 is the proportion of those with unconfirmed smear status. This upper limit was based on assuming that the smear-positive proportion in those with missing smear results is the same as that in those with

recorded smear results. As such, we assigned a Beta (12.46;11.50) prior distribution, with a mean of 0.52 and standard deviation of 0.1, for this parameter. Lastly, we set the proportion of smear-positives in HIV-positive patients to be 0.62 times that in HIV-negative individuals (0.326/0.523) (260).

3.4. Modelling tuberculosis transmission

We define the force of infection (λ_{ly}) as the daily rate at which a susceptible individual of sex l in age group y gets infected; new infections are updated at monthly. The number of susceptible individuals who get infected in each time step is represented by the expression below:

$$\lambda_{ly} = \sum_{g} \sum_{x} c_{gx} \rho_{gxly} \sum_{i \epsilon \{\Omega_{gx}\}} \frac{I_i}{N_{ly}} \beta$$

Where c_{gx} is the frequency of contacts per day (daily rate) that individuals of sex g and age group x have with other individuals (Table 3-5). This crude contact rate is obtained directly from data on the frequency of close contacts in a South African study (261). Also obtained directly from social mixing pattern data, ρ_{gxly} represents the proportion of contacts between an individual of sex g and age x, with individuals of sex *l* and age *y* (Table 3-5). Next, I_i represents the relative infectiousness of individual i, which depends on smear positivity; Ω_{gx} is the subset of the active TB population with age group *x* and sex g. Then N_{ly} is the number of individuals of sex *l* and age *y*. Lastly, β represents the probability of transmission per contact if a smear-positive individual has contact with a susceptible individual.

Table 3-5: Age- and sex-stratified proportions of social contacts in different age and sex groups and total mean contact rates (last column)

		Female contacts					Male contacts					
	Age	0-4	5-12	13-25	26-45	>45	0-4	5-12	13-25	26-45	>45	Total Mean
Female	10-17	0.016	0.042	0.494	0.124	0.021	0.015	0.027	0.169	0.081	0.012	6.84
	18-25	0.052	0.073	0.269	0.168	0.09	0.049	0.046	0.092	0.11	0.05	5.70
	26-45	0.058	0.083	0.155	0.238	0.07	0.051	0.058	0.089	0.145	0.05	5.40
	>45	0.029	0.066	0.162	0.194	0.1	0.046	0.062	0.13	0.117	0.09	5.30
Male	10-17	0.016	0.029	0.225	0.091	0.017	0.015	0.040	0.438	0.115	0.015	6.60
	18-25	0.024	0.032	0.155	0.119	0.08	0.022	0.045	0.302	0.15	0.07	5.50
	26-45	0.026	0.042	0.123	0.166	0.07	0.029	0.04	0.124	0.294	0.09	4.70
	>45	0.037	0.047	0.117	0.144	0.12	0.03	0.058	0.13	0.184	0.13	4.70

3.4.1. The transmission probability per daily contact

We allow for the transmissibility of smear-positive TB to change over time, because as treatment delays reduce, we would expect fewer TB patients to progress to the more advanced (and more infectious) disease stages prior to treatment. We note that the assumption for a declining trend in smear-positive infectivity overtime may lead to more optimistic predictions of the impact of improved case detection and treatment initiations. To model transmission, we define $\beta(t)$ to be the transmission probability per daily contact between a smear-positive TB case and a susceptible individual in year t, and $\beta(0)$ is the corresponding average transmission probability in the period before 2000. The prior distribution assigned to represent the uncertainty in this transmission parameter $\beta(0)$ is a Gamma (1; 400) distribution with mean = 0.0025 and standard deviation = 0.0025. Although this parameter value is set arbitrarily, it was chosen based on whether the chosen value yielded reasonable transmission rates. In the initial model fitting, the parameter value was set at 0.02, however it yielded implausibly high rates of transmission, and so we selected a prior distribution with a lower mean but high variance.

We define r_i as the ratio of the minimum infectivity (when the treatment delay is zero) to the baseline infectivity (given the treatment delay in the period before 2000). $S(t)$ represents the average smear-positive treatment delay, approximated as $U(t)/R(t)$, where $U(t)$ is the number of untreated smear-positive TB cases at the start of year *t* and $R(t)$ is the number of smear-positive TB patients who are treated in year t. $S(0)$ represents the average smear-positive treatment delay before 2000.

Because we lack data on smear grade distributions in South Africa before 2000, we conservatively estimated r_i based on the smear grade distribution observed by Singla *et al.* (262) in an Indian population with poor treatment access. In this study, the distribution of smear-grades in TB patients were 27% for smear-grade <2+; 25% for smear-grade 2+ and 48% for smear-grade 3+ (262). We assumed the same relative levels of infectiousness by smear grade as measured by Acuña-Villaorduña *et al.*, who estimated that infectivity increased by 1.45 times and 4.25 times in patients with smear grades 2+ and smear grades 3+ respectively, compared to TB patients with smear grade 1+ (263). Then we have $r_i =$

$1/(0.27 + 0.25 \times 1.45 + 0.48 \times 4.25) = 0.37$, on the assumption that if there was no treatment delay all smear-positive TB cases would have smear-grade <2+.

To allow this transmission probability to change with disease severity (indicated by smear-grade distributions), we assume that for $t \geq 2000$,

$$\beta(t) = \beta(0)(1 - (1 - r_i)[1 - S(t-1)/S(0)]).$$

3.4.2. Infectiousness in smear-positive and smear-negative active TB

We rely on evidence from Andrews *et al*., who estimated the relative infectivity of smear-negative compared with smear-positive individuals to be 0.22 (95% CI 0.16-0.32) (52). We define I_i as the relative infectiousness of individual i and specified a Beta (41.73; 147.9) prior distribution for the uncertainty around the relative infectiousness of smear-negative TB, with a mean of 0.22 and standard deviation of 0.03 (52).

3.4.3. Social mixing patterns

The primary data source for the social mixing parameters in the model is the Dodd *et al*. study (83). The data from this study were based on a social contact survey conducted in eight communities in the Western Cape. In the study, interviewees reported contacts that occurred approximately 24 hours before the interviews. We chose these data because they provide both an age and gender stratification. However, the data are limited to age groups >18 years (264). Therefore, for ages 10-18 years, we use data from Johnstone-Robertson *et al*. (210). This Johnstone-Robertson study was also conducted in the Western Cape, although the setting was limited to one township and the data were not differentiated by sex. Based on several social mixing studies, the majority of close contacts in this age group occur in school settings among children of similar age groups (210,265,266). For simplicity, we assumed the sex structure in the age groups 10-18 years (Johnstone-Robertson *et al*. data (210)) would be similar to that observed in the 19-25-year age group (Dodd *et al*. data (83)).

The average contact rates across the age groups in the Johnstone-Robertson *et al.* study (210) were higher than those observed in Dodd *et al.* (83) study. This may be due to differences in study settings and definitions of "close contacts". In the Dodd *et al*. study, close contacts were defined as contacts involving a face-to-face conversation longer than a greeting and

within an arm's reach (83). In Johnstone-Robertson *et al*. study, they were defined as contacts involving physical touch or those that involved a two-people conversation with three or more words in the physical presence of another person without physical touch (210). The former definition is more restrictive than the latter, hence limiting the number of contacts recorded.

In order to have consistency in the mixing patterns in our assumptions (which are based on the Dodd *et al*. study (83)) and those observed in Johnstone-Robertson *et al.* study, we applied the ratio of mean contacts for 10-17-year-olds to 18-25 year- olds in the Johnstone-Robertson *et al.* study to the 18-25-year-old group in Dodd *et al.* (210). That is, the ratio 19.0 /15.9 = 1.2 multiplied by our study's average contact rate for the 18-25 years age group. The resulting contact rates and social mixing proportions are in Table 3-5.

3.5. Modelling the tuberculosis natural history and the effects of human immunodeficiency virus and antiretroviral therapy

3.5.1. Progression to active tuberculosis disease: fast progression and reactivation

Following infection with LTBI, a proportion of individuals progress directly to active TB disease ('fast progression'). We specified the value of this proportion of fast progressors at 0.1 to be consistent with previous modelling studies (142,169,177). The remainder of individuals are assumed to stay latently infected and may develop active TB disease at an annual rate through reactivation. This rate might be estimated as 0.0024, based on assuming 0.0866 as the rate of fast progression in the first year after infection and 0.028 as the relative risk of progression in the fifth year, as estimated by Vynnycky & Fine ($0.0024 = 0.0866 \times 0.028$) (80). A prior distribution to represent the uncertainty around this reactivation rate parameter was specified as a Gamma (4; 1666.7) distribution. The corresponding mean and standard deviation were 0.0024 and 0.0012 respectively.

To model the effect of HIV on progression to TB disease, we consider the following parameters: 1) θ, the relative rate of TB incidence per 100 cells/µl increase in CD4 count; and 2) π relative rate of TB incidence on ART after controlling for CD4 count.

To set the effect of CD4 count on TB disease risk (θ), we use the meta-analysis by Ellis *et al*., which estimated that an increase in 100 CD4 cells/µl was associated with a 30%

reduction in TB risk (IRR 0.70, 95% CI 0.53 – 0.86) (98). As such, we set a Beta (19.52; 7.97) prior distribution to represent the uncertainty around this θ parameter.

Secondly, we assume HIV viraemia has an effect on developing TB disease, independent of CD4 count. That is, a person with untreated HIV might be at increased risk of TB disease when compared to an HIV-negative person with the same CD4. Because we cannot measure this parameter directly, we use, as a proxy, the effect of ART on TB disease (independent of CD4) since ART generally suppresses viraemia (5,267). We set the relative rate of TB incidence while on ART, controlling for CD4 count (π), based on Fenner *et al.*'s study which estimated that unsuppressed viral load (1000-9999 compared to <1000) was associated with an increased risk of TB disease (adjusted RR 1.23, 95% CI 1.08 – 1.41) (5). Using this study (Fenner *et al.*), the assumed protective effect of ART is $\pi = 1/1.23 = 0.81$, and a Beta (49.05; 11.51) prior distribution is specified for the uncertainty around this parameter.

In the model, the relative effect of HIV on TB incidence in HIV-positive individuals who are not on ART is represented by:

$$H(s) = \pi^{-1}\theta^{(a-s)/100},$$

$H(s)$ is used as rate ratios applied to rates of slow and fast progression to TB.

The relative effect of HIV on TB incidence in HIV-positive individuals on ART is represented by:

$$A(s,d) = \theta^{(a\,-\,s_d)/100},$$

Where $A(s,d)$ is used as rate ratios applied to rates of slow and fast progression to TB,

a: average CD4 count in HIV-negative individuals

s: average CD4 count in HIV-positive individuals not on ART (for a given CD4 compartment)

s_d: CD4 count for those on ART at the treatment duration d

θ: relative rate of TB incidence per 100-cell increases in CD4 count

π: Relative rate of TB incidence on ART (controlling for CD4).

3.5.2. Partial immunity

In the model, we assume that individuals with LTBI have partial immunity and that the relative risk of developing TB is 0.21 if they are re-infected. This relative risk of developing TB is based on Andrews *et al*., who showed that individuals with LTBI had a 79% reduced risk of developing TB disease (95% CI 70–86%) (61). Therefore, we fixed this parameter for partial immunity in HIV-negative individuals (represented by parameter y) at a mean of 0.79.

There is a lack of data regarding partial immunity in HIV-positive individuals and the effect of ART. We extrapolate from assumptions made in the modelling study by Menzies *et al*. who assumed a 0.25 (range: 0.14–0.39) reduction in the risk of developing TB disease among HIV-positive individuals with CD4 counts > 350 cells/μl, and no partial immunity for the those with CD4 count < 350 cells/μl (169). In our model, the effect of HIV on partial immunity is modelled as a function of CD4 count. We set p, the relative rate of partial immunity against TB disease per 100-cell increase in CD4 for HIV-positive individuals at 1.1. This relative rate is applied to the parameter (y) representing the reduction in TB incidence in previously infected HIV-negative individuals in the model.

This partial immunity effect for HIV-positive individuals is

$$I(s) = yp^{(s-a)/100},$$

where

a: average CD4 count in HIV-negative individuals.

s: the current CD4 count in HIV-positive individuals

p: relative rate of partial immunity against TB per 100-cell increase in CD4 count, for HIV-positive individuals

y: the reduction in TB incidence in latently infected individuals who are HIV-negative.

3.5.3. Natural recovery (untreated tuberculosis)

Studies from the pre-antibiotic era have shown that a certain proportion of patients do not die in the absence of treatment and presumably recover naturally without treatment (76). Based on Tiemersma *et al.*'s review of studies conducted during the pre-chemotherapy era, case fatality rates among untreated TB cases were estimated to be 0.7 among smear-positive and 0.2 among smear-negative individuals; the duration of active TB disease was estimated at 3.3 years (76). As these case fatality rates represent cumulative mortality risks, we convert them into annual mortality rates in the model. For the annual mortality rate in smear-negative (μ_{smn}) and smear-positive (μ_{smp}) individuals, and for the annual natural recovery rate in smear-negative (n_{smn}) and smear-positive individuals (n_{smp}), we have the following relationships: duration of smear-positive TB disease is $1/(\mu_{smp} + n_{smp}) = 3.3$, and the same duration is assumed for smear-negative TB. Similarly the case fatality ratio for smear-positive TB is $\mu_{smp} / (\mu_{smp} + n_{smp}) = 0.7$ and $\mu_{smn} / (\mu_{smn} + n_{smn}) = 0.2$. Given these expressions, for smear-positive individuals, we get $\mu_{smp} = 0.212$ and $n_{smp} = 0.091$; for smear-negative individuals, we have $\mu_{smn} = 0.061$ and $n_{smn} = 0.242$ (76).

For HIV-negative individuals, we specified a Gamma (20.25; 225) prior distribution with mean of 0.09 and standard deviation of 0.02 for the uncertainty around the rates of natural recovery among smear-positive (n_{smp}). For natural recovery among smear-negative, we specified a Gamma (23.04; 96) prior distribution with mean 0.24 and standard deviation of 0.05 (n_{smn}).

There is limited evidence on how HIV and ART affect natural recovery. As with partial immunity, we specified the relative rate of natural recovery dependent on CD4 count, extrapolating from a previous modelling study by Menzies *et al*. who assumed an annual rate of recovery of 0.2 (range: 0.15–0.025) in those who were HIV-negative, 0.1 (range: 0.06–0.16) in those with CD4 counts > 350 (169), and zero in those with a CD4 count of 350 and less.

In the model, the rate of natural recovery is modelled as follows:

$$R(s,d) = nv^{(s-a)/100}$$

v: relative rate of natural recovery per 100-cell increase in CD4 for HIV-positive individuals. We set $v = 1.2$ to be roughly consistent with Menzies *et al* (169).

n: natural recovery rates in smear-positive (n_{smp}) or smear-negative (n_{smn}) individuals who are HIV-negative.

s: the current CD4 count in HIV-positive individuals.

3.5.4. Untreated active tuberculosis mortality

As described in the section on Natural recovery, the untreated annual mortality rates in HIV-negative individuals with TB can be estimated as $\mu_{smp} = 0.212$ and $\mu_{smn} = 0.061$ for smear-positive and smear-negative TB respectively (268). We specified a prior distribution for smear-positive mortality that was Gamma (25; 117.9) with mean 0.212 and standard deviation of 0.042. For smear-negative mortality, we similarly specified a prior distribution that was Gamma (25; 409.8), with a mean of 0.061 and standard deviation of 0.012. (these rates relate to HIV-negative individuals aged 55+). The effects of HIV, ART, and age on TB mortality are explained in section 3.7.3 (due to the lack of data on the effect of these covariates in untreated TB, we make the same assumption about these factors for treated and untreated TB mortality).

3.6. Modelling the tuberculosis diagnostic pathway

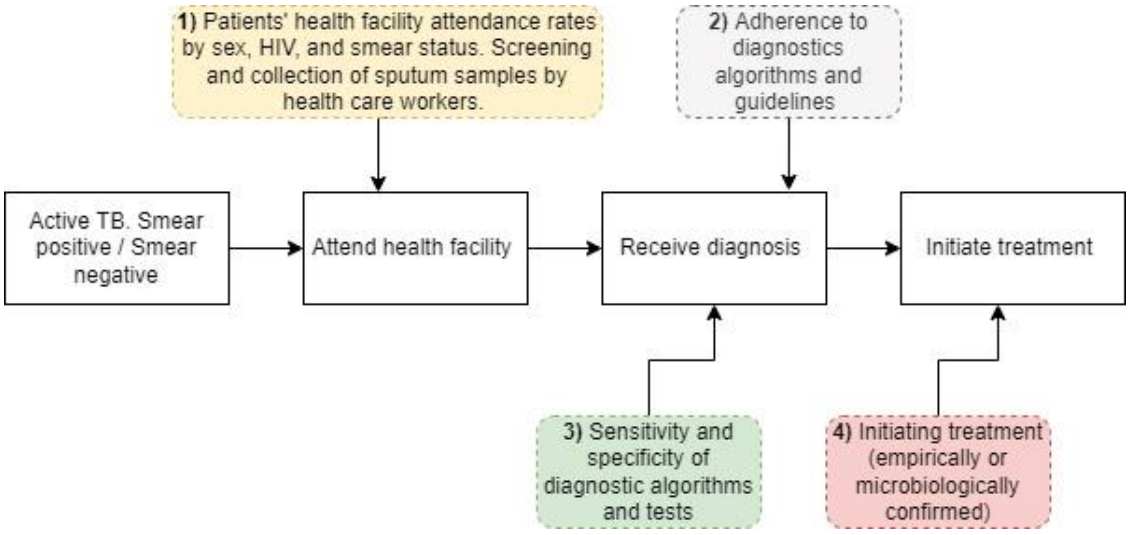
The path to TB diagnosis and care involves multiple steps; in the model, we consider the following:

- health-seeking rates, which vary by symptoms, smear status, HIV status and sex
- the proportion of sputum samples submitted for microbiological testing
- sensitivity and specificity of diagnostic algorithms
- treatment initiation and initial loss to follow-up (before treatment initiation) following a microbiological confirmation
- empirical treatment.

Treatment outcomes are further described in section 3.7.

Figure 3-3 summarises these steps above. At the entry point into the care cascade and treatment pathway, we consider health-seeking behaviours in people with active TB disease as well as health seeking unrelated to TB in the general population. We define $\gamma_m(a, g, s, t)$ as the rate of health-seeking for individuals of smear status a (0 = smear-negative, 1 = smear-positive), of sex g (0=male, 1=female) and HIV stage s (as defined in Thembisa 4.1) at any time t. Here $m = 1$ represents active TB individuals seeking treatment for TB symptoms, $m = 2$ represents individuals in the general population who are seeking treatment for other conditions and $m = 3$ represents individuals in the general population seeking treatment for TB- like symptoms. The health-seeking rates are defined such that for any t, $\gamma_1(a, g, s, t)$, $\gamma_2(g, s, t)$ and $\gamma_3(g, s, t)$ depend on smear status, sex, and HIV status.

Figure 3-3: Illustration of the modelled tuberculosis diagnostic pathway



We also assume some prevalence ($v_A(a)$) of TB symptoms in the active TB population seeking care for other conditions, for smear status a and we assume v_G to be the prevalence of respiratory symptoms in the general (non-active TB) population. Following interaction with health facility workers, some individuals will be requested to submit their sputum samples for testing. Thus, we let $p_1(t)$ represent the proportion of individuals with active TB disease, seeking treatment for their TB symptoms, who submit their samples to be tested microbiologically; and $p_2(t)$ the proportion of individuals with TB-like respiratory symptoms, seeking treatment for other conditions, who get microbiologically tested.

We allow the diagnosis of TB to depend on the sensitivity ($Se(a, s, t)$) and specificity ($Sp(t)$) of the diagnostic algorithm for smear status a and HIV state s, at time t. We consider

the sensitivity and specificity of the first line microbiological diagnostic tests – GeneXpert MTB/RIF and smear microscopy – as well as culture (assumed to be 100%). The diagnostic algorithm is given by:

Equation 1: Diagnostic algorithm sensitivity

$$Se(a,t,s) = M(t)\left[Se_M(a) + \left(1 - Se_M(a)\right)C_M(s,t)\right]$$

$$+ \left(1 - M(t)\right)\left[Se_G(a) \; + \left(1 - Se_G(a)\right)C_G(a,s,t)\right]$$

And

Equation 2: Diagnostic algorithm specificity

$$Sp(t) = M(t)Sp_M + \left(1 - M(t)\right)Sp_G$$

where $Se_M(a)$ and $Se_G(a)$ represent the sensitivity of smear microscopy and GeneXpert MTB/RIF in active TB patients, respectively; Sp_M and Sp_G represent the specificity of smear microscopy and GeneXpert MTB/RIF, respectively. Given the recommendations that negative test results after an initial test require follow-up testing (particularly in the case of previously treated and HIV-positive cases (75,269)), we allow individuals to be followed up for a second test.

To represent the national-level implementation of the specific diagnostic tools, we define $M(t)$ to be the proportion of TB suspects who are initially tested by smear microscopy in year t and the remainder $(1 - M(t))$ are tested by GeneXpert MTB/RIF initially. We then define $C_G(a,s,t)$ to represent the proportion of active TB cases followed-up for further culture testing after an initial negative GeneXpert MTB/RIF test; $C_M(s,t)$ is the proportion of active smear-negative TB cases who have further culture testing done after initial negative microscopy tests.

The estimated number of microbiological tests performed yearly $T(t)$ is given by

Equation 3: Number of microbiological tests

$$T(t) = \sum_g \sum_s N(g,s,t)\left(\gamma_2(g,s,t)v_G p_2(t) + \gamma_3(g,s,t)p_1(t)\right) +$$
$$\sum_a \sum_g \sum_s A(a,g,s,t)\left(\gamma_2(g,s,t)v_A(a)p_2(t) + \gamma_1(a,g,s,t)p_1(t)\right)$$

where $N(g,s,t)$ is the number of adults in the general population (not having active TB) and $A(a,g,s,t)$ is the number of active TB cases at time t.

Following a positive diagnosis, some patients get lost before treatment initiation. Therefore, we let $L(t)$ be the proportion of individuals lost to initial follow-up. The number of people with a positive laboratory diagnosis is represented by $R_1(t)$ in Equation 4 and the number of people with a positive diagnosis who initiate treatment is estimated as $R_1(t)(1-L(t))$.

Equation 4: Number of positive diagnoses

$$R_1(t) = \sum_g \sum_s N(g,s,t)\big(\gamma_2(g,s,t)v_G p_2(t) + \gamma_3(g,s,t)p_1(t)\big)\big(1-Sp(t)\big) + \sum_a \sum_g \sum_s A(a,g,s,t)\big(\gamma_2(g,s,t)v_A(a)p_2(t) + \gamma_1(a,g,s,t)p_1(t)\big)Se(a,t,s)$$

3.6.1. Modelling tuberculosis health-seeking patterns

i. *The prevalence of tuberculosis symptoms by smear status*

We set the prevalence of TB-related respiratory symptoms based on studies that report TB symptoms for the active or non-active TB populations (where the studied populations are at least generalisable). Based on the review by Onozaki *et al*. (270) of TB prevalence surveys in Asian populations, the average prevalence of TB symptoms in bacteriologically confirmed TB cases was 43% (270). A positive symptom screen was defined as a cough of more than two to three weeks or blood in sputum. A Zambia/South Africa TB and AIDS Reduction (ZAMSTAR) study also surveyed respiratory symptoms (31). Among individuals with TB, the proportion of people experiencing persistent cough for more than two weeks was 20.5%, compared to 5.2% among those without TB (31). Den Boon *et al.* in a Cape Town based study conducted in 2002, estimated the prevalence of TB symptoms to be 48% in patients with active TB (60% among smear-positive active TB patients and 22% among smear-negative individuals) (271).

We consider the prevalence observed in the ZAMSTAR (31) and the Den Boon *et al.* (271) studies to be likely over-estimates of the prevalence of symptoms in smear-negative TB ($v_A(0)$) because smear-negative TB is less symptomatic than smear-positive TB. To represent the uncertainty around this parameter we specified a Beta (3;12) prior with mean of 0.2 and standard deviation of 0.1. Then we set v_G the prevalence of respiratory symptoms in the general non-active TB population at 5.2% based on the ZAMSTAR study (31).

We use the review of prevalence surveys conducted in Asia between 1990–2012 by Onozaki *et al*., to estimate the ratio of the prevalence of TB symptoms in smear-positive individuals compared to smear-negative individuals with TB (270). From this review, the prevalence ratio of TB symptoms in smear-positive individuals compared to smear-negative individuals differed between countries and ranged between 1.0 and 2.72; the average was 1.62 (270). From the countries in which more than one survey was included (Cambodia, Philippines, Korea), the ratio declined over time, suggesting that the ratios might be lower as screening and treatment services improve. In the Den Boon *et al.* study, this ratio was at 2.7 (270,271).

In the model, we define f to be the ratio of symptoms in smear-positive compared to smear-negative individuals. To represent the uncertainty around f we specified a Gamma (19.36; 8.8) prior with mean 2.2 and standard deviation of 0.5.

ii. *Health-seeking patterns by sex*

To model the effect of sex, we define z to be the relative rate of health-seeking in females compared to males. We use the male-to-female ratio for prevalence-to-notification ratio estimated in the systematic review and meta-analysis by Horton *et al.* (2) to estimate sex differences on the pathway to TB care and TB testing. This ratio was estimated at 1.55 (2). To represent the uncertainty around this parameter z, we assign a Gamma (83.13; 53.63) prior distribution with a mean of 1.55 and a standard deviation of 0.17. We acknowledge the limitation that we did not allow the health-seeking parameters to be age dependent whereas it is possible that older people are more likely to be attending health facilities for conditions unrelated to TB than younger adults.

iii. *Health-seeking patterns by HIV status*

We assume that the attendance rate for HIV-positive individuals will be higher compared to that of HIV-negative individuals as HIV-positive individuals are more likely to be engaged with health care facilities and possibly because, in individuals with active TB, the development of symptoms may be more rapid than in HIV-negative individuals (272). In addition, HIV-positive individuals who are on ART would also be more likely to attend health care facilities as they engaged in care. We relied on Corbett *et al* and the South African National prevalence survey which suggested higher health-seeking in HIV-positive individuals than HIV-negative individuals (17,272).

We define h to be the relative rate of health seeking in HIV-positive individuals (compared to HIV-negative individuals). We expect $h>1$. To represent the uncertainty around this parameter h, assign a Gamma (9; 3) prior distribution with a mean of 3.0 and a standard deviation of 1 (17,272).

i. Setting overall health-seeking rates

For any time t, we define the health-seeking rates such that they depend on the variables:

- sex (g): male sex is represented by $g = 0$; female $g = 1$.
- HIV status (s): HIV-negative status is represented by $s = 0$; HIV-positive by $s > 0$.
- smear status (a): smear-negative TB represented by $a = 0$; smear-positive by $a = 1$.

The definitions of the health-seeking rates are below (***a***–***c***), and as defined earlier:

- f is the ratio of symptoms in smear-positive compared to in smear-negative individuals;
- z is the relative rate of health-seeking in females compared to males;
- h is the relative rate of health seeking in HIV-positive individuals (compared to HIV-negative individuals).

a. Health-seeking rate for active TB population seeking treatment for TB symptoms ($\gamma_1(a, g, s, t)$)

We let γ_1 represent the rate of health-seeking for HIV-negative men with smear-negative active TB, seeking treatment for TB symptoms, and define $\gamma_1(a, g, s, t)$, the health-seeking rate for adults with active TB as below.

For smear-negative individuals ($a = 0$),

$$\gamma_1(a, g, s, t) = \begin{cases} \gamma_1 \text{ for } g = 0 \text{ and } s = 0, \forall t \\ \gamma_1 z \text{ for } g = 1 \text{ and } s = 0, \forall t \\ \gamma_1 h \text{ for } g = 0 \text{ and } s > 0, \forall t \\ \gamma_1 z h \text{ for } g = 1 \text{ and } s > 0, \forall t \end{cases}$$

For smear-positive individuals ($a = 1$),

$$\gamma_1(a,g,s,t) = \begin{cases} \gamma_1 f \text{ for } g = 0 \text{ and } s = 0, \forall t \\ \gamma_1 zf \text{ for } g = 1 \text{ and } s = 0, \forall t \\ \gamma_1 hf \text{ for } g = 0 \text{ and } s > 0, \forall t \\ \gamma_1 zhf \text{ for } g = 1 \text{ and } s > 0, \forall t \end{cases}$$

Based on the interquartile range of 1.3–3.4 prevalent infections per notification in men, from the review by Horton *et al.* (2), we have annual notification rates of between 0.29 (= 1/3.4) and 0.77 (= 1/1.3). Because many TB cases who seek treatment do not get screened, we estimate the rate of health-seeking by dividing the notification rate by the % screening, which ranges between 3% and 49% in South African studies (273–275). By taking the median of the South African studies estimates as 24%, we get the resulting range in the rates of health-seeking: 1.21 (=0.29/0.24) to 3.08 (=0.77/0.24). We specify a Gamma (19,07;8.91), prior distribution with mean = 2.14 and standard deviation = 0.49 per annum to represent the uncertainty around γ_1.

b. Health-seeking rate for the general population seeking treatment for other conditions ($\gamma_2(g,s,t)$)

Second, we define the health-seeking rate for adults in the general population as

$$\gamma_2(g,s,t) = \begin{cases} \gamma_2 \text{ for } g = 0 \text{ and } s = 0, \forall t \\ \gamma_2 z \text{ for } g = 1 \text{ and } s = 0, \forall t \\ \gamma_2 h \text{ for } g = 0 \text{ and } s > 0, \forall t \\ \gamma_2 zh \text{ for } g = 1 \text{ and } s > 0, \forall t \end{cases}$$

where γ_2 represents the rate of health seeking in HIV-negative men in the general population. We estimate this based on the average public health facilities attendance from the SADHS (259,276). This represents individuals who attend health facilities for other health conditions. The average attendance rates from the 1998 and 2003 SADHS reports were 0.186 and 0.2 per month, respectively. We take the average of these and get 0.193 per month, which gives an annual rate of 2.3 (= 0.193 × 12). We set this as an upper bound so $\gamma_2 < 2.3$ because of telescoping bias – when surveyed, people tend to report things as happening more recently than they actually happened. Also, we would expect this to be an upper bound because the base rate (γ_2) applies to men who are HIV-negative, and we expect HIV-negative men to have lower rates of health seeking (generally) than women and people living with HIV. We specify a Gamma (5.29;4.6) prior distribution with mean = 1.15 and standard deviation = 0.5 to represent the uncertainty in γ_2.

c. Health-seeking rate for the general population (no TB) seeking treatment for TB-like symptoms $\gamma_3(g, s, t)$

Third, we define the health-seeking rate for the general population without TB, seeking treatment for TB-like symptoms as

$$\gamma_3(g,s,t) = \begin{cases} \gamma_3 \text{ for } g = 0 \text{ and } s = 0, \forall t \\ \gamma_3 z \text{ for } g = 1 \text{ and } s = 0, \forall t \\ \gamma_3 h \text{ for } g = 0 \text{ and } s > 0, \forall t \\ \gamma_3 zh \text{ for } g = 1 \text{ and } s > 0, \forall t \end{cases}$$

where γ_3 represents the rate at which HIV-negative men in the general population seek treatment for TB-like symptoms that are not due to TB. There are limited studies that show the proportions of individuals from the general population who attend health facilities due to TB-like symptoms only. We expect $\gamma_2 > \gamma_3$ – that is, the rate of health facility attendance (γ_2) will be greater than that for TB-like symptoms (γ_3). Based on the South African General Household Survey in 2011 (277) on use of health facilities, 9.6% of South Africans reported being ill or injured in the previous month, and 77.5% of these reported consulting a health worker. This suggests an annual health-seeking rate of approximately 0.89 (= 0.096 × 0.775 × 12) (277). Of the people who were ill or injured in the month before the survey, 63.7% reported having flu or acute respiratory tract infections; and 2.9% reported having suffered from TB or severe cough with blood. From this, we approximate a lower bound of 0.0258 (= 0.029 × 0.89) and an upper bound of 0.593 (= (0.637 + 0.029) × 0.89), recognising that there is substantial overlap between TB symptoms and flu/acute respiratory symptoms (although it is unlikely that all flu/respiratory symptoms would be attributable to TB). We specify a Gamma (2.15;9.78) prior distribution with mean = 0.22 and standard deviation = 0.15 to represent the certainty around γ_3.

3.6.2. Specimens submitted for microbiological testing

To estimate the proportions of individuals seeking treatment who are screened and have their sputum samples collected by health care workers for microbiological testing, we use estimates of the proportions reported in the few available empirical studies from South Africa (273–275). We allow these proportions to depend on patients' reasons for attending the health facility, i.e., TB symptoms or other health conditions reported by patients (Table 3-6). Although all these studies rely heavily on patients' recall and may lead to biased assumptions,

they give an idea of what happens at the health facility level. The Kweza *et al*. study was conducted across Eastern Cape district facilities, whereas the Claassens *et al*. study was limited to two primary health care facilities in one sub-district in the Western Cape. The Claassens *et al.* study also had a low response rate, suggesting it is less generalisable (278). The Chihota *et al.* study was a pragmatic cluster randomised trial assessing whether health care worker practice in examining people with TB symptoms changed when the initial test for TB switched from smear microscopy to GeneXpert MTB/RIF, so the results were presented separately for the two trial arms.

Table 3-6: Proportions of patients with TB symptoms who are screened and submit sputum specimens

Study	Reason for attending a health facility: TB symptoms $p_1(t)$	Reason for attending a health facility: Other reasons $p_2(t)$	Ratio $r = p_1(t)/p_2(t)$
Claassens *et al.* (2013) (278)	0.028	0.003	10.750
Chihota *et al.* (2015) (275)			
GeneXpert MTB/RIF	0.491	0.154	3.94
Microscopy	0.299	0.136	2.195
Kweza *et al.* (2018) (273)	0.181	0.037	4.893

In these three studies (273–275), individuals were classified as attending health facilities due to TB-related (respiratory) symptoms if they reported having any symptoms, including cough, loss of weight, fever, and night sweats. This is a less specific definition than we considered in defining symptomatic TB for the prevalence of TB symptoms (v_A, v_G). As such, we note that the TB symptoms prevalence we use is an under-estimate of the true proportion of cases that could be screened.

We defined $r(t) = p_1(\mathrm{t})/p_2(t)$ to be the ratio of microbiological testing in symptomatic individuals seeking treatment for TB symptoms compared to those seeking treatment for other reasons (who coincidentally have TB-like symptoms) in year t. We let $p_1(t)$ represent the proportion of individuals with active TB seeking treatment for their TB symptoms who get tested microbiologically, and $p_2(t)$ the proportion of individuals with TB-like respiratory symptoms seeking treatment for other conditions who get microbiologically tested.

There is limited data and evidence to show how $r(t)$ has changed over time. However, the $r(t)$ estimates in Table 3-6 are highest when screening rates are lowest, suggesting that $r(t)$ has declined as the intensity of screening has increased. We used a piecewise-linear function to represent the change in $r(t)$ over time. First, we assume a constant ratio up to 2005. For this period, the ratio $r(t)$ was estimated by a fitting function $(\exp(2.04 - 10.84 \times p_2(\mathrm{t})) + 1)$ for the relationship between the ratio and the screening rates in Table 3-6, which gives 8.71 when $p_2(\mathrm{t}) = 0$. We assigned a Gamma (12.14; 1.394) prior distribution with a mean of 8.71 and a standard deviation of 2.5 for $r(t)$ in the period up to 2005 (i.e., assuming screening rates were close to zero in the period before 2005). We then linearly interpolated between the 2006 and 2011 ratios for the intervening years; and assigned $r(t)$ a Gamma (11.11; 2.78) prior distribution with a mean of 4 and a standard deviation of 1.2 for the period

from 2012. The latter prior distribution is based on the studies summarized in Table 3-6, which were mostly conducted in the period after 2011.

Then $p_1(t)$ will be estimated from $R_1(t)$, the total number of positive tests in year t, by rearranging the terms in Equation 4. We relied on the National Institute for Communicable Diseases data (2004-2019) for the numbers of microbiological diagnoses (24). Then, $p_1(t)$ was estimated as in Equation 5. We relied on the National Institute for Communicable Diseases data (2004-2019) for the numbers of microbiological diagnoses shown in Table 3-7 (24). We assumed the testing rates in 1985 (when the model was initiated) were half of the 2004 testing rates; and assumed that for the period 1985-2004, the screening rates increased linearly.

Equation 5: proportion of individuals with active TB who seek treatment for their TB symptoms who get tested microbiologically

$$p_1(t) = R_1(t)\left(\sum_g\sum_s N(g,s,t)\big(\gamma_2(g,s,t)v_G r(t)^{-1} + \gamma_3(g,s,t)\big)\big(1 - Sp(t)\big) + \sum_a\sum_g\sum_s A(a,g,s,t)\big(\gamma_2(g,s,t)v_A(a)r(t)^{-1} + \gamma_1(a,g,s,t)\big)Se(a,t,s)\right)^{-1}$$

Table 3-7: Recorded numbers of laboratory confirmed tuberculosis cases by year

Year	Estimated number of microbiologically confirmed TB cases
2004	307385
2005	345694
2006	385496
2007	395907
2008	422134
2009	321558
2010	320125
2011	348400
2012	321206
2013	313013
2014	298389
2015	289136
2016	262454
2017	249090
2018	261743
2019	232483

Sources: Data for years 2004-2008 obtained from Nanoo *et al*. (24) and adjusted for 10% probable overcounting. Data for years 2009-2019 obtained from the National Institute for Communicable Diseases (NICD) dashboard: https://mstrweb.nicd.ac.za/MicroStrategy/asp/Main.aspx?Server=NICDSANDMSTRI01&Project=Surveillance&Port=0&evt=2048001&src=Main.aspx.2048001&documentID=4236FF364F683E2F257DA5AC647F5BA6&currentViewMedia=1&visMode

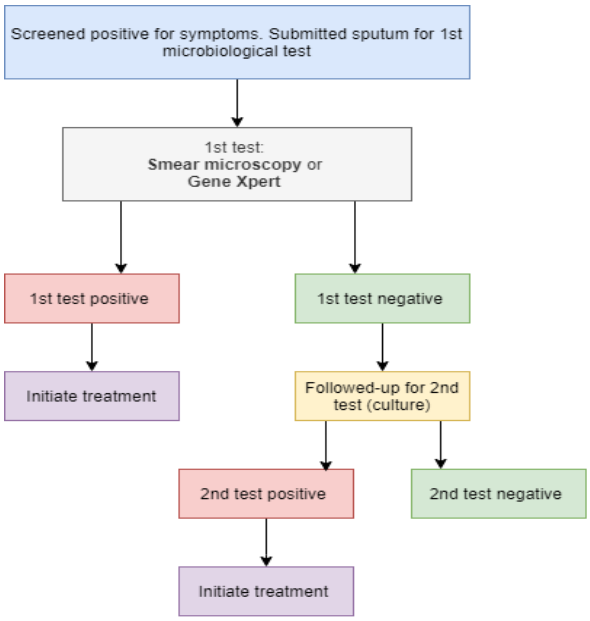
3.6.3. Sensitivity and specificity of diagnostic algorithms

In the model, we assumed sputum smear microscopy was the first-line diagnostic test before 2010. From 2011, we assume a gradual phase-in of GeneXpert MTB/RIF as the recommended first-line test (279). We let $M(t)$ be the proportion of individuals tested microbiologically by smear microscopy in year t. The remainder $(1 - M(t))$ is the fraction who have an initial test by GeneXpert MTB/RIF. Thus $M(t)$ varies with time depending on GeneXpert MTB/RIF utilisation as the first-line tool for diagnosing TB in South Africa. For 2010 and years before, we assume the level of GeneXpert MTB/RIF utilisation was 0% and gradually phased in over time. These proportions were set to be the same as those assumed by Sumner *et al*. and Hippner *et al*. based on expert opinion (188,190) (Table 3-8).

Table 3-8: Utilisation of GeneXpert MTB/RIF as a first-line diagnostic test in South Africa

Year	% GeneXpert MTB/RIF used ($\mathbf{1} - \boldsymbol{M(t)}$)
2010 and before	0
2011	22
2012	43
2013	65
2014	73
2015	80
2016 and onwards	80

Figure 3-4: Simplified diagnostic algorithm considered in the model



Note: second tests by culture mostly apply to HIV-positive individuals who are suspected to have TB disease and those with a history of TB treatment, but who test negative at the initial test.

As per the national TB guidelines (2008, 2009 and 2014), following a negative test result, it is recommended that some patients (i.e., HIV-positive individuals who are suspected to have TB disease and those with a history of TB treatment) be followed up for second tests by culture (30,269,279). In the model, we let the proportion of active TB cases of any smear status a, who have further culture tests performed after an initial negative GeneXpert MTB/RIF test, be represented by $C_G(a, s, t)$. $C_M(s, t)$ represents the proportion of smear-negative active TB cases with further culture testing after an initial negative smear microscopy test. These proportions of individuals followed up for second tests are based on studies which have evaluated follow-up tests by culture (Table 3-9) (280–282).

Table 3-9: Assumptions on follow-up tests by culture

Initial test	HIV status	Data sources description	Parameter value
Smear negative	HIV-negative	Based on the ~30% fraction of retreatment cases from various studies conducted in the Western Cape, and a roughly 80% rate of culture testing in retreatment cases who are smear-negative and HIV-negative (281,282).	$C_M(s = 0, t)$ = 0.24
	HIV-positive	Based on the average of the low rate (28%) in the McCarthy *et al.* study (281) and the high rate (80%) in the Naidoo *et al.* study (282).	$C_M(s > 0, t)$: Before 2006: = 0.24. In 2006: = 0.4. After 2007: = 0.55.
GeneXpert MTB/RIF negative	HIV-negative	Based on the ~30% fraction of retreatment cases and ~50% rate of culture testing in retreatment cases who are smear-negative and HIV-negative (282).	$C_G(a, s = 0, t)$ = 0.15
	HIV-positive	The average of the low rate (11%) in the McCarthy *et al.* (281) study and the high rate (50%) in the Naidoo *et al.* study (282).	$C_G(a, s > 0, t)$ = 0.3

We further let a TB diagnosis depend on the sensitivity ($Se(a, t, s)$) and specificity ($Sp(t)$) of the diagnostic algorithm for smear status a, at time t and HIV status s (as defined in equations 1 and 2). $Se_M(a)$ and $Se_G(a)$ represent the sensitivity of smear microscopy and GeneXpert MTB/RIF in active TB patients, respectively; Sp_M and Sp_G represent the specificity of smear microscopy and GeneXpert MTB/RIF, respectively. The culture test is assumed to be 100% sensitive and 100% specific. The assumed values for the other tests are shown in Table 3-10 (283–286).

Table 3-10: Assumed sensitivity and specificity of diagnostic tests by smear-status

	Value	Source
Sensitivity of GeneXpert MTB/RIF ($Se_G(a)$)		
Smear-positive ($Se_G(1)$)	0.98	Horne 2019 (286)
Smear-negative ($Se_G(0)$)	0.67	Horne 2019 (286)
Sensitivity of smear microscopy ($Se_M(a)$)		
Smear-positive ($Se_M(1)$)	1	Assumed
Smear-negative ($Se_M(0)$)	0	Assumed
Specificity of tests		
GeneXpert MTB/RIF (Sp_G)	0.995	Horne 2019; Parker 2019 (286,287)
Microscopy (Sp_M)	0.98	Steingart 2006 (288)

3.6.4. Treatment initiation and initial loss to follow-up

Following a positive diagnosis, some individuals are lost to follow-up before initiating treatment – this is referred to as initial loss to follow-up (ILTFU). The definition of ILTFU depends on the follow-up period at which individuals would be regarded as lost to follow-up. In most studies (289,290), individuals are classified as lost to initial follow-up if they do not initiate treatment one to six months after receiving a positive diagnosis and do not get recorded in the TB treatment registers maintained at health facilities.

A systematic review of 16 South African studies reported a pooled estimate of 19.4% (95% CI 14.4–24.3%) of ILTFU (289). However, there was high variation among the studies included in this review (I^2 = 95.85%). Factors associated with initial loss to follow-up include diagnostic tools – the longer the turnaround to test results, the more likely it is to lose patients on the treatment pathway. Because GeneXpert MTB/RIF is a point of care test with a quicker turnaround, a lower ILTFU is generally observed with its use. The average proportion of initial loss to follow-up in studies where GeneXpert MTB/RIF was used was 14.2%. In study settings where smear microscopy was used, the average proportion of initial loss to follow-up was 21.6% (289).

In another earlier review, Macpherson *et al.* (2014) estimated an initial loss to follow up of 18.0% (95% CI 13.0–22.0%) based on studies from African countries (290). Only one study in this review (Botha *et al.* 2008 (291)) traced patients who were initially lost to follow-up. In this study, 58 bacteriologically confirmed TB cases were initially classified LTFU. Upon follow-up of these individuals, 24.1% (n=14) had died, 44.8% (n=26) could not be traced and 31.0% (n=18) were traced (291). Of these 18 that were traced, 11 were found to have started treatment late, and seven were traced but had not started treatment for various reasons. This study showed that based on the definition used by various studies, particularly those with a short follow-up period, there is a chance of misclassifying a certain proportion of individuals who initiate treatment as lost to follow-up. That is, the proportion of initial loss to follow-up may be overestimated.

In the model, we set $L(t)$, the proportion of initial loss to follow-up in year t, based on the systematic review of South African studies, adjusted for the likely over-estimation identified by Botha *et al.* We adjust by the fraction of ILTFU cases that eventually get back into the health system and on treatment. Based on the Botha *et al.* study still, and assuming that those

who were not traced were as likely to be on treatment as those who were traced (non-differential with respect to initiating treatment), we can assume the actual initial loss to follow-up is (14+7) / (58–26) = 66%. We apply this factor of 0.66 to the assumed initial loss to follow-up. So, when Xpert is used, $L(t) = 0.142 \times 0.66 = 0.094$ and when smear microscopy was used, $L(t) = 0.216 \times 0.66 = 0.143$. The number of individuals who start treatment after a diagnosis is a shown in Equation 4.

3.6.5. Modelling empirical treatment

Empirical TB treatment – the administration of TB treatment to individuals being assessed for TB disease who do not have laboratory confirmation of TB – is recommended by WHO guidelines in resource-limited settings when ambulant HIV- radiography findings compatible with TB do not respond to broad-spectrum antimicrobial therapy (292). In South Africa, clinicians are recommended to initiate HIV-positive individuals on TB treatment when two sputum smear microscopy tests or a single sputum GeneXpert MTB/RIF is negative for TB, chest radiograph findings are compatible with TB, and symptoms do not respond to antibiotics (30). Empirical treatment is more beneficial in situations where the probability of active TB before a test is high, and when the diagnostic test used is less sensitive (30). As such, in some situations, even when the guidelines recommend a laboratory-confirmed test before TB initiation, clinicians initiate patients on TB treatment without testing first. Additionally, in some cases, empirical treatment can happen when bacteriological tests have been performed, but not yet confirmed. This may happen in cases where clinicians believe a patient likely has TB disease and further delay in treatment initiation may pose the risk of transmission.

In our model, we account for individuals who initiated treatment on an empirical basis through the calibration process among the people who initiated treatment. In modelling empirical treatment, we make an implicit allowance for extrapulmonary TB (as it is difficult to diagnose and the majority of extrapulmonary TB cases are not diagnosed based on microbiological investigation (293)).

First, we define Y as the proportion of active TB cases seeking treatment for TB symptoms who get treated empirically before any microbiological test is conducted. This proportion is based on two studies. The first study is by Pepper *et al*., which found the proportion to be 13% in Khayelitsha (based on a large sample in 2007-9 before GeneXpert MTB/RIF was

introduced) (104). The second is by Pronyk *et al.*, estimating a much higher rate (38%) in Agincourt, based on a relatively small number of cases (43). However, these studies may overestimate the true proportion. For example, if TB cases that come to the clinic with symptoms but never get screened are included in the denominator, the proportion will be lower. This bias would be more likely when there are lower treatment rates (i.e., as in the Pronyk *et al.* study conducted in a rural area before the rollout of major TB programmes)[1]. Therefore, the average of these two studies (25%) is assumed as the upper bound. We then specify a Uniform (0;0.25) prior distribution for Y, with a mean of 0.125 and standard deviation of 0.144.

Second, we let Z represent the proportion of smear-negative active TB cases seeking treatment for TB symptoms, treated empirically after an initial negative smear. In the period before GeneXpert MTB/RIF (i.e., before 2011), the proportion of all treated TB cases treated empirically was between 30% and 45% (224,294,295). It is nonetheless difficult to quantify the parameter based on the available data, and therefore we assign a non-informative prior, U (0; 0.667) to represent the uncertainty in Z, with a mean of 0.33 and standard deviation of 0.236.

Thirdly, we let R be the relative rate of empirical treatment in people with respiratory symptoms that are not due to TB, compared to people who do have TB. This R parameter is difficult to estimate from published studies due to a lack of evidence. However, we expect it to be < 1 since chest radiography is often used to exclude patients who do not have TB, and many empirically treated patients are only started on treatment if they fail to respond to an initial short course of broad-spectrum antibiotics. Based on van 't Hoog *et al.*'s meta-analysis, the sensitivity of chest X-rays in detecting TB was 95% based on the studies that evaluated chest X-rays in patients who had symptoms; the specificity was 55% (296). This suggests that if chest X-rays tested everyone with symptoms, the value of R would be 0.47 (= (1 – 0.55)/0.95). However, this might be an overestimate because not everyone is examined with chest X-rays; therefore, we specified a non-informative prior Uniform (0,1), (mean=0.5; standard deviation=0.236) to be conservative.

[1]Suppose A is the number of TB cases who are tested microbiologically, B is the number who are treated empirically (without microbiological testing) and C are the number of symptomatic TB cases that don't get treated. We define Y as B/(B+C), however, the Pepper and Pronyk studies report B/(A+B). If C > A, as one might expect, given the low rates of screening historically, then the Pronyk and Pepper studies are over-estimating the proportions we are interested in.

Fourthly, we define H as the relative rate of empirical treatment in patients who have TB symptoms (but came to the clinic for other reasons) relative to patients who came to the clinic because of TB-like symptoms. This parameter is also difficult to estimate from the literature. We expect that people who came to the clinic for other reasons would, on average, have less severe disease than those who came because of TB-like symptoms. As such, we assume health workers would perhaps be more cautious about putting them on treatment without microbiological confirmation. Therefore, we would expect H to be < 1 and again we assigned a non-informative prior (Uniform (0, 1), (mean=0.5; standard deviation=0.236) to be conservative.

Lastly, we define G to be the extent to which the introduction of GeneXpert MTB/RIF reduces empirical treatment after an initial negative test result. (We assume that the introduction of GeneXpert MTB/RIF does not cause any change in the rate of empirical treatment in people who have never been tested, i.e., it modifies Z but not Y). Hermans *et al*. showed that the proportion of patients empirically treated dropped from 32% in 2010 (before the introduction of GeneXpert MTB/RIF) to 18% in 2014 (224). Rees *et al*. observed a more modest reduction in empirical treatment from 37.5% in 2012 to 29.4% in 2015 (297). We thus set G, the reduction in empirical treatment after a negative screen due to GeneXpert MTB/RIF at 0.5 based on these studies.

These Y, Z, R and H parameters will be estimated by calibrating the model to the number of active TB cases that are initiating treatment as recorded in the ETR and the numbers of microbiological diagnoses. Although the difference between the two gives a crude measure of the extent of empirical treatment, a limitation is that there is limited empirical data to calibrate the model.

3.7. Modelling tuberculosis treatment and treatment outcomes

In South Africa, the standard TB treatment for drug susceptible TB lasts for six months, consisting of two phases. The first (intense) phase lasts two months, and the second (continuation) phase lasts four months (269). The commonly reported treatment outcomes include default, success (cure and completion), failure and death. The definitions are as in Table 3-11. These outcomes are reported as percentages in the District Health Barometer, and the primary data source is the ETR.

Table 3-11: Definitions of data used for treatment outcomes as per the electronic tuberculosis register

Symbol	Description	Source
m	Treatment completion: Proportion of patients whose smear (or culture) was positive at the beginning of treatment and have completed treatment but does not have negative smear /culture in the last month of treatment and on at least one previous occasion more than 30 days before. The numerator is the number of patients who have completed treatment as per definition, and the denominator is the total number of TB patients on treatment that year (75).	Electronic tuberculosis register (75,269).
c	Cured: Proportion of patients whose smear (or culture) was positive at treatment initiation and is smear/ culture-negative in the last month of treatment and on at least one previous occasion more than 30 days before. The numerator is the number of patients who are cured as per definition, and the denominator is the total number of TB patients on treatment that year (75).	
f	Treatment failure: Proportion of patients whose baseline smear (or culture) was positive and remained or becomes positive again at five months or later during treatment. This also includes patients with no significant clinical improvement and no significant weight gain after 4-5 months of treatment. A clinician establishes the diagnosis of the failure. The numerator is the number of patients who have failed treatment as defined, and the denominator is the total number of TB patients on treatment that year (75).	
d_1	Death: Proportion of patients who die for any reason during TB treatment. The numerator is the number of patients who die on treatment as defined, and the denominator is the total number of TB patients on treatment that year.	
d_2	Treatment discontinuation/default: Proportion of patient whose treatment was interrupted for two consecutive months or more during the treatment course. The numerator is the number of patients who have treatment interruption as per definition, and the denominator is the total number of TB patients on treatment that year (75).	

Note: definitions do not explicitly describe how people get classified if they start treatment without a positive microbiological test.

We model four possible outcomes: cure (κ) and treatment failure (γ) after treatment completion, treatment discontinuation (δ) and death on treatment (μ). These outcomes are estimated from the annual percentages reported by the ETR (Table 3-12). The ETR outcomes are defined differently from our model, as in the ETR treatment success is defined as a combination of cure and completion of the treatment course, whereas we consider 'cure after treatment completion' and also allow for cure in some patients who discontinue treatment.

Based on the six-month treatment duration, we convert the percentages (Table 3-12) from the ETR into annual rates that correspond to model parameters shown in Table 3-13.

Patients classified as cured in ETR (with bacteriological confirmation) would have completed the 6-months treatment course. For those classified as 'completed treatment', it is uncertain whether they have been cured. Using the ETR proportions, we estimate rates to represent transitions out of the 6-months treatment state. From the proportion of treatment success, we use the proportion of those cured (c) to estimate a cure rate (κ). This κ represents a transition to the recovered state after 6-months of treatment. Following treatment failure (γ), individuals are assumed to move back to active TB states, assuming the same distribution of smear status as for new active TB cases.

Among those who experience treatment discontinuation, at annual rate δ, we assume a proportion $(1-\phi)$ will move back to the active TB states and that ϕ move to the recently treated recovered state (post-treatment short term). Here ϕ represents the efficacy of partial/incomplete treatment, and we set this based on previous studies. Based on what was observed in a retrospective cohort study assessing treatment outcomes (298), among those who defaulted during TB treatment, ~35% developed TB disease within two years. Using these results, we assume that of those discontinue TB treatment, 65% would be cured and move to the recovered state (298).

Lastly, patients on treatment die at a rate of μ. One of the problems with TB deaths on treatment is under-reporting which is usually due to deaths being classified as treatment discontinuation (a loss to follow-up/default) (299). In the context of HIV and ART, under-ascertainment of deaths in HIV-positive individuals due to loss to follow-up has been corrected using factors ranging between 1.64 and 2.19 (300). In South Africa, it has been shown that only 35% (95% CI 34.2–35.8%) of ART patient deaths recorded in the vital registration system were also captured in patient records at health facilities (241), although higher rates of ascertainment might be expected in the case of TB given the DOTS requirements for regular patient contact. Given the similar challenges of under-reporting of TB deaths in patients on treatment, we use this observation to adjust for TB deaths. As such, we assume the true mortality rate is double the reported mortality rate. More details on how these parameters are set and adjusted follow in the next sub-sections below.

Table 3-12: Electronic Tuberculosis Register Treatment outcomes by year (2004–2016) sex and HIV-status expressed as proportions

		HIV-positive					HIV-negative					HIV-unknown				
Sex	**Year**	**Completed**	**Cured**	**Died**	**Discontinued**	**Failed**	**Completed**	**Cured**	**Died**	**Discontinued**	**Failed**	**Completed**	**Cured**	**Died**	**Discontinued**	**Failed**
		m	c	d_1	d_2	f	m	c	d_1	d_2	f	m	c	d_1	d_2	f
Female	2004	0.468	0.245	0.060	0.220	0.008	0.396	0.445	0.022	0.128	0.009	0.452	0.202	0.085	0.256	0.006
	2005	0.454	0.259	0.086	0.192	0.008	0.314	0.538	0.021	0.117	0.010	0.458	0.220	0.093	0.222	0.007
	2006	0.455	0.266	0.092	0.176	0.010	0.325	0.522	0.025	0.117	0.011	0.475	0.225	0.098	0.196	0.007
	2007	0.458	0.248	0.105	0.179	0.009	0.372	0.455	0.031	0.129	0.013	0.466	0.234	0.100	0.192	0.007
	2008	0.465	0.237	0.116	0.174	0.009	0.433	0.380	0.041	0.137	0.009	0.477	0.221	0.098	0.197	0.007
	2009	0.472	0.243	0.109	0.167	0.009	0.463	0.359	0.040	0.129	0.009	0.500	0.228	0.095	0.171	0.006
	2010	0.472	0.235	0.100	0.185	0.008	0.465	0.338	0.040	0.149	0.008	0.477	0.227	0.093	0.195	0.007
	2011	0.482	0.264	0.095	0.149	0.010	0.477	0.351	0.040	0.123	0.009	0.505	0.232	0.087	0.168	0.007
	2012	0.479	0.275	0.095	0.140	0.011	0.485	0.351	0.043	0.113	0.008	0.499	0.248	0.080	0.167	0.007
	2013	0.510	0.262	0.086	0.134	0.008	0.532	0.315	0.040	0.107	0.006	0.502	0.227	0.080	0.185	0.006
	2014	0.594	0.153	0.073	0.170	0.009	0.603	0.210	0.038	0.143	0.006	0.522	0.117	0.083	0.264	0.015
	2015	0.685	0.121	0.079	0.107	0.007	0.695	0.175	0.037	0.088	0.005	0.639	0.086	0.081	0.178	0.017
	2016	0.641	0.161	0.078	0.114	0.006	0.630	0.237	0.037	0.090	0.006	0.627	0.114	0.073	0.180	0.006
Male	2004	0.415	0.238	0.074	0.258	0.014	0.342	0.487	0.019	0.134	0.019	0.410	0.218	0.079	0.285	0.008
	2005	0.417	0.264	0.093	0.213	0.012	0.271	0.530	0.027	0.161	0.011	0.422	0.230	0.089	0.251	0.009
	2006	0.390	0.285	0.102	0.214	0.010	0.275	0.500	0.032	0.178	0.015	0.435	0.236	0.095	0.225	0.009
	2007	0.422	0.249	0.110	0.208	0.012	0.321	0.444	0.042	0.178	0.015	0.428	0.240	0.100	0.223	0.009
	2008	0.429	0.238	0.124	0.200	0.010	0.381	0.384	0.051	0.172	0.012	0.433	0.232	0.100	0.227	0.008
	2009	0.439	0.240	0.121	0.190	0.009	0.407	0.373	0.051	0.158	0.012	0.442	0.243	0.097	0.209	0.008
	2010	0.436	0.236	0.111	0.208	0.009	0.408	0.352	0.051	0.179	0.011	0.420	0.250	0.094	0.227	0.008
	2011	0.444	0.259	0.111	0.175	0.011	0.417	0.363	0.052	0.157	0.010	0.443	0.253	0.089	0.208	0.008
	2012	0.447	0.275	0.108	0.160	0.011	0.422	0.370	0.054	0.145	0.010	0.425	0.282	0.087	0.198	0.008
	2013	0.478	0.267	0.094	0.152	0.009	0.463	0.342	0.049	0.136	0.009	0.440	0.266	0.077	0.207	0.009
	2014	0.562	0.161	0.082	0.185	0.010	0.547	0.230	0.047	0.167	0.009	0.480	0.149	0.077	0.278	0.015
	2015	0.655	0.130	0.083	0.124	0.008	0.626	0.202	0.047	0.118	0.008	0.579	0.123	0.087	0.197	0.013
	2016	0.611	0.176	0.080	0.125	0.008	0.566	0.263	0.046	0.117	0.008	0.569	0.158	0.069	0.198	0.007

Table 3-13: Electronic Tuberculosis Register Treatment outcomes by year (2004 – 2016), sex and HIV-status expressed as rates*

		HIV-positive				HIV-negative				HIV-unknown			
Sex	**Year**	**Failed (γ)**	**Cure (κ)**	**Discontinuation (δ)**	**Death (μ)**	**Failed (γ)**	**Cure (κ)**	**Discontinuation (δ)**	**Death (μ)**	**Failed (γ)**	**Cure (κ)**	**Discontinuation (δ)**	**Death (μ)**
	2004	0.066	1.934	0.444	0.331	0.039	1.961	0.249	0.104	0.054	1.946	0.518	0.513
	2005	0.062	1.938	0.294	0.476	0.037	1.963	0.223	0.097	0.061	1.939	0.378	0.541
	2006	0.075	1.925	0.228	0.505	0.043	1.957	0.215	0.116	0.059	1.941	0.278	0.552
	2007	0.072	1.928	0.207	0.586	0.055	1.945	0.233	0.149	0.061	1.939	0.262	0.563
	2008	0.070	1.930	0.164	0.651	0.046	1.954	0.235	0.199	0.057	1.943	0.279	0.558
	2009	0.068	1.932	0.159	0.604	0.051	1.949	0.213	0.194	0.054	1.946	0.206	0.518
Female	2010	0.069	1.931	0.237	0.562	0.046	1.954	0.269	0.198	0.058	1.942	0.287	0.523
	2011	0.072	1.928	0.144	0.504	0.050	1.950	0.199	0.189	0.060	1.940	0.216	0.469
	2012	0.074	1.926	0.116	0.499	0.043	1.957	0.167	0.203	0.052	1.948	0.231	0.424
	2013	0.062	1.938	0.123	0.440	0.040	1.960	0.157	0.188	0.054	1.946	0.284	0.437
	2014	0.107	1.893	0.256	0.389	0.059	1.941	0.256	0.184	0.224	1.776	0.553	0.508
	2015	0.114	1.886	0.068	0.391	0.060	1.940	0.115	0.171	0.336	1.664	0.263	0.435
	2016	0.070	1.930	0.090	0.386	0.047	1.953	0.121	0.170	0.096	1.904	0.287	0.392
	2004	0.112	1.888	0.549	0.445	0.074	1.926	0.271	0.088	0.073	1.927	0.647	0.498
	2005	0.090	1.910	0.346	0.539	0.042	1.958	0.328	0.134	0.076	1.924	0.493	0.536
	2006	0.065	1.935	0.330	0.594	0.057	1.943	0.371	0.162	0.070	1.930	0.383	0.559
	2007	0.093	1.907	0.287	0.644	0.065	1.935	0.350	0.214	0.073	1.927	0.363	0.590
	2008	0.080	1.920	0.225	0.731	0.062	1.938	0.310	0.263	0.069	1.931	0.378	0.594
	2009	0.076	1.924	0.202	0.699	0.061	1.939	0.271	0.257	0.066	1.934	0.323	0.560
Male	2010	0.074	1.926	0.286	0.650	0.058	1.942	0.334	0.263	0.059	1.941	0.392	0.557
	2011	0.081	1.919	0.179	0.622	0.055	1.945	0.266	0.265	0.062	1.938	0.339	0.504
	2012	0.076	1.924	0.142	0.587	0.053	1.947	0.228	0.268	0.056	1.944	0.311	0.486
	2013	0.067	1.933	0.153	0.500	0.052	1.948	0.215	0.239	0.069	1.931	0.364	0.433
	2014	0.118	1.882	0.281	0.449	0.071	1.929	0.306	0.240	0.185	1.815	0.625	0.480
	2015	0.112	1.888	0.102	0.421	0.078	1.922	0.171	0.223	0.198	1.802	0.307	0.489
	2016	0.083	1.917	0.114	0.400	0.059	1.941	0.169	0.219	0.081	1.919	0.351	0.374

*Adjustment: Applied a factor of 2 to the ETR TB deaths and assume that unrecorded deaths are incorrectly classified as a loss to follow-up. We then subtracted from the proportion of those lost-to-follow-up for the fraction that gets added to deaths

3.7.1. Modelling cure and failure

To estimate cure and failure rates, we assume that the ratio of failures to cures is the same in the treatment completers with missing outcomes as in those with recorded cure or failure outcomes.

We estimate the annual rate at which treatment is completed in cured patients as:

$$\kappa = \left(\frac{c}{c+f}\right)/0.5$$

and the rate at which treatment is completed in patients who are failing as:

$$\gamma = \left(\frac{f}{c+f}\right)/0.5$$

We thus have $\kappa + \gamma = 2$, implying a treatment duration of half a year among those who complete treatment. Then we define $d = d_1 + d_2$ as the proportion of patients who have died or have discontinued their treatment. From μ, the annual mortality rate on treatment, and δ, the annual treatment discontinuation rate, we define the rate $D = \mu + \delta$. From the above, we have $d_1 + d_2 = \frac{\mu+\delta}{\mu+\delta+\kappa+\gamma}$ so $d = \frac{D}{D+2}$. D can then be expressed as $D = \frac{2d}{1-d}$. In the absence of any correction for under-ascertainment of mortality, we would have μ and δ expressed as $\mu = \frac{d_1 D}{d}$ and $\delta = \left(1 - \frac{d_1}{d}\right) D$. If we assume the true mortality rate is double the reported mortality rate, we have $\mu = \frac{2d_1 D}{d}$ and $\delta = \left(1 - \frac{2d_1}{d}\right) D$. We used the ETR data and set the cure rate at $\kappa = 1.92$, roughly the average across all years (Table 3-13) for those who complete the six months treatment course.

3.7.2. Modelling treatment discontinuation

In the model, we specify a fixed parameter for the annual rate of treatment discontinuation. Based on the ETR data, males have higher treatment discontinuation rates than females (Table 3-14). This treatment discontinuation parameter is calculated as the average discontinuation rates across years and HIV strata, and we set it at 0.309 in males and 0.237 for females. Using the ETR data, the ratio of male to female average discontinuation rate aggregated across age and HIV strata is 1.307 (= 0.309/0.237). Berry *et al.'s* study using the ETR data for Gauteng Province (Ekurhuleni Metropolitan Municipality and the City of

Johannesburg), estimated a similar relative risk of treatment discontinuation for males compared to females, 1.299 (301).

Table 3-14: Average treatment discontinuation and death rates by HIV status, based on the ETR

	HIV-positive		HIV-negative		HIV-unknown		Overall	
	discontinuation	death	discontinuation	death	discontinuation	death	discontinuation	death
Female	0.195	0.486	0.204	0.166	0.311	0.495	0.236	0.382
Male	0.246	0.560	0.276	0.218	0.406	0.512	0.309	0.430
Male: Female ratio	1.263	1.151	1.354	1.311	1.305	1.035	1.308	1.166

3.7.3. Modelling tuberculosis deaths on treatment

Based on the ETR data, we set the mortality rates on TB treatment to be at 0.192 (average for both males and females, Table 3-14), averaged across years in the HIV-negative strata. The subsequent sections describe the effects of disease severity, age, HIV and ART on TB mortality in treated individuals.

i. *Modelling the effect of changes in tuberculosis disease severity on mortality*

We allow for treated TB mortality rates to change over time, since changes in delays between disease incidence and treatment should imply changes in the average severity of treated TB cases. Due to limited empirical evidence, it is difficult to assess how smear grades have changed over time as levels of diagnosis and treatment have improved. In the model we define (as in the earlier section: 3.4.1) the average smear-positive treatment delay in year t, $S(t)$, as $U(t)/R(t)$, where $U(t)$ is the number of untreated smear-positive TB cases at the start of year t and $R(t)$ is the number of smear-positive TB patients who are treated in year t. As $S(t)$ declines towards zero, we assume a corresponding decline in mortality toward a theoretical minimum that might be expected if all smear-positive TB cases were graded scanty or 1+ at treatment initiation. To simplify, we assume that TB diagnosis and treatment levels in South Africa were low during the period before 2000 and that any improvements that occurred before 2000 were minor.

We suppose $\mu_g(t)$ represents the mortality rate in smear-positive HIV-negative treated TB patients of sex g in year t, and that $\mu_g(0)$ represents the corresponding mortality rate in the

period before 2000. We also suppose that $S(0)$ is the value of $S(t)$ in 1999, which we take to represent the period before 2000. We assume that for $t \geq 2000$,

$$\mu_g(t) = \mu_g(0)\,(1 - (1 - r_m)[1 - S(t-1)/S(0)]),$$

where r_m is the ratio of the minimum mortality (when the treatment delay is zero) to the baseline mortality (given the treatment delay in the period before 2000). Thus, $\mu_g(t)$ will be close to $\mu_g(0)$ when the average treatment delay is close to that before 2000, while $\mu_g(t)$ will be close to $\mu_g(0)\, r_m$ when the treatment delay is close to zero. We use $S(t-1)$ rather than $S(t)$ in the above equation because $S(t)$ is only calculated at the end of year *t*.

We estimated the r_m parameter using random-effects meta-analysis results based on studies that reported the relative mortality levels in patients with different smear grades (262,302–306) (Table 3-15). The resulting pooled odds ratio for smear-grade 2+ vs smear-grade <2+ was 1.30 (95% CI: 1.02-1.67) and the odds ratio for smear-grade 3+ vs smear-grade <2+ was 1.68 (262,263,302–308).

Table 3-15: Odds ratios for mortality in the 2+ and 3+ categories, relative to the <2+ category

Study	2+ versus <2+ (Odds ratio, 95% CI)	3+ versus <2+ (Odds ratio, 95% CI)
Singla *et al.* (262)	1.28 (0.52-3.17)	1.97 (0.98-4.30)
Vree *et al.* (302)	1.07 (0.58-1.89)	0.96 (0.43-1.94)
Kayigamba *et al.* (303)	2.04 (0.28-22.9)	4.35 (0.80-43.7)
Osawa *et al.* (304)	2.75 (0.97-7.61)	1.08 (0.38-2.96)
Muttath *et al.* (305)	2.33 (0.03-186.4)	9.16 (1.18-408.6)
Kolappan *et a.l* (306)	1.27 (0.94-1.73)	1.81 (1.38-2.37)
Meta-analysis	1.30 (1.02-1.67)	1.68 (1.26-2.23)

We assumed a 'baseline' smear grade distribution corresponding to that observed by Singla *et al*. in India (262). In this study, the proportions of TB patients in different smear grades were 0.27 for smear-grade <2+; 0.25 for smear-grade 2+ and 0.48 for smear-grade 3+ (262). We assume the Indian data would be most representative of what might be expected in a resource-limited setting, i.e., with limited screening. We then calculate

$$r_m = 1/(0.27 + 0.25 \times 1.30 + 0.48 \times 1.68) = 0.71,$$

based on the assumption that if there was no treatment delay, all newly treated smear-positive TB cases would have a smear grade <2+.

ii. *Modelling the effect of age on tuberculosis mortality*

Age is an independent predictor of TB mortality both in HIV-positive and HIV-negative individuals (103,104,309,310). The Cape Town-based study by Kaplan *et al*. reported that age is independently associated with TB mortality (adjusted HR 1.28, 95% CI 1.17–1.40, for every 10 year increase) (103). Pepper *et al*. reported similar relative hazards, of approximately 1.5 for every ten year increase of age (104). In most studies assessing TB mortality by age, the higher risk of death is in the 50+ years age categories (28,104,311). Based on these two studies, we specify a Gamma (196; 140) prior distribution to represent the uncertainty around α the relative rate of an increase in mortality per 10-year increase in age. The corresponding mean and standard deviations are 1.4 and 0.1, respectively. Studies assessing the effect of age on TB mortality were conducted in patients on treatment, and due to the lack of similar studies in untreated TB patients we rely on these same studies in setting assumed age effects for untreated patients.

iii. *Modelling the effect of human immunodeficiency virus and the use of antiretroviral therapy on tuberculosis mortality*

Here we describe how we incorporated the effect of HIV on both treated and untreated TB mortality rates. There are limited studies on the natural history of TB in people living with HIV and most of the studies on TB mortality rates in people living with HIV have been conducted among patients receiving TB treatment. As such, for the purpose of setting the assumptions about the effect of HIV on untreated TB mortality we rely on the literature from treated TB patients.

We first define the relative rate of TB mortality per 50 cell increase in CD4 count in HIV-positive individuals, and estimate this parameter based on the findings from Kaplan *et al.* (103). The study sought to determine changes in TB treatment outcomes among HIV-positive TB individuals; and relied on data of adult TB patients newly registered on the electronic TB register in Cape Town (2009-2013). From this analysis, an increase in 50 CD4 cells/µl was associated with a decrease in mortality risk (HR 0.87, 95% C1 0.84–0.89). A Beta (38.49; 5.75) prior was specified for the relative risk of death per 50 cell increase in CD4 count; and standard deviation of 0.05.

Secondly, we assume there is an effect of HIV viremia on TB mortality (312), which is independent of CD4 count. We estimate this effect of viremia by comparing ART patients to untreated patients, on the assumption that treated patients would mostly be virally suppressed. We define the relative rate of TB mortality if on ART, based on the average of estimates from two studies that reported the effect of ART on TB mortality, Kaplan *et al*. (RR 0.53, 95% CI 0.46–0.60) and Pepper *et al*. (RR 0.60, 95% CI 0.50– 0.70) (104,309). Both studies relied on the electronic tuberculosis treatment register data from the Western Cape, Pepper *et al.* using 2007-2009 data and Kaplan *et al.* using 2010-2011 data (104,309). Taking the average of the estimates from these studies, we specify a Beta (20.72; 16.95) prior with a mean of 0.55 and standard deviation of 0.08.

In the model, mortality for HIV-positive individuals who are not on ART is represented by

$$M(x,s) = \mu\alpha^{(x-55)/10}\gamma^{-1}\vartheta^{(s-a)/50},$$

and the mortality for those on ART is represented as by

$$M(x,s,d) = \mu\alpha^{(x-55)/10}\vartheta^{(s_d-a)/50}$$

where

x: age in years

μ: the mortality rate in HIV-negative individuals

α: increase in TB mortality per 10-year increase in age

ϑ: relative rate of TB death per 50 cell/µl CD4 increase

γ: relative rate of TB mortality for those on ART vs not on ART

a: average CD4 count in HIV-negative individuals

s: CD4 count if untreated, or baseline CD4 count if treated,

d: duration on ART

s_d: current CD4 count for those on ART, with baseline CD4 count s, at a given year of treatment duration d.

3.8. Tuberculosis recurrence

Recurrent TB is a TB episode that occurs after the previous TB episode has been considered cured. True relapse occurs when tuberculosis bacilli persist even though bacteriological tests suggested a cure at treatment completion (313). This relapse is viewed as endogenous reactivation of the previous TB strain (313). Factors that contribute to relapse include inadequate regimen and poor adherence. According to most studies, relapse is time-dependent, and the highest risk is within the first 3–6 months following successful treatment (22,206,314).

On the other hand, TB recurrence due to reinfection results from re-exposure to TB and occurs at a relatively constant risk over time (314). The risk of recurrent TB due to reinfection depends on ongoing TB transmission in the community and prevalent factors that increase the risk of fast progression to active TB disease. We note that reinfection in re-treatment individuals is usually measured as the number of new active TB disease cases rather than latent TB infection, thus reflecting fast progression in those experiencing a second (or subsequent) episode of active TB disease (206,314).

Korenromp *et al*. showed that recurrence rates decreased with an increase in follow-up time after treatment completion (314). Among HIV-positive individuals, there were 4.5 recurrences (95% CI 3.2–5.8) per 100-person years, whereas there were 1.9 recurrences (95% CI 1.2–2.7) per 100-person years among HIV-negative individuals (314). The time trend in reinfection and relapse is more apparent among those without HIV than in those with HIV (314).

3.8.1. Short-term post-treatment

As evidence suggests that after treatment, the risk of relapse is highest within the first six months following treatment completion (22,207,313,314); for the model, we set the average time spent in the first post-treatment state to be six months. That is, cured and recovered individuals will move out of the state at a rate of 1/6 per month. We then assume that relapse occurs at an annual rate of 0.1 during the short-term post-treatment state, based on previous Korenromp *et al*. study (314). Due to limited data on the effect of HIV on relapse, we assume no differences in relapse rates between HIV-positive and HIV-negative individuals.

3.8.2. Long-term post-treatment

We handle individuals in this long-term post-treatment state the same way as treatment naïve, latent TB individuals in that they are at risk of both reactivation and reinfection. However, we assume that due to prior TB episode, an individual has an elevated of TB. To allow the effect of treatment history, we apply an adjustment factor to the rate of TB incidence and estimate it through calibration. Based on epidemiological studies that have estimated the relative odds/risks of developing TB in treatment-experienced compared to treatment naïve individuals, as a start, we assume this factor is greater than 1.0 and likely to lie in the range 1.8–5.9 (315,316). This is based on two studies: firstly Marx *et al.*'s study, which reported a TB prevalence of 3.81% and 2.13% in previously treated and treatment-naïve individuals, respectively, suggesting a relative risk of 1.8 (316). Secondly, Den Boon *et al.*'s study found the prevalence of TB was 10/338 (2.96%) in people who had previously been treated, compared to 16/3145 (0.51%) that do not have the previous TB, suggesting a relative risk of 5.8 (315). We specified a Gamma (5.444; 1.556) prior distribution with a mean of 3.5 and a standard deviation of 1.5 for this effect of previous TB.

For this long-term post-treatment state, the effect of HIV on reinfection in HIV-positive individuals is modelled in the same way as it is applied on fast progression to active TB. Similarly, for reactivation, we apply the HIV effects described earlier.

3.9. Modelling the effect of isoniazid preventative therapy

To incorporate the effect of IPT in the model, we define additional variables. We let k represent the following groups: 0 = uninfected individuals, 1 = latently infected individuals with no TB history, and 2 = previously treated individuals (we do not consider individuals with active TB as IPT would not be recommended for such individuals). We also define $\lambda(t, s, d, k)$ to represent the annual rate of IPT initiation in HIV-positive individuals with CD4 count *s* and ART duration *d* (0 if ART-naïve, 1 for duration <1 year, 2 for duration >1 year), in year t. Lastly, define $R(k)$ as the relative rate of IPT initiation for individuals in TB state k relative to latently infected individuals. The model assumptions on IPT duration and the associated guidelines are shown in Table 3-16.

Table 3-16: Isoniazid Preventative Therapy eligibility, requirement, and duration

Year	Isoniazid Preventative Therapy eligibility, requirement, and duration	Model assumption	Guideline
2010 – 2012	Eligibility: all HIV-positive individuals with no signs or symptoms suggestive of active TB TST requirement: TST no longer essential prior to IPT, IPT can be started at the first visit if the patient is asymptomatic. IPT duration: 6 months of continuous treatment (can be completed over 9 months).	Duration: 6 months (0.5 years), the average IPT treatment completion rate = 1/0.5 years = 2 per year.	2010, (139)
2013 – present	Eligibility: All people living with HIV with negative symptom-based TB screening. TST requirement: Use TST if available IPT duration • TST positive: 36 months (if pre-ART (CD4>350) / on ART) • TST negative: 6 months (if pre-ART) and 12 months (if on ART) • No TST: 6 months (if pre-ART / on ART)	Duration: 36 months (3 years), then average IPT treatment completion rate = 1/3 years = 0.33 per year.	2013, (317)

3.9.1. Isoniazid preventative therapy initiation by LTBI/TST status

There are limited studies that show the rates of initiation of IPT by TST status among those eligible. Van Ginderdeuren *et al*. reported low rate of TST testing ranging between 0 – 5% at various health facilities (233). The relative rate of IPT initiation in uninfected individuals is highly uncertain. As a start, we set $R(0) = 0.5$. We set this assumption as a compromise between the highly optimistic assumption of $R(0) = 0$ (perfect screening, which accurately distinguishes between LTBI and no LTBI) and the highly pessimistic assumption of $R(0) = 1$ (no screening or TST produces high rates of false positivity due to BCG exposure). For simplicity, we assume rates of IPT initiation are the same in individuals who have never been treated for TB and those who have previously been treated (i.e., $R(1) = R(2) = 1$). We also assume that there is no IPT initiation in individuals on TB treatment and individuals with active TB.

3.9.2. Isoniazid preventative therapy initiation by CD4 count

The second parameter we define is $H(s)$, the relative rate of IPT initiation in CD4 category *s*, relative to that at CD4 counts <200 cells/μl. A study conducted in Gauteng found that rates of IPT initiation at CD4 counts ≥500 cells/μl were significantly lower than those at CD4 counts <500 cells (adjusted OR 0.46, 95% CI: 0.24–0.82) (233). Therefore, to be consistent with this study and the Thembisa HIV model assumptions on relative rates of ART initiation in different CD4 categories (244), we set the relative rates of IPT initiation to be 0.4 at CD4 counts ≥500, 0.5 at CD4 counts 350–499 and 0.7 at CD4 counts 200–349 (in all cases, relative to CD4 <200 cells/μl).

3.9.3. Isoniazid preventative therapy initiation by ART status

The third parameter that we define is $P(d)$, the relative rate of IPT initiation at ART duration *d* when compared to ART-naïve individuals (by definition, $P(0) = 1$). The Gauteng study cited previously found that individuals on ART had a higher rate of IPT initiation (OR 2.03, 95% CI: 0.88–5.87) and that approximately half of all IPT initiations after ART initiation occurred in the first year of ART (the median time between ART initiation and IPT initiation was 374 days) (233). The Thembisa model for Gauteng estimates that over the 2015-16 period (the period when the study was conducted), approximately 14% of adult ART patients had started ART in the last year. The finding that 50% of IPT in ART patients was initiated in the first year of ART thus implies that $0.5 = 0.14 \times \mathrm{P}(1) \,/\, [0.14 \times \mathrm{P}(1) + 0.86 \times \mathrm{P}(2)]$. Solving this equation, we get a $\mathrm{P}(1)/\mathrm{P}(2)$ ratio of 0.16. The finding of an OR of 2.03, in turn, implies that $2.03 \approx 0.14 \times \mathrm{P}(1) + 0.86 \times \mathrm{P}(2)$. Substituting the $P(2)/P(1)$ ratio into this equation, we get $P(1) = 7.3$ and $P(2) = 1.2$.

Having defined the intermediate variables, we calculate

$$\lambda(t, s, d, k) \;=\; \lambda(t)\, H(s)\, P(d)\, R(k),$$

where $\lambda(t)$ is the rate of IPT initiation in year *t* in the 'base' category (i.e. ART-naïve, HIV diagnosed adults with latent TB infection). We estimate this base rate from the reported numbers of IPT initiations in year *t*, $T(t)$. If $N(t, s, d, k)$ is the model estimates of the number of HIV-diagnosed adults at the start of year *t*, in CD4 category *s*, with ART duration *d*, in TB

state k (excluding individuals with active TB and treated for TB, and excluding individuals who are already on IPT), then

$$T(t) = \lambda(t) \sum_{s} \sum_{d} \sum_{k} N(t,s,d,k) H(s) P(d) R(k)$$

$\lambda(t)$ is solved for, by rearranging the terms in this equation above. $T(t)$ values are taken from the District Health Information System (DHIS) (Table 3-17). Due to the frequent changes in guidelines and barriers to implementation of IPT policies at health care facilities, data on IPT uptake has been limited, and the quality may be affected as well, particularly in the earlier years (before 2010). A significant shift in the guidelines was made in 2010 where the strict requirement for a positive TST to be eligible to initiate IPT was removed (318). We assume zero IPT uptake before 2010, as the DHIS data suggest minimal IPT before 2010; these data were available until 2016-17. For years 2017 and beyond, IPT uptake in the baseline category ($\lambda(t)$) was linearly interpolated between the 2016-17 rate and a rate of 1.2% in 2021.

Table 3-17: Number of HIV-positive new eligible individuals initiated on isoniazid preventative therapy

Year	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17
Number of patients initiating IPT	244888	379063	385338	427336	422541	385007	396915

Source: District Health Information System

3.9.4. Isoniazid preventative therapy completion/drop-out

Based on the Southern African studies assessing completion over six months of treatment and the reported completion proportions, IPT drop-out ranged between 6% - 37% (319–323). By taking the median of the five studies, 13.2%, the drop-out rate over six months is roughly ~0.024 per month. The recommendations for IPT eligibility have changed over time. For the years between 2010 and 2012, we assume six months; from 2013, we assume 36 months. Using the 0.024 dropout rate per month, the average net time on IPT is then 5.2 months = (1/(0.024 + 1/6)) in the period up to 2012. Similarly, after 2012 we assume the average time on IPT is 19.3 months (1/(0.024 + 1/36)).

3.9.5. Effectiveness of isoniazid preventative therapy

We base the effectiveness of IPT at 52%, based on the estimated RR of 0.48 (95% CI 0.29–0.82) among LTBI individuals (those with a positive TST) in the meta-analysis by Ayele *et al.* (324). However, among individuals with no LTBI (negative TST), the effect of IPT was inconclusive (RR 0.79, 95% CI 0.58–1.08) (324); as such, we assume 0% effectiveness for this group. In addition, we assume that when an individual stops taking IPT, there will be no effect of IPT, as shown by Churchyard *et al.* (231). In the model, the protective effect of IPT is implemented such that it reduces the risk of progressing to TB disease (this includes reactivation rate and the rate of fast progression due to reinfection) in individuals with latent TB infection and in people with a history of TB disease treatment by 52% (324). The protection is assumed to cease when an individual stops treatment or after completion.

3.10. Modelling the effect of tuberculosis risk factors on tuberculosis incidence

To explore factors that could be important in explaining age and sex differences in TB incidence, we considered the following risk factors: poorly controlled diabetes, undernutrition/underweight, tobacco smoking and alcohol abuse. These risk factors are selected based on their established effect of increasing the risk of developing TB disease and their relatively high prevalence in the South African population (Table 3-18). In computing the cumulative effect of these risk factors, we assume the effects are independent and multiplicative.

Table 3-18: Age- and sex-specific prevalence (%) of risk factors: HbA1c > 6.5%, underweight, alcohol abuse and tobacco smoking

	HbA1c > 6.5%		Underweight (BMI < 18.5 kg/m²)		Alcohol abuse		Current smoking	
Age	Males	Females	Males	Females	Males	Females	Males	Females
15-24	2.0	0.9	22.05	9.7	20.7	5.1	29.5	4.95
25-34	3.4	4.5	6.4	3.3	36.1	6.1	43.50	7.80
35-44	6.6	11.8	11.4	2.8	31.8	6.0	43.90	7.00
45-54	11.7	20.8	8.2	2.1	27.8	4.4	45.00	11.0
55-64	23.0	28.7	12.4	2.9	25.7	3.7	37.80	11.3
65-90	21.1	30.1	6.0	3.7	20.9	2.0	24.90	7.80

BMI=body mass index. HbA1c= Glycated hemoglobin. Data sources. For underweight (BMI < 18.5) SANHANES-1 survey (112); For HbA1c > 6.5%, alcohol abuse, and current smoking: 2016 SADHS (89).

3.10.1. Poorly controlled diabetes (HbA1c > 6.5%)

Individuals with diabetes have a 3.59-fold increased risk of TB disease compared to those without diabetes, as estimated by Al-Rifai *et al*. in a meta-analysis and systematic review (325). This estimate is based on studies which defined uncontrolled diabetes as HbA1c > 6.5% or HbA1c > 7.0% or Fasting Blood Glucose > 120 mg/dl. We use the 2016 SADHS data for HbA1c > 6.5% prevalence to be relatively consistent with these definitions (89). In the model, we defined the effect of diabetes as an increase in TB incidence due to having diabetes (HbA1c > 6.5%), set at $\theta_{i=1}$= 2.59 for (risk factor $i = 1$). We specified a Gamma (9.74; 3.76) prior distribution for the uncertainty around the parameter, with a mean of 2.59 and a standard deviation of 0.83. Given the age- (x) and sex- (g) specific prevalence (p_{1gx}) of poorly controlled diabetes, the multiplicative increase in TB incidence due to diabetes in individuals of age x and sex g (relative to a hypothetical population in which there is no diabetes) is calculated as:

$$RR_{1gx} = 1.0 + p_{1gx}\theta_1 .$$

3.10.2. Underweight (BMI <18.5 kg/m²)

The meta-analysis of Lönnroth *et al*. (73) suggests that TB incidence declines steadily as BMI increases. We set the effect of low BMI on the risk of developing TB disease based on Leung *et al.*, which was a cohort study of 42 116 individuals who were 65 years or older enrolled in health centres across Hong Kong, China (326). The relative risk for culture-confirmed TB was 2.21 when not excluding other potential TB risk factors (this is likely to be an upper bound on the true effect of low BMI, due to confounding with smoking and other factors); and 1.39 when excluding TB risk factors (probably a lower bound because baseline is defined as normal BMI, not all BMI >18.5 kg/m²); 1.8 is the midpoint between these two (105). Although this study may have been conducted in a relatively older population, they adjusted for most confounders, including smoking, alcohol, diabetes, sex and age (unlike the Lönnroth *et al.* meta-analysis).

Based on Leung *et al.* we specify the prior distribution for the increase in TB risk due to low BMI parameter (θ_2) to be a Gamma (10.24;12.8) distribution with a mean of 0.8 and standard deviation of 0.25 (326). The age- (x) and sex- (g) specific prevalence (p_{2gx}) for underweight

is based on the SANHANES-1 survey (Table 3-18) (112). In the model, the age- and sex-specific multiplicative increase in TB incidence due to underweight is calculated as

$$RR_{2gx} = 1.0 + p_{2gx}\theta_2.$$

3.10.3. Tobacco smoking

Given that the effect of tobacco smoking on the risk of developing active TB depends on current exposure and duration of smoking, we incorporate both effects (current exposure and duration) in the model. The effects were estimated from a case-control study in India (327). In the study, men aged 20-50 years with TB were randomly matched by age with non-TB controls. The estimated odds ratios of active TB for smokers with <10 years, 11–20 years, and >20 years of smoking were 1.72, 2.45, and 3.23, respectively, compared to non-smokers (327).

Using this study by Kolappan and Gopi, we estimate the effect of current exposure to smoking (risk factor $i = 3$) is a 1.47-fold increase in TB risk, and the TB risk increases by a factor of 1.38 per ten years of smoking. In the model, we set the prior distribution for the increase in TB risk if currently smoking to be a Gamma (1.45;3.09) distribution with a mean of $\theta_{3,1}$= 0.47 and standard deviation of 0.39; and the increase in TB risk per 10-year increase in the duration of smoking to follow a Gamma (10.03;26.39) distribution with a mean of $\theta_{3,2}$ = 0.38 and standard deviation 0.12. The multiplicative increase in TB incidence due to smoking is calculated as follows:

$$RR_{3gx} = \left(1.0 + \theta_{3,1}p_{3gx}\right)\left(1 + \theta_{3,2}\right)^{smd(g,x)/10}$$

p_{3gx} is represents the current smoking prevalence and $smd(g,x)$ is the average smoking duration calculated for each sex (g) and age (x). We used the age-specific prevalence of current smoking to generate the distribution of duration of smoking. We assumed there is no smoking before the age of 15 years. The $smd(g,x)$ was calculated as follows:

- First, note that current smoking prevalence (p_{3gx}) is given in age categories as obtained from the SADHS (Table 3-18) (89).
- We assume that the prevalence of current smoking represents the prevalence at the median age of each category.

- e.g., for females aged 20-24 years, the prevalence of 5.8% represents current smoking for females aged 22 years.

- Then we linearly interpolated between the mid-points in each age category to get prevalence estimates for the other ages.

- The overall average smoking duration at each subsequent age is calculated as the cumulative smoking prevalence for all previous years to the age 15, e.g.

$$smd(1,23) = \sum_{x=15}^{22} p_{3,1,x}$$

3.10.4. Alcohol abuse

The estimated relative effect of alcohol abuse on developing TB disease is almost 3-fold (relative risk 2.94, 95% CI: 1.89–4.59) (69). In this meta-analysis, alcohol abuse was defined as consuming 40g or more, of alcohol per day, or as a clinical diagnosis of an alcohol use disorder (69). The prevalence of alcohol abuse (or risky alcohol consumption), based on the 2016 South African DHS, was estimated at 28% males and 5% females reported risky drinking habits (Table 3-18) (89). In the survey, risky drinking habits was defined as drinking least 5 drinks on one occasion in past 30 days (68).

We note that we are using different definitions of alcohol abuse from the meta-analysis for the effect of alcohol on developing TB disease (69) and for the prevalence of alcohol abuse from the survey (328). However, there is possibly some overlap between these definitions as it is suggested that one standard drink contains between 5-14g of pure alcohol (328), therefore, roughly, 5 drinks on one occasion contain between 25-70g of pure alcohol. These definitions both the meta-analysis and surveys do not specify the frequency of drinking occasions over a given period. For instance, it was not specified whether individuals were drinking at least 40g per day, on every day of the month/year or how often. Altogether these highlight the is uncertainty around the effect of alcohol.

To represent the uncertainty around the effect of heavy alcohol consumption on TB incidence, we specify a Gamma (8.91; 4.59) prior distribution with a mean of $\theta_4 = 1.94$ and a standard deviation of 0.65 (69). This prior distribution is based on the estimated 95% confidence interval Lonroth *et al*.'s review (69). In addition, we assume the age- (x) and sex-

(g) specific prevalence (p_{4gx}) of alcohol abuse (binge drinking) as presented in the SADHS Table 3-18 (89). The age- and sex-specific multiplicative increase in TB incidence due to alcohol abuse is calculated as:

$$RR_{4gx} = 1.0 + p_{4gx}\theta_4$$

3.10.5. Combined effect of TB risk factors

The overall adjustment in the model (relative to a hypothetical population in which there are no TB risk factors) is computed as the cumulative multiplicative effect of the risk factors ($i = 1, \ldots, 4$) described above (RR_{igx}):

$$F_{gx} = \prod_{i=1}^{4} RR_{igx}$$

F_{gx} represents the relative risk of TB in people of sex g and age x due to diabetes, underweight, smoking, and alcohol abuse compared to individuals of the same age and sex with none of these risk factors. These F_{gx} are applied to the rate of progression from infection to active TB disease in the model. Table 3-19 shows examples of F_{gx} factors for select ages 15 to 40 years, calculated from the means of the prior distributions specified previously.

Table 3-19: Cumulative age- and sex- effect of selected tuberculosis risk factors HbA1c > 6.5%, underweight, smoking and alcohol abuse

	HbA1c > 6.5 ($\theta_1 = 2.59$)		Underweight (BMI < 18.5) ($\theta_2 = 0.8$)		Current smoking ($\theta_{3,1} = 0.47$ $\theta_{3,2} = 0.38$)		Alcohol abuse ($\theta_4 = 1.94$)		Overall	
Age	**Male**	**Females**	**Male**	**Females**	**Male**	**Females**	**Male**	**Females**	**Male**	**Females**
15	1.052	1.023	1.479	1.281	1.031	1.007	1.229	1.031	1.970	1.361
16	1.052	1.023	1.479	1.281	1.063	1.014	1.229	1.031	2.032	1.371
17	1.052	1.023	1.479	1.281	1.098	1.022	1.229	1.031	2.100	1.382
18	1.052	1.023	1.327	1.073	1.128	1.025	1.229	1.031	1.935	1.161
19	1.052	1.023	1.327	1.073	1.160	1.028	1.229	1.031	1.989	1.164
20	1.052	1.023	1.327	1.073	1.193	1.032	1.592	1.167	2.652	1.322
21	1.052	1.023	1.327	1.073	1.230	1.035	1.592	1.167	2.732	1.326
22	1.052	1.023	1.327	1.073	1.268	1.039	1.592	1.167	2.818	1.331
23	1.052	1.023	1.327	1.073	1.287	1.042	1.592	1.167	2.860	1.335
24	1.052	1.023	1.327	1.073	1.306	1.045	1.592	1.167	2.902	1.339
25	1.088	1.117	1.117	1.060	1.326	1.048	1.700	1.118	2.740	1.388
26	1.088	1.117	1.117	1.060	1.346	1.052	1.700	1.118	2.781	1.393
27	1.088	1.117	1.117	1.060	1.366	1.056	1.700	1.118	2.823	1.398
28	1.088	1.117	1.117	1.060	1.387	1.059	1.700	1.118	2.866	1.402
29	1.088	1.117	1.117	1.060	1.408	1.063	1.700	1.118	2.910	1.407
30	1.088	1.117	1.117	1.060	1.430	1.067	1.700	1.118	2.955	1.413
31	1.088	1.117	1.117	1.060	1.450	1.069	1.700	1.118	2.997	1.416
32	1.088	1.117	1.117	1.060	1.471	1.071	1.700	1.118	3.040	1.419
33	1.088	1.117	1.117	1.060	1.492	1.074	1.700	1.118	3.084	1.421
34	1.088	1.117	1.117	1.060	1.514	1.076	1.700	1.118	3.128	1.424
35	1.171	1.306	1.208	1.051	1.535	1.078	1.617	1.116	3.247	1.652
36	1.171	1.306	1.208	1.051	1.557	1.080	1.617	1.116	3.294	1.655
37	1.171	1.306	1.208	1.051	1.580	1.082	1.617	1.116	3.341	1.658
38	1.171	1.306	1.208	1.051	1.602	1.084	1.617	1.116	3.666	1.661
39	1.171	1.306	1.208	1.051	1.625	1.086	1.617	1.116	3.719	1.665
40	1.171	1.306	1.208	1.051	1.649	1.089	1.617	1.116	3.772	1.668

BMI=body mass index. HbA1c= Glycated hemoglobin.

3.11. Calibration data sources and defining likelihoods

We used a Bayesian approach to calibrate the model and estimate various parameters. Because our model is slow to run, and because the Bayesian calibration process is particularly slow to converge when there are many parameters being included in the uncertainty analysis, we proceed through a series of three calibration steps. Each step allowing for uncertainty in a different subset of the model parameters, and in each step fixing the parameters that are not included in the uncertainty analysis at the posterior means identified in previous calibration steps. The likelihood functions were kept the same in all three steps. In the first step (Chapter 3) we considered mainly the TB transmission and natural history parameters. In the second step (Chapter 4) we considered the parameters that determine the impact of TB interventions. In the third (Chapter 5) and final step we considered the parameters that are important in explaining the age and sex differences in TB incidence. The prior distributions, means and standard deviations have been specified previously but are summarized in Table 3-20, together with an indication of which parameters are varied in each of the three calibration steps.

Table 3-20: Summary of model parameters with prior means and standard deviations, posterior means and 95% confidence intervals from the previous calibration analysis, and summary of those varied in this present analysis

Parameter description	Mean	Standard deviation	Uncertainty analysis		
			step 1 / chapter 3	step 2 / chapter 4	step 3 / chapter 5
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.0025	0.0025	✓	✓	✓
The annual rate of reactivation in HIV-negative individuals	0.0024	0.0012	✓		
Relative rate of TB incidence per 100 cell increase in CD4	0.71	0.085	✓		✓
Annual recovery rate in smear-positive TB, HIV-negative individuals	0.09	0.02	✓		
Annual recovery rate in smear-negative TB, HIV-negative individuals	0.24	0.05	✓		
Relative infectivity of smear-negative TB compared to smear-positive individuals	0.22	0.03	✓		
Increase in TB risk if previously experienced TB	3.499	1.5	✓		
Smear-negative TB mortality (untreated)	0.061	0.012	✓		
Smear-positive TB mortality (untreated)	0.212	0.042	✓		
The relative rate of TB mortality per 50 cell increase in CD4 count if HIV+	0.87	0.05	✓		✓
Proportion of cough >2 weeks in individuals with smear-negative TB	0.2	0.1	✓		
The proportion of incident TB cases in HIV-negative adults that are smear-positive	0.52	0.1	✓		
Relative ratio of symptoms in patients with smear-positive TB, compared to smear-negative TB	2.2	0.5	✓		
Relative rate of TB incidence for those on ART (controlling for CD4)	0.81	0.05		✓	✓
Relative rate of TB mortality if on ART	0.55	0.08		✓	✓

Parameter description	Mean	Standard deviation	Uncertainty analysis		
			step 1 / chapter 3	step 2 / chapter 4	step 3 / chapter 5
The annual rate of health-seeking in males with smear-negative TB	2.14	0.49		✓	✓
The annual rate of health-seeking in males in the general population	1.15	0.5		✓	
The annual rate of health-seeking in males due to TB-like symptoms	0.22	0.15		✓	
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.125	0.144		✓	
The proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test	0.33	0.236		✓	
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.5	0.289		✓	
Relative rate empirical treatment if symptoms are not due to TB	0.5	0.289		✓	
Relative rate of health-seeking in women, compared to men	1.55	0.17		✓	✓
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	3	1		✓	
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: initial	8.71	2.5		✓	
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: ultimate	4	1.2		✓	
Increase in TB mortality rate per 10-year increase in age	1.4	0.1			✓
Increase in TB incidence due to alcohol misuse	1.94	0.65			✓
Increase in TB incidence due to diabetes (HbA1c > 6.5%)	2.59	0.83			✓
Increase in TB risk if currently smoking	0.47	0.39			✓
Increase in TB risk per 10-year increase in duration of smoking	0.38	0.12			✓
Increase in TB risk due to low BMI	0.8	0.25			✓

ART=antiretroviral therapy; BMI=body mass index. TB=tuberculosis. Ticks indicate the parameters which were varied in the respective steps.

In this section we describe the likelihood functions to represent the goodness of fit to the calibration targets. The model calibration targets included the numbers of recorded TB deaths; numbers of TB cases initiated on TB treatment; the proportion of cases in the electronic TB register that are HIV-positive; the proportion patients dying during TB treatment recorded in the electronic TB register; the number of laboratory tuberculosis tests (24) and the prevalence of TB (17).

3.11.1. The likelihood for recorded number of tuberculosis deaths

i. Cleaning the mortality data

To get the number of recorded deaths on the South African vital register, we considered deaths where TB is the underlying cause of death. These TB deaths are broadly classified using the codes A15-19. We also included deaths for which HIV was recorded as the broad

underlying cause of death (codes B20-B24), and TB is listed as a contributing cause of death (i.e., HIV underlying cause AND TB is either first, second, third, or fourth contributing cause of death). For TB deaths with unknown/unspecified age and sex, we adjusted by proportionally distributing the unknown age and sex deaths to the age and sex categories in which TB deaths were recorded most frequently.

We also adjusted for 1) incomplete reporting of deaths (the deaths that do not get documented) and 2) ill-defined causes of deaths. To adjust for the incompleteness of reported deaths, we applied age-specific completeness proportions previously computed by Johnson *et al.*, which change over time (244). ICD codes R00-R99 represents missing and garbage codes. For each sex and 5-year age group, the total adjusted number of TB deaths was computed using the following expression:

$$\frac{T + H}{\left(1 - \frac{M}{N}\right) C}$$

where T is the number of deaths for which TB (A15-19) is the recorded underlying cause of death. H is the total number of deaths for which HIV (B20-B24) is recorded as the underlying cause of death and TB is recorded as a contributing cause of death (i.e. TB (A15-19) is Cause A or Cause B or Cause C or Cause D). N represents all the deaths recorded in the vital register. M represents the missing and garbage code. C represents completeness, which is the proportion of deaths that get recorded. This completeness ratio was computed as a ratio of the recorded SA deaths (N) and the total number of deaths produced by the Thembisa 4.1 model (O) (Table 3-21) (244). These adjustments are shown in Table 3-21, and the last column (Y) represents the total adjusted deaths.

Figure 3-5: Flow for cleaning mortality data from the vital register

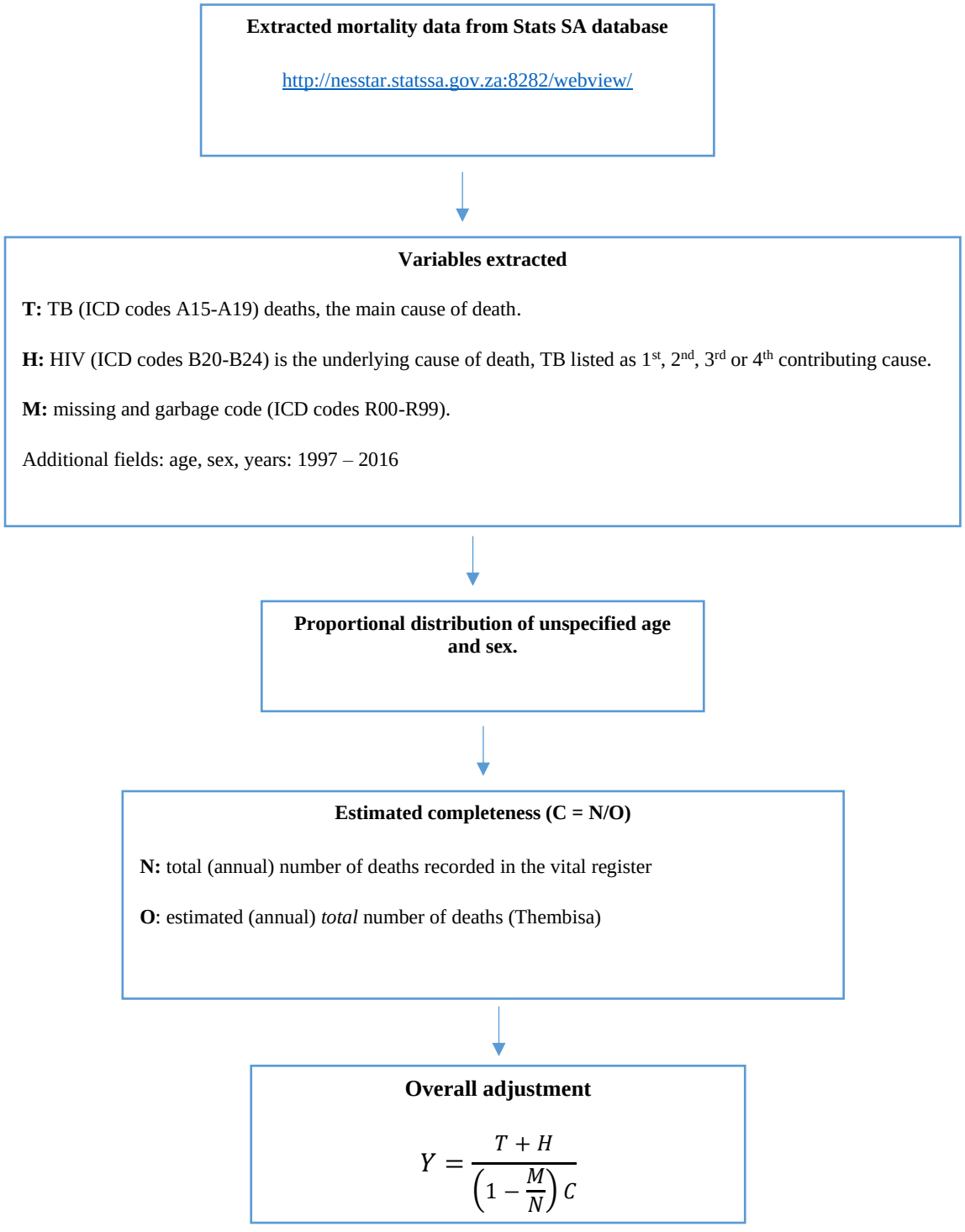


Table 3-21: Number of tuberculosis deaths and adjusting for completeness of deaths recorded in the South African vital register

Death year	TB Underlying cause of death (T)	HIV is the underlying cause, and TB contributing (H)	Missing/garbage code (R00-R99) (M)	Total recorded deaths (N)	Thembisa Total deaths output (O)	Completeness: % total deaths that get recorded (C)	Overall adjusted TB deaths (Y)
1997	22152	1801	42399	323854	369395	0.88	31437
1998	28656	2164	51165	374351	408861	0.95	38990
1999	34377	2858	47436	394656	423352	0.93	45399
2000	42581	2945	52334	429825	456393	0.94	55042
2001	51444	2605	58221	470502	493844	0.95	64742
2002	60715	3168	63448	516700	528490	0.98	74487
2003	68251	3301	70762	573139	570371	1.00	81236
2004	71034	3985	71547	594299	616324	0.96	88447
2005	74767	4731	75078	613506	652376	0.94	96322
2006	77775	5240	83818	628632	658129	0.96	100281
2007	77292	4974	84855	620595	652047	0.95	100126
2008	75542	5765	82084	613239	635166	0.97	97229
2009	70226	7222	80675	598291	616844	0.97	92295
2010	63668	7633	74955	566712	595311	0.95	86316
2011	55489	7153	70690	531840	567092	0.94	77033
2012	48825	8290	67285	509994	536539	0.95	69220
2013	42041	10075	60746	492261	525201	0.94	63431
2014	39695	9083	59117	492048	520086	0.95	58598
2015	34042	7165	58289	487607	517478	0.94	49669
2016	29513	6576	60335	468573	514123	0.91	45450

C = N/O; Y= (T + H)/((1 – M/N)C).

ii. The likelihood for recorded number of tuberculosis death

We consider adult deaths at ages 15 years and older, disaggregated by sex. We assume the number of recorded TB deaths follows a Log-Normal distribution and specify the likelihood of observing the recorded number of deaths if the model represents the expected number of deaths. We assume the log-normal distribution as it is appropriate in modelling non-negative values, and the data may have large variance due to both random and systematic biases in the data reporting/handling.

We let $D_{g,t}$ represent the number of recorded deaths from the vital register (after adjustment, as described in the previous section), in individuals of sex g, each year t. Let $\mathrm{M}_{g,t}(\phi)$ represent the model estimates for the numbers of deaths for individuals with sex g per year t. We let $\boldsymbol{\phi}$ represent the set of input parameter values.

A review and meta-analysis assessing causes of deaths using autopsies, reported that TB accounted for 37.2% (95% CI 25.7–48.7%) of HIV-related deaths and that 45.8% (95% CI 32.6–59.1%) of TB remains undiagnosed at the time of death. Among African studies, the pooled estimate was 43.2% (95% CI 38.0–48.3) (329). In the model we introduced the parameter γ (a ratio of model the estimated ('true') TB deaths to the number of recorded deaths classified as TB) to correct for potential bias in the recorded TB death data. By this, we are assuming that the bias is relatively stable over time, and similar for males and females.

We estimated γ as

$$\gamma = \frac{\sum_g \sum_t \mathrm{M}_{g,t}}{\sum_g \sum_t \mathrm{D}_{g,t}}$$

Then we specify the likelihood function for TB deaths as

$$L(\boldsymbol{D}|\phi) = \prod_g \prod_{t=1997}^{2016} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(- \frac{\left[\ln\left(D_{g,t}\gamma\right) - \ln\left(\mathrm{M}_{g,t}(\phi)\right)\right]^2}{2\sigma^2} \right)$$

And the variance (σ^2) was set at 0.01.

3.11.2. The likelihood for expected tuberculosis deaths in people living with HIV

i. *Estimating the number of HIV deaths that are due to tuberculosis*

In the model, we approximate the expected number of HIV deaths due to TB using the proportion of 0.43 estimated by the Gupta *et al.* meta-analysis for African settings (329) (described in the previous section 11.1). Then, the proportion 0.43 is applied to the total AIDS deaths produced by the Thembisa 4.4 model (248). (The Thembisa model has been calibrated to all-cause mortality data, stratified by age and sex, and has been validated against estimates of AIDS deaths from the National Burden of Disease study (330), and these estimates of total AIDS deaths are produced independently of the TB model.) These expected numbers are shown in Table 3-22.

ii. *Definition of the likelihood for expected tuberculosis deaths in people living with HIV*

Let D_t represent the number of TB deaths in adults living with HIV, in year t. These D_t are not pure data obtained from a specific source; we approximated them by applying the 0.43

proportion of expected TB deaths in HIV individuals estimated by the Gupta *et al.* meta-analysis (329) to the total AIDS deaths produced by the Thembisa 4.4 model (Table 3-22). We consider only deaths over the 1997-2010 period, (a) because Thembisa is not calibrated to vital registration data before 1997, and (b) because the meta-analysis of African studies only covers data collected up to 2010 and it is possible that the proportion of deaths in PLHIV that are due to TB might be different in the post-2010 period because of greater ART uptake.

Then let $\mathrm{E}_t(\phi)$ be model estimate of the number of TB deaths in adults who are HIV positive, where ϕ represents the set of model input parameters. Then we specify a Log-Normal likelihood function as follows

$$L(\boldsymbol{D}|\phi) = \prod_{t=1997}^{2010} \frac{1}{\sqrt{2\pi\sigma_t^2}} \exp\left(-\frac{[\ln(D_t) - \ln(\mathrm{E}_t(\phi))\,)]^2}{2\sigma_t^2}\right)$$

The variance (σ_t^2) was estimated[2] from the confidence intervals of AIDS deaths estimated in Thembisa 4.4 (248) and from the confidence intervals for the proportion of expected TB deaths in HIV individuals (0.43 (95% CI: 0.38 – 0.48)) (329), all converted to the log scale.

[2] standard error = ((upper limit–lower limit) / 3.92)

Table 3-22: Expected number of tuberculosis deaths in people living with HIV

Year	Thembisa 4.4 AIDS deaths	TB deaths in HIV-positive ($\boldsymbol{D_t}$)	Standard errors*
1997	52 149	22424	0.1733
1998	71 563	30772	0.1725
1999	94 202	40507	0.1714
2000	119 458	51367	0.1710
2001	143 624	61758	0.1704
2002	168 832	72598	0.1701
2003	193 813	83339	0.1698
2004	220 214	94692	0.1696
2005	228 122	98092	0.1697
2006	215 892	92833	0.1705
2007	192 528	82787	0.1718
2008	172 663	74245	0.1719
2009	157 785	67847	0.1711
2010	142 992	61487	0.1706

*On log scale, estimated from the upper and lower limits of the proportion of expected TB deaths (Gupta estimate) and Thembisa AIDS deaths.

3.11.3. The likelihood for recorded number of tuberculosis cases initiated on treatment

We use the number of notified TB deaths from the ETR, accessed through and cleaned by the Desmond Tutu TB/HIV Centre (Table 3-23) (28). The database relies on data from TB Blue cards - the primary medical record for people who have been diagnosed with TB and have initiated treatment (331). This information gets transcribed into the TB register, and is then fed into the sub-district, district, provincial and national TB registers. Some of the challenges of the ETR include the under-reporting of TB cases, duplicates of patient data, and losses to follow-up due to deaths or transfers of patients to other facilities (331).

Table 3-23: Number of tuberculosis cases initiated on treatment by year, sex and HIV status

Year	Sex	HIV-positive	HIV-negative	Total
2004	Female	91 112	31 645	280 611
	Male	99 295	58 559	
2005	Female	93 769	43 727	308 483
	Male	90 448	80 539	
2006	Female	97 209	52 545	328 756
	Male	94 345	84 657	
2007	Female	114 842	46 414	350 339
	Male	114 409	74 674	
2008	Female	134 549	49 640	392 695
	Male	130 061	78 445	
2009	Female	142 000	51 989	414 277
	Male	137 783	82 505	
2010	Female	139 652	51 977	408 213
	Male	135 793	80 791	
2011	Female	131 416	54 730	400 317
	Male	129 912	84 259	
2012	Female	115 005	51 266	366 730
	Male	119 516	80 943	
2013	Female	102 440	51 371	348 674
	Male	112 391	82 472	
2014	Female	93 737	48 878	332 352
	Male	108 452	81 285	
2015	Female	81 389	44 769	299 883
	Male	97 592	76 133	
2016	Female	70 298	38 361	265 917
	Male	88 696	68 562	

i. *Likelihood for tuberculosis cases recorded on the electronic tuberculosis treatment register*

We assume that the number of TB cases initiated on treatment follows a Log-Normal distribution. The analysis is restricted to the years 2004 to 2016 as we were granted access to the cleaned dataset (2004–2016). In recent years, the National Department of Health of South Africa has made a shift from using the ETR system to the district health information system (DHIS) (332). We calibrated only to sex-stratified data; although the data includes age, we did not calibrate to age-stratified recorded TB cases.

We let $E_{g,t}$ represent the number of people initiated on TB treatment as recorded in the ETR, for individuals of sex g, and each year t (Table 3-23). These ETR data are subject to biases. For instance, there may be under-reporting because in most cases the ETR does not include TB cases in tertiary care, and, the ETR only includes drug-sensitive TB (331,333). Also, the ETR does not include TB cases treated in the private sector; it is estimated that approximately 8% of symptomatic TB cases who seek treatment, seek in the private sector (17). We therefore apply an adjustment factor (γ) defined as the ratio of the true number of TB cases receiving treatment to the number of TB cases recorded in the ETR. We let $\mathrm{D}_{g,t}(\phi)$ represent the model estimate for the numbers of people initiated on TB treatment for individuals with sex g, in year t; where $\boldsymbol{\phi}$ represents the set of input parameters values. We then estimated γ as follows

$$\gamma = \frac{\sum_g \sum_t D_{g,t}}{\sum_g \sum_t E_{g,t}}$$

We restricted the factor γ to range between 1.0 and 1.3 based on the studies which have attempted to estimate the ETR data bias (331,334). From the model, we estimated γ to be 1.08 (95% CI 1.01 – 1.18).

Then the likelihood function is given by

$$L(\boldsymbol{E}|\phi) = \prod_g \prod_{t=2004}^{2016} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(- \frac{\left[\ln\left(E_{g,t}\gamma\right) - \ln\left(\mathrm{D}_{g,t}(\phi)\right)\right]^2}{2\sigma^2} \right)$$

and the variance (σ^2) is set at 0.01.

3.11.4. The likelihood for tuberculosis deaths in the electronic tuberculosis treatment register

We rely on the ETR to calibrate the model to the proportion of TB deaths while on treatment. We let $R_{g,t}$ represent the proportion of TB deaths recorded in the ETR, for individuals of sex g in year t (obtained from the outcomes data, deaths on treatment, Table 3-12). We define exp(γ) as the ratio of the *true* odds of death to the odds of a death recorded on ETR of deaths in TB patients get recorded on the treatment register (allowing for the possibility that the recorded number of deaths is less than the true number of deaths). The model produces

estimates of the proportion of deaths in TB patients on treatment of sex g in year t, $D_{g,t}(\phi)$, where ϕ is the set of input parameters. Then γ is estimated as:

$$\gamma = \frac{1}{13 \times 2} \sum_{t=2004}^{2016} \sum_{g=0}^{1} \text{logit}\left(D_{g,t}\right) - \text{logit}\left(R_{g,t}\right)$$

We set a lower limit of zero (i.e., assuming deaths are not over-reported).

Then, we also apply a logit transformation to the proportions ($D_{g,t}$ and $R_{g,t}$) and specify the likelihood as follows:

$$L(\boldsymbol{R}|\phi) = \prod_{g} \prod_{t} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(\frac{\left[\text{logit}\left(R_{g,t}\right) - \text{logit}\left(D_{g,t}(\phi)\right) - \gamma\right]^2}{2\sigma^2} \right)$$

σ^2 is assumed to be at 0.01.

3.11.5. The likelihood for HIV prevalence in the electronic tuberculosis register

We let $\mathrm{M}_t(\phi)$ be the estimated prevalence of HIV in people who are on TB treatment in the model, where $\boldsymbol{\phi}$ represents the set of model input parameters values; and H_t represent the prevalence of HIV in people recorded on the treatment register (based on the ETR data, Table 3-23). We restricted the calibration to HIV prevalence between 2009-2016 because in earlier years, HIV status information was incomplete and there was a high proportion of unknown/unspecified HIV status. We have thus decided to include data from 2009 in which HIV testing coverage was at least 50% (335).

We then define the likelihood as follows

$$L(\boldsymbol{H}|\phi) = \prod_{t=2009}^{2016} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(\frac{[\text{logit}(M_t(\phi)) - \text{logit}(H_t)]^2}{2\sigma^2} \right)$$

The variance is set to be 0.01, equivalent to a 95% confidence interval of 55-64% if prevalence is 60%.

3.11.6. The likelihood for the numbers of microbiological tuberculosis tests performed

We also calibrated our model to the recorded number of microbiological tests performed by the South African National Health Laboratory Service (NHLS). We relied on the Nanoo *et al.* study for these data which were available for the years 2004 to 2011 (Table 3-24) (24). Although we requested more recent data from the NHLS, we were not able access the data. These data are based on the samples submitted to the NHLS for TB testing and have unique patient identifiers. In the absence of the unique patient identifiers, a probabilistic record-linking process is used to match multiple specimen records to individual patients, which may be subject to bias (24). We apply a factor of 0.9 to these recorded number of laboratory tests to account for a 10% over-estimation in NHLS due to under-linking (informed by personal commutation with Harry Moultrie, National Institute for Communicable Diseases).

We assume that the number of microbiological tests performed follows a Log-Normal distribution and specify a Log-Normal likelihood function for the years 2004 to 2011. We let D_t represent the recorded number of microbiological tests in year t as reported by Nanoo *et al.* (Table 3-24). Then let $\mathrm{M}_t(\phi)$ represents the model estimates for the number of tests performed in year t where ϕ represents the set of input parameters.

Table 3-24: Recorded numbers of microbiological tuberculosis test performed by year

Year	Total microbiological tests (adjusted)
2004	1259747
2005	1571753
2006	1844658
2007	2214799
2008	2555539
2009	2713728
2010	3061440
2011	3175857

Data source: Nanoo *et al*. (24).

We then specify the likelihood as follows:

$$L(\boldsymbol{D}|\phi) = \prod_{t=2004}^{2011} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{[\ln(D_t\gamma) - \ln(\mathrm{M}_t(\phi))\,)]^2}{2\sigma^2}\right)$$

The variance is set to be 0.01 and $\gamma = 0.9$.

3.11.7. The likelihood for the prevalence of bacteriologically confirmed active tuberculosis

In the 2018 national TB prevalence survey, the prevalence of bacteriologically confirmed pulmonary TB in individuals who were 15 years and older was 1 094 (95% CI 835–1 352) per 100 000 and 675 (95% CI 494–855) per 100 000 for males and females, respectively (17).

We let P_g be the prevalence of bacteriologically confirmed TB for individuals of sex g, as reported for the 1st South African National Prevalence Survey (2018) (17). Then let $M_g(\phi)$ represent the model estimates of the prevalence of pulmonary TB, of sex g; where ϕ is the set of input parameter values.

Based on the South African studies by Pepper *et al.* and Gupta *et al.*, the estimated proportion of TB cases that are exclusively extra-pulmonary tuberculosis (EPTB) in HIV-negative individuals was 13.5% and 8.2%, respectively (104,260). The South African TB prevalence survey report assumed that the proportion of TB cases that were exclusively extra-pulmonary TB was 9.7% (17). In our model we assumed the proportion of TB cases that are exclusively EPTB ($\mathrm{p}_{s=0}$) for those with HIV-negative status ($s = 0$) to be 10%. Among HIV-positive individuals, the proportion of TB cases that are exclusively EPTB is slightly higher, estimated at 26.3% and 17.6% by Pepper *et al.* and Gupta *et al.*, respectively (104,260). We therefore assumed 22%, the average from these two studies (104,260) to represent the proportion of TB cases that are exclusively EPTB in HIV-positive ($\mathrm{s} = 1$) individuals ($\mathrm{p}_{s=1}$).

Then, for H_g the total number of active TB cases in HIV-positive individuals; N_g the total number of active TB cases in HIV-negative individuals; and T_g the total number of people in the population, for sex g, we estimated the prevalence of pulmonary TB as

$$M_g = \left(N_g(1.0 - \mathrm{p}_0) + H_g(1.0 - \mathrm{p}_1)\right) / T_g.$$

We applied a logit transformation to these prevalence proportions from the prevalence survey (P_g) and model ($M_g(\phi)$). Then the likelihood is represented by:

$$L(\boldsymbol{P}|\phi) = \prod_g \frac{1}{\sqrt{2\pi\sigma_g^2}} \exp\left(-\frac{\left[\mathrm{logit}(P_g) - \mathrm{logit}(M_g(\phi))\right]^2}{2\sigma_g^2}\right)$$

and the variance is calculated as:

$$\sigma_g^2 = \left(\frac{0.1 s_g}{P_g(1-P_g)}\right)^2$$

where P_g is the point prevalence and s_g is the survey standard error estimated from the confidence intervals. We multiplied the survey standard error by a factor of 0.1 to ensure the model produced a better fit to the TB prevalence survey data (as the TB prevalence survey would otherwise get very little weight relative to other data sources and our initial attempts to fit the model did not give good fits to the survey prevalence without the 0.1 adjustment).

3.11.8. Generating posterior distributions

The posterior distributions were simulated numerically by implementing the Incremental Mixture Importance Sampling (IMIS) algorithm (336) in the following steps:

1. $N_0 = 10\,000$ input parameters were randomly drawn from the prior distributions in Table 3-20. Here ϕ_i, for $i = 1,\ 2,\ 3, \ldots, N_0$, is the set of different parameter combinations.

2. For each parameter set ϕ_i, a likelihood L_i was calculated, by multiplying together the likelihood expressions in sections 11.1-11.7.

3. Weights w_i^0 were calculated as a ratio of the likelihood L_i over the sum of all likelihoods.

$$w_i^0 = \frac{L_i}{\sum_{j=0}^{N_0} L_j}$$

4. Importance sampling was then performed to concentrate sampling in regions of parameter spaces that yield the highest likelihood values. The following steps were repeated (*k*-times) until a stopping criterion was met.

    - The weights were sorted, and the maximum weight was found and set as the centre of the new sampling distribution $\phi_i^{(k)}$.

- Mahalanobis distances between the centre $\phi_i^{(k)}$ and other prior points ϕ_i were calculated. These were sorted, and the smallest distances were recorded. Finally, the Mahalanobis distances were calculated with respect to the covariance of prior distributions.

- B prior points ϕ_i with the smallest distance to $\phi_i^{(k)}$ were selected as a set. Then a weighted covariance of these points in B was calculated.

- New inputs were sampled from a Gaussian distribution. (These points are those with the smallest distance from the max weight $\phi_i^{(k)}$).

- Then a new likelihood was calculated using the new inputs. The new inputs were then combined with previous inputs from prior distributions and used to calculate new weights

$$w_i^k = cL_i \times \frac{p(\phi_i)}{q^{(k)}(\phi)}$$

Where c is chosen so that the weights add to 1 and $q^{(k)}$ is the mixture sampling distribution:

$$q^{(k)} = \frac{N_0}{N_k} p + \frac{B}{N_k} \sum_{s=1}^{(k)} H_s$$

And N_k is the total number of inputs up to the k-th iteration.

5. From the posterior sample, J = 1 000 parameter combinations were resampled. The posterior means for the model estimates were calculated as the average of all outputs generated over 1000 samples. 95% intervals were calculated by taking the 0.25^{th} and the 0.975^{th} percentiles of the outputs.

The stopping criterion was set to be reached when the expected fraction of unique parameter combinations in the posterior sample is at least 0.4. The expected number of unique parameter combinations is calculated as

$$\frac{1}{N_k} \sum_{i=1}^{N_k} (1 - (1 - w_i)^J)$$

N_k is the total number of inputs up to the k-th iteration, and J is the number of resamples.

3.12. Results from model calibration

3.12.1. Comparison of prior and posterior distributions

As indicated in Table 3-20, most of the TB natural history parameters were estimated in a separate analysis and fixed in this current analysis. Table 3-25 below shows the prior and posterior distributions for parameters varied in this current analysis. Most of the prior and posterior distributions means are similar and the 95% confidence intervals overlap. However, there were some differences with other parameters, in particular the parameters representing empirical treatment and relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions (in earlier years). This reflects the uncertainty associated with the parameter due to limited empirical evidence to inform the prior distributions.

Table 3-25: Comparison of prior and posterior distributions for model parameters

Parameter description	Prior mean (95% confidence interval)	Posterior mean (95% confidence interval)
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.005 (0.0 – 0.0148)	0.0030 (0.0026–0.0034)
The annual rate of reactivation in HIV-negative individuals	0.0024 (0.0 – 0.005)	0.00148 (0.0014–0.00155)
Relative rate of TB incidence per 100 cell increase in CD4	0.71 (0.054 – 0.877)	0.703 (0.693–0.712)
Annual recovery rate in smear-positive TB, HIV-negative individuals	0.09 (0.051 – 0.129)	0.075 (0.067–0.081)
Annual recovery rate in smear-negative TB, HIV-negative individuals	0.24 (0.142 – 0.338)	0.224 (0.198–0.247)
Relative infectivity of smear-negative TB compared to smear-positive individuals	0.22 (0.161 – 0.279)	0.206 (0.196–0.218)
Increase in TB risk if previously experienced TB	3.5 (0.56 – 6.440)	3.03 (2.55–3.53)
Smear-negative TB mortality (untreated)	0.061 (0.037 – 0.085)	0.049 (0.046–0.052)
Smear-positive TB mortality (untreated)	0.212 (0.129 – 0.295)	0.196 (0.174–0.221)
The relative rate of TB mortality per 50 cell increase in CD4 count if HIV+	0.87 (0.772 – 0.968)	0.949 (0.944–0.954)
Proportion of cough >2 weeks in individuals with smear-negative TB	0.2 (0.004 – 0.396)	0.198 (0.149–0.263)
The proportion of incident TB cases in HIV-negative adults that are smear-positive	0.52 (0.324 – 0.716)	0.51 (0.48–0.54)
Relative ratio of symptoms in patients with smear-positive TB, compared to smear-negative TB	2.2 (1.22 – 3.18)	3.03 (2.74–3.23)

ART = antiretroviral therapy; TB=tuberculosis. The ratio of model the estimated ('true') tuberculosis cases to the number of recorded deaths classified as TB (described in section 11.1)) was estimated at 1.26 (95% CI 1.22 – 1.29).

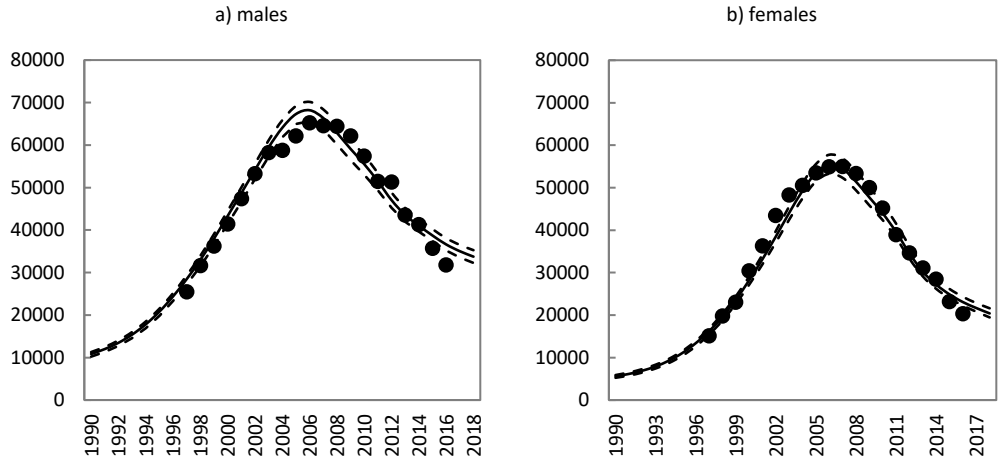
3.12.2. Calibration graphs

The figures below show the comparison of model estimates and data sources data described in Figure 3-6 to Figure 3-12. In all figures, model estimates are represented by the solid black

lines and the dashed lines represent the 95% confidence intervals for model estimates. The data points are represented by the black dots.

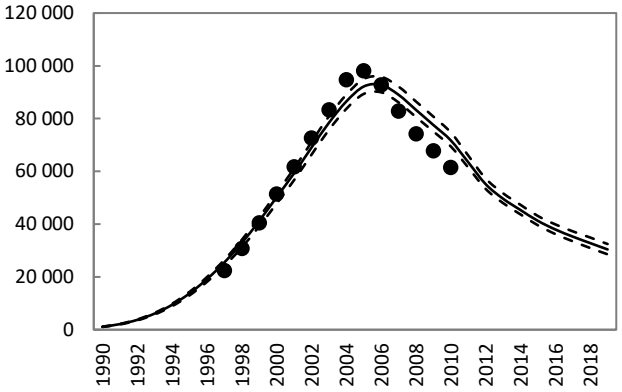
1. Figure 3-6 shows the model fit to adjusted recorded mortality data in males (a) and female (b). Overall, the model resulted in a good fit to the data; however, the model slightly over-estimated the number of TB deaths in 2016 onwards. This may be due to reporting delays in the death data (late recording) because when 2016 data were released, not all the 2016 deaths had been processed. The model slightly under-estimates male TB deaths over the 2008–2012 period. This is consistent with the Thembisa model slightly under-estimating all-cause mortality in men over the 2008–2012 period (337).

Figure 3-6: Recorded number of tuberculosis deaths (adjusted) and model estimated deaths in adults (15+ years)



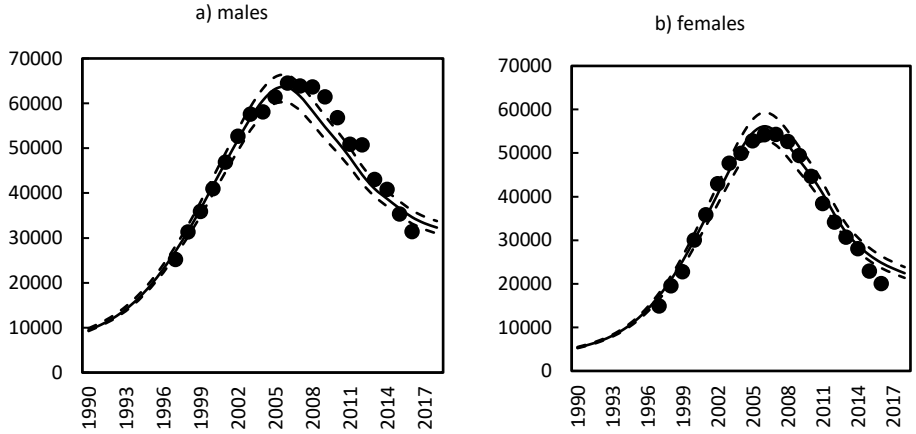
2. Figure 3-7 shows the expected TB deaths in people living with HIV and model estimated tuberculosis deaths in HIV-positive individuals. The model was fairly consisted with the expected TB deaths in HIV-positive individuals but slightly overestimated the deaths from 2007 onwards.

Figure 3-7: Expected tuberculosis deaths in people living with HIV and model estimated tuberculosis deaths in HIV-positive adults (15+ years)



3. Figure 3-8 shows the model fit to adjusted recorded ETR treatment initiations for male (a) and females (b) respectively. The model resulted in an earlier peak in treatment initiations than the ETR data suggest; this could be because the earlier ETR data were less complete. The model was also limited and did not perfectly capture the sex differences in treatment initiations.

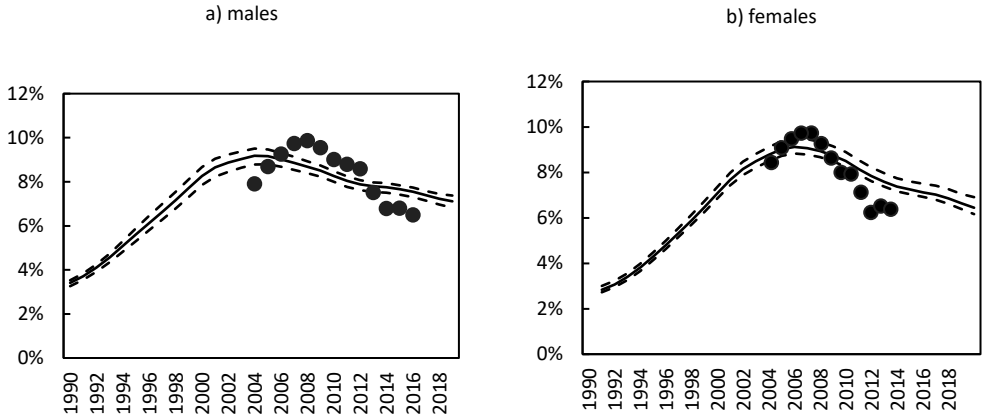
Figure 3-8: Recorded number of tuberculosis cases initiated on treatment (adjusted) and model estimated tuberculosis cases on treatment in adults (15+ years).



4. Figure 3-9 shows the proportions of TB deaths recorded in the ETR for males (a) and females (b). The model did not match the observed data well. Although we adjusted for incomplete recording of deaths, we did so on the assumption that completeness levels

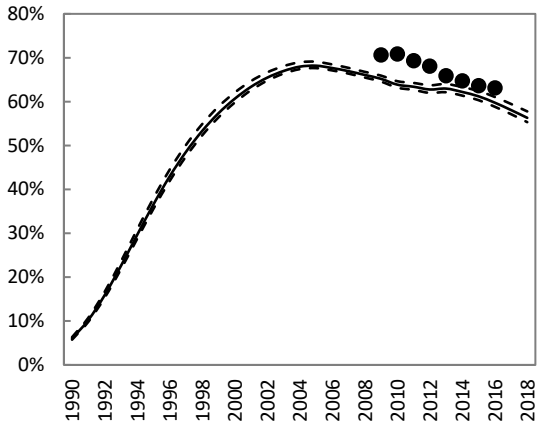
remained constant over time, which might be unrealistic. In ART programmes it has been noted that the recording of mortality in patient record systems has become significantly less complete over time (241), which might explain why we do not match the significant reduction in the recorded deaths in the more recent years.

Figure 3-9: Proportion of tuberculosis deaths recorded in the electronic tuberculosis treatment register and model estimates for proportion of tuberculosis deaths on treatment for adults (15+ years)



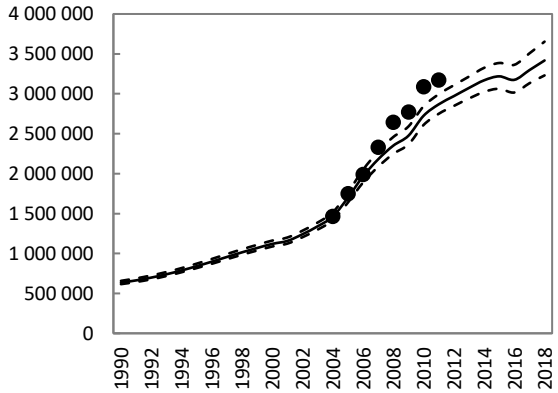
5. Figure 3-10 shows the model fit to the prevalence of HIV in individuals on treatment. The model did not to fit the ETR HIV prevalence well (underestimating the observed data) before 2014. This is possibly because over the period 2014-2016, 95% of people in the ETR were tested (had known HIV status), while testing was less complete in the earlier years (e.g., in 2009, only 53% people were tested). Thus, it is possible that the earlier (less complete) data overstated the true TB prevalence if HIV testing was biased towards people suspected of being at HIV risk, or if there was a bias due to people on ART being known HIV-positive cases.

Figure 3-10: HIV prevalence in the electronic tuberculosis register and model estimated HIV prevalence in adults (15+ years) on treatment



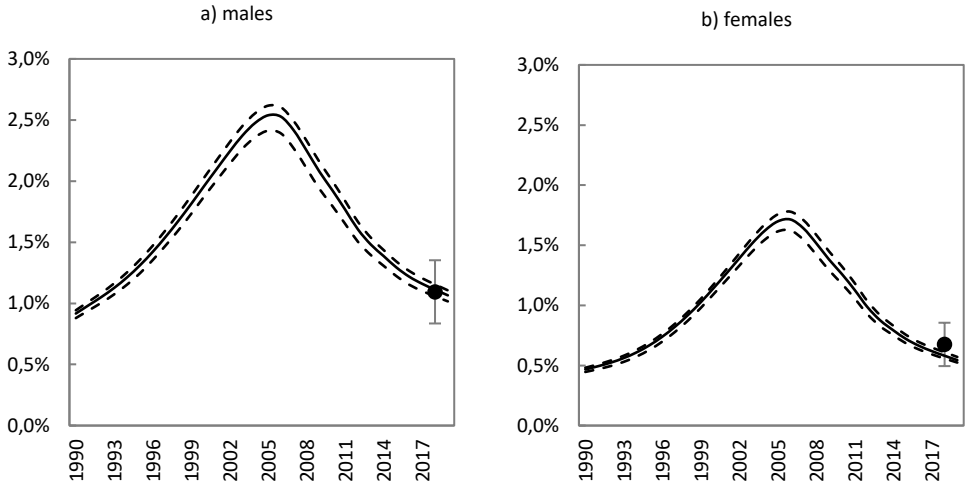
6. Figure 3-11 shows the model fit to the number of microbiological TB tests performed. The model captured in the increasing trend for numbers of TB tests but slightly underestimated the reported data in recent years.

Figure 3-11: The numbers of microbiological tuberculosis tests performed and model estimates for microbiological tests performed



7. Figure 3-12 shows the model fit to the prevalence of TB for males (a) and females (b). Overall, the model resulted in a good fit for the observed prevalence data.

Figure 3-12: The prevalence of bacteriologically confirmed active tuberculosis and model estimated prevalence of tuberculosis adults (15+ years)



3.13. Comparison with other model estimates

The World Health Organization (WHO) (3) and the Institute for Health Metrics and Evaluation (IHME) (7) are two main agencies that produce global, regional, and national TB burden estimates, and South Africa relies on their reports for TB burden estimates. In this section, the TB burden estimates produced by our model (Thembisa TB/HIV) will be compared to the 2019 South African TB burden estimates produced by the WHO and IHME to assess the overall consistency between the models.

Overall tuberculosis burden

Overall, our model had major differences with the number of new TB cases estimated by the IMHE and WHO: WHO and IHME estimates were 32% and 55% higher respectively than Thembisa estimates (Table 3-26), but the models were closer in their estimates of total TB deaths. We note that the WHO and IMHE estimates include all ages whereas we only consider the adult (15+ years) population in our model. The proportion of TB of all forms in children (<15 years) is estimated at approximately 11% in South Africa (264). As such, we would expect our estimates to be relatively lower than both the WHO and IMHE estimates (Table 3-26).

Table 3-26: Comparison of 2019 tuberculosis disease burden estimates by the three models: Thembisa, IHME and WHO

	Thembisa TB/HIV	IMHE‖	WHO*
New tuberculosis cases			
HIV-positive	156 000	203 700	209 000
HIV-negative	117 000	218 800	151 000
% new TB in HIV-positive	57%	48%	58%
Totals	273 000	422 500	360 000
Tuberculosis deaths			
HIV-positive	34 000	40 100	36 000
HIV-negative	18 000	19 820	22 000
% TB deaths in HIV-positive	65%	67%	62%
Totals	52 000	59 920	58 000

Source: Author's own estimates (Thembisa). Ledesma *et al*. (7); 2020 WHO TB report (3). Note: both WHO and IHME report for all ages, whereas for Thembisa, we report for adults only (15+ years). ‖IMHE figures obtained from summing HIV-sex-disaggregated data. *WHO sex-specific data obtained from reading a graph so may not be the exact.

Another apparent difference between our estimates and the IHMEs was that the IMHE estimated a relatively low proportion of TB incidence in HIV-positive individuals (48%). In contrast, the WHO and Thembisa TB/HIV estimated a higher proportion of TB cases in HIV-positive individuals, with proportions of 58% and 57%, respectively. For mortality, all models estimated a similarly high proportion of TB deaths in HIV-positive individuals (62-67%).

Sex differences

For 2019, the WHO and Thembisa TB/HIV model estimated a high proportion of TB cases in males with 59% and 60%, respectively, whereas the IMHE estimated a lower proportion of TB cases in males, 42% (Table 3-27). There was however some consistency between our model and the IHME's estimates for mortality, with both models estimating a higher proportion of TB deaths in males than in females. The WHO did not report mortality by sex.

Table 3-27: Comparison of 2019 tuberculosis disease burden estimates by the three models, by sex: Thembisa, IHME and WHO

	Thembisa TB/HIV	IMHE‖	WHO*
New tuberculosis cases			
Males	164 000	179 500	214 000
Females	109 000	243 000	146 000
% of TB in males	60%	42%	59%
Totals	273 000	422 500	360 000
Tuberculosis mortality			
Males	31 000	32 800	
Females	21 500	27 120	
% of TB deaths in males	60%	54%	
Totals	52 000	59 920	

Sources: Ledesma *et al*. (7); 2020 WHO TB reported (3). ‖IMHE figures obtained from summing HIV-sex-disaggregated data. *WHO sex-specific data obtained from reading a graph so may not be the exact.

The notable differences described above may be driven by differences in the methodological approaches for estimating the tuberculosis burden and the data sources used for inputs (Table 3-28). The IMHE relies largely on mortality data and indirectly estimates incidence from case fatality ratios estimated from a regression model (7). The WHO on the other hand relied on the 2018 prevalence survey and assumptions about TB disease duration to estimate TB incidence (3). The WHO's estimates of disease duration are based on literature reviews and a simple dynamic model of three compartments (susceptible, untreated TB, and treated TB) (239). Prior to 2019 (i.e., before the release of the South African TB prevalence survey), to estimate incidence for South Africa, the WHO mainly relied on TB notification data combined with expert opinion about case detection gaps (239,338).

We have used a dynamic transmission model which considers the tuberculosis natural history (i.e., disease progression, recovery), transmission dynamics, health-seeking behaviours and diagnostic algorithms, and intervention impacts, whereas the IHME estimates are not based on dynamic modelling. To simulate the effects of HIV on tuberculosis incidence and mortality in our model, we used available evidence to estimate relative risks (which varied by CD4 count and ART status) of TB incidence and mortality for HIV positive individuals. Additionally, we performed a formal Bayesian calibration process to ensure the estimates are consistent with epidemiological data, including the recorded mortality data, notified cases initiating treatment and the latest 2018 TB prevalence survey.

To estimate mortality in HIV-negative individuals the WHO uses the vital register data; however, the data were adjusted for TB/HIV miscoding (the WHO obtains these adjusted data from the IMHE) (239,338). For the HIV-positive population, the WHO applies HIV-specific case-fatality ratios to the estimated TB incidence (3). The IMHE uses a mixed-effects regression model to estimate the proportion of HIV-TB cases among all TB cases, then they estimate relative risks of TB deaths in HIV-positive individuals (7). Based on this, they estimate the proportions of TB deaths attributable to HIV (7).

To further understand what influences the differences between these models, a systematic analysis involving a comparison of the methods and data sources would be required. Garcıa-Basteiro *et al.*, performed an analysis which compared the 2015 TB mortality estimates produced by the WHO and IHME, and explored the factors that drove the observed differences (339). Overall, it seems the differences in estimation approaches and data sources used led to these differences. The authors suggested that differences in the use of prevalence survey data and case detection rates may explain most of the observed differences in the mortality estimates produced by the WHO and IHME (339).

Table 3-28: General differences between Thembisa TB/HIV, the Institute for Health Metrics and Evaluation and the World Health Organization for 2019 TB burden estimates

	Thembisa TB/HIV	IMHE	WHO
Modelling and approach	Dynamic transmission model Includes: TB natural history natural history (i.e., disease progression, recovery), transmission dynamics, health-seeking behaviours, and diagnostic algorithms, and impacts of interventions.	Static model. Meta-regression approach including covariates such as smoking prevalence, diabetes, indoor air pollution, alcohol, and health system access.	Simple dynamic model to estimate TB disease duration accounting the effect of HIV and ART. Use case fatality ratios estimated in the literature.
Data sources	2018 national TB prevalence survey Recorded deaths from the vital registry cleaned and adjusted (1997-2016), electronic tuberculosis register (2004-2019). Literature review on model parameters.	Recorded deaths from the vital registry and verbal autopsies	Recorded deaths – vital register, national TB prevalence survey. Case fatality ratios estimated in the literature
Strata	HIV, CD4 stage, ART, Sex, age	HIV, sex, age	HIV, sex, age
Modelling TB incidence	Depends on fast progression, reactivation, relapse. Incorporated the effect of HIV, ART and CD4 count.	Used meta-regression to estimate mortality-to-incidence ratios. Then use mortality-to-incidence ratios and cause-specific mortality estimates to compute incidence. (Did not use the 2018 South African TB prevalence - based on communication with Hmwe Kyu)	TB prevalence surveys combined with estimates of the duration of disease.
Modelling TB mortality	Assumed death rates for TB treated and untreated cases. Incorporated the effect of HIV, ART and CD4 count.	Use vital registry and verbal autopsy data. Use mixed-effects regression models to estimate the proportion of HIV-TB cases among all TB cases. Estimated relative risks of TB deaths in HIV-positive individuals, then use a population attributable fraction approach to estimated deaths attributable to HIV.	For HIV-negative individuals: used vital registry data cleaned and analyzed by the IHME. For HIV-positive individuals, apply case fatality ratios to TB incidence, accounting for antiretroviral treatment's protective effect.

ART: antiretroviral therapy; IHME: Institute for Health Metrics and Evaluation; TB=Tuberculosis; WHO: World Health Organization

Chapter 4. The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: A mathematical modelling analysis

Kubjane M, Osman M, Boulle A, Johnson LF. The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: A mathematical modelling analysis. Int. J. Infect. Dis. 2022; (doi.org/10.1016/j.ijid.2022.07.047).

Publication status: Published; International Journal of Infectious Diseases.

Relevance of this manuscript to the thesis: The analysis in this manuscript addresses the first objective of this thesis.

Author contributions: MK, LJ, and AB contributed to the study conceptualization, analysis, and interpretation of the results. LJ and MK wrote the code for the mathematical model. LJ and AB were the study supervisors. MO curated the electronic tuberculosis register data and contributed to interpretation of results. MK wrote the first manuscript draft, and all authors critically reviewed versions of the manuscript and agreed on the final version to be submitted for publication.

4.1. Abstract

Objectives: To quantify the South African adult tuberculosis incidence and mortality attributable to HIV between 1990–2019; and to estimate the reduction in tuberculosis incidence due to directly observed therapy (DOTS), antiretroviral therapy (ART), isoniazid preventative therapy (IPT), increased tuberculosis screening, and Xpert MTB/RIF.

Methods: We developed a dynamic tuberculosis transmission model for South Africa. A Bayesian approach was used to calibrate the model to South African-specific data sources. Counterfactual scenarios were simulated to estimate tuberculosis incidence and mortality attributable to HIV, and the impact of interventions on tuberculosis incidence.

Results: Between 1990 and 2019, 8.8 million (95% confidence interval (CI) 8.3–9.3 million) people developed tuberculosis, and 2.1 million (95% CI 2.0–2.2 million) died from tuberculosis. 55% and 69% of the tuberculosis incidence and mortality were due to HIV, respectively. Overall, tuberculosis screening and ART substantially reduced tuberculosis incidence by 28.2% (95% CI 26.4–29.8%) and 20.0% (95% CI 19.2–20.7%) respectively, in 2019; other interventions had minor impacts.

Conclusion: HIV has dramatically increased tuberculosis incidence and mortality in South Africa. The provision of ART and intensification of tuberculosis screening explained most recent declines in tuberculosis incidence.

4.2. Introduction

South Africa is ranked among the World Health Organization top 20 high tuberculosis burden countries (25). The tuberculosis epidemic grew rapidly in the early 1990s, primarily driven by HIV (140). HIV infection is the strongest individual-level tuberculosis risk factor, increasing the risk of progression to tuberculosis disease and reactivation of latent tuberculosis infection (LTBI), worsening treatment outcomes and increasing mortality (4). Although the effect of HIV on tuberculosis has been established, very few studies have quantified its population-level effect on incidence and mortality over time. South Africa has implemented tuberculosis control interventions, including directly observed therapy (DOTS), which was scaled up in 1996 (125). This strategy had multiple components, including directly observed treatment, political commitment, improved microscopy services, surveillance and monitoring, and quality treatment (125). Other interventions which were scaled up in the mid-2000s included the provision of isoniazid preventive therapy (IPT) and antiretroviral therapy (ART) for HIV-positive individuals (23,340).

Declines in tuberculosis notifications and mortality from 2008 have largely been attributed to ART, which was made widely available during the mid-2000s (18,341,342). This is supported by the established individual-level effectiveness of ART in reducing tuberculosis incidence and mortality (100,343). In addition, IPT also reduces the risk of developing tuberculosis in people living with HIV (324,343). However, few studies have shown the population-level effect of IPT.

There has also been substantial effort invested in identifying tuberculosis cases in South Africa. Between 2004 and 2012, the annual number of microbiological tuberculosis tests performed doubled (24), and Xpert MTB/RIF was introduced in 2011 to replace smear microscopy (130,344). Although earlier modelling studies anticipated substantial health benefits from Xpert MTB/RIF implementation compared to microscopy (169), clinical trials have found minimal or no impact on tuberculosis mortality (130). To understand these dynamics better, modelling studies with detailed diagnostic algorithms that account for empirical treatment are required.

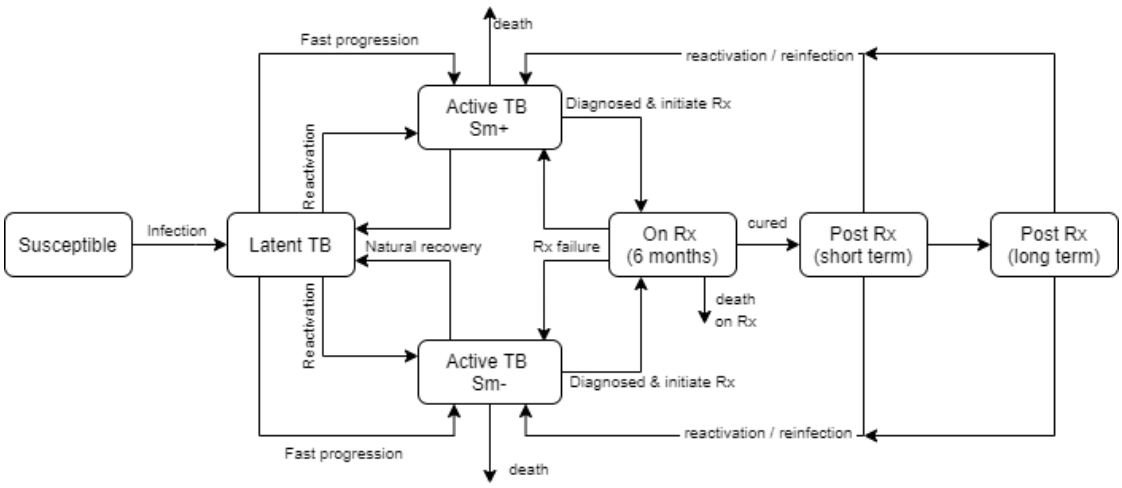
There have been no formal analyses to quantify the contribution of the abovementioned tuberculosis interventions on the declining tuberculosis trends. Such evaluations are essential in assessing which South African tuberculosis programme components are most critical to decreasing tuberculosis incidence. Therefore, we sought to 1) describe the South African tuberculosis epidemic trends between 1990 and 2019; 2) assess the burden of tuberculosis attributable to HIV; 3) and assess the impact of tuberculosis interventions including DOTS, increased tuberculosis screening, Xpert MTB/RIF as an additional first line diagnostic tool replacing smear microscopy, IPT, and ART on tuberculosis incidence.

4.3. Methods

We developed an age- and sex-structured deterministic compartmental model of tuberculosis and HIV for the South African adult population (ages 15 years and older). The core tuberculosis states are modelled following conventions described by previous studies (169). Transitions between states include tuberculosis infection, progression to tuberculosis disease, natural recovery, diagnosis and treatment initiation, death, and treatment cure. Age- and sex-specific relative risks were applied to rates of progression to tuberculosis disease to capture age and sex differences in tuberculosis risk factors.

After cure by tuberculosis treatment, two post-treatment states dependent on time since cure are defined – short-term (within six months after cure) and long-term (six or more months after cure). In both states, individuals are at risk of reinfection, whereas in the short-term, individuals are assumed to have a high likelihood of relapse (315). The natural history parameters are described in Table 4-1. The model structure is shown in Figure 4-1. A detailed description of the model is provided in the supplementary material (Chapter 3). The risk of infection depends on the mean contact rates, age- and sex- mixing patterns (83), the probability of transmission per contact, and the prevalence of infectious tuberculosis.

Figure 4-1 Structure of the tuberculosis model



TB = tuberculosis. Rx = treatment. Sm+ = smear-positive. Sm- = smear negative.

The Thembisa HIV model forms the HIV component of the model (337). Thembisa is a compartmental model of the South African HIV epidemic designed to answer policy questions relating to HIV prevention and treatment. The model is age- and sex- structured, and the HIV epidemic is simulated dynamically from 1985. HIV-positive sub-populations are further stratified by HIV testing history, CD4 count, and duration since ART initiation. The model also captures changes in the ART guidelines over time (337) and is calibrated to South African data. HIV is assumed to affect the tuberculosis natural history parameters. These HIV effects are modelled as relative risks, which vary by CD4 count and duration since ART initiation (Table 4-1).

Table 4-1: Key model parameters

Parameter description	Mean	Standard deviation	Varied / fixed	Section described in supplementary material^
The proportion of incident TB cases in HIV-negative adults that are smear-positive	0.51		Fixed	3
TB transmission probability per contact per day (if an infectious individual is smear-positive)	0.0025	0.0025	Varied	4
Relative rate of infectivity smear-negative compared to smear-positive	0.206		Fixed	4
The annual rate of reactivation in HIV-negative individuals	0.00148		Fixed	5
The proportion of individuals experiencing fast progression	0.112		Fixed	5
Reduction in TB incidence in previously infected individuals if HIV-negative	0.79		Fixed	5
Relative rate of immunity to TB per 100-cell increase in CD4	1.1		Fixed	5
Reduction in TB incidence per 100-cell increase in CD4[$]	0.703		Fixed	5
Annual natural recovery rate in smear-positive TB, HIV-negative individuals	0.075		Fixed	5
Annual natural recovery rate in smear-negative TB, HIV-negative individuals	0.224		Fixed	5
Smear-negative TB mortality (untreated)	0.049		Fixed	5
Smear-positive TB mortality (untreated)	0.196		Fixed	5
Relative rate of TB incidence on ART (controlling for CD4)	0.81	0.05	Varied	5
Prevalence of cough >2 weeks duration in individuals with smear-negative TB	0.198		Fixed	6
Ratio of symptoms in patients with smear-positive compared to smear-negative TB	3.03		Fixed	6
The annual rate of health-seeking in males with smear-negative TB	2.14	0.49	Varied	6
The annual rate of health-seeking in males in the general population	1.15	0.5	Varied	6
The annual rate of health-seeking in males due to TB-like symptoms	0.22	0.15	Varied	6
The proportion of active TB cases seeking treatment who are treated empirically if no microbiological test is done	0.125	0.144	Varied	6
The proportion of smear-negative TB cases who are treated empirically if they initially screened negative on smear test	0.333	0.236	Varied	6
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.5	0.289	Varied	6
Relative rate empirical treatment if symptoms are not due to TB	0.5	0.289	Varied	6
Reduction in empiric treatment after a negative screen due to Xpert MTB/RIF	0.5	0.18	Fixed	6
Relative rate of health-seeking in women, compared to men	1.55	0.17	Varied	6
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	3	1	Varied	6
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: initial[¶]	8.71	2.5	Varied	6

Parameter description	Mean	Standard deviation	Varied / fixed	Section described in supplementary material^
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: ultimate‖	4	1.2	Varied	6
Probability of cure if a patient dropped out before completing TB treatment	0.65		Fixed	7
Increase in TB mortality rate per 10-year increase in age	1.4		Fixed	7
The annual mortality rate in HIV-negative individuals receiving TB treatment*	0.192		Fixed	7
The relative rate of TB mortality per 50-cells increase in CD4 count if HIV+	0.95		Fixed	7
Relative rate of TB mortality if on ART	0.55	0.08	Varied	7
Increase in TB risk if previously experienced TB	3.03		Fixed	8
Rate of relapse in short term post-treatment state	0.1		Fixed	8
Increase in TB incidence due to alcohol abuse	1.94†		Fixed	10
Increase in TB incidence due to diabetes (HbA1c > 6.5%)	2.59†		Fixed	10
Increase in TB risk if currently smoking	0.47†		Fixed	10
Increase in TB risk per 10-year increase in the duration of smoking	0.38†		Fixed	10
Increase in TB risk due to low BMI	0.8†		Fixed	10

ART=antiretroviral therapy; BMI=body mass index; HbA1c= Glycated hemoglobin. TB=tuberculosis. All rates are annual rates unless specified otherwise. $ TB incidence adjustments apply to both the reactivation rate and the fast-progression proportion. ^The supplementary material / Chapter 3 and the indicated sections provides further descriptions and references for the model parameters. ‖This is a time-varying parameter. The initial rate applies up to 2005, the ultimate rate applies from 2012, with linear interpolation over the intervening years (2006-2011). *Applies when most people get treated in the very advanced stages of disease (i.e., when screening rates are close to zero). †A value of 1.94, for example, is equivalent to a relative risk of 2.94 when comparing individuals with the exposure to individuals in the baseline category supplementary material / Chapter 3.

IPT is modelled for individuals with latent tuberculosis infection (LTBI) who are HIV-positive and eligible as per guidelines (317). Uptake is dependent on CD4 count, duration on ART and latent tuberculosis status. IPT uptake started in 2010; the number of IPT initiators were obtained from the District Health Information System. Assumptions on IPT duration, completion, and efficacy are in Chapter 3.

The assumed health-seeking patterns in the model are based on South African studies. We assume different health facility attendance rates for individuals: 1) with tuberculosis, attending health facilities due to tuberculosis-related symptoms; 2) without tuberculosis, attending due to other health conditions; 3) and without tuberculosis, attending due to tuberculosis-like symptoms. We assume females are more likely to seek care than males (2), HIV-positive individuals have higher health seeking rates than HIV-negative individuals (216), and smear-positive individuals experience more tuberculosis symptoms than smear-negative individuals (270). We consider smear microscopy and Xpert MTB/RIF as the first-

line diagnostic tools, accounting for the phased implementation of Xpert MTB/RIF from 2011 onwards. To estimate the numbers of true and false-positive tuberculosis diagnoses, we specified the sensitivity and specificity of these tests. Following initial negative test results, we assume a proportion of individuals are followed up for a second test by culture.

The model also allows for treatment initiation in a proportion of individuals who do not have laboratory-confirmed tuberculosis (empirical treatment). Health seeking parameters and rates of tuberculosis screening are estimated through calibration by fitting the model to the numbers of microbiological tests performed (24) and numbers of cases treated. Once individuals start the 6-month tuberculosis treatment course, the following outcomes are considered: cure, failure, discontinuation, and death (with the rates of cure and failure depending on treatment discontinuation rates). Treatment outcome assumptions are based on the electronic tuberculosis treatment register (ETR.net) data for drug susceptible tuberculosis and are shown in Chapter 3.

4.3.1. Calibration targets and data sources

A Bayesian approach was used to calibrate the model. Prior distributions were set to represent uncertainty in key model parameters (Table 4-1). Four main data sources were used for the calibration targets. First are the sex-stratified recorded numbers of tuberculosis deaths from the vital register for 1997-2016. These mortality data were adjusted for misclassification and under-reporting (Chapter 3). Second, we relied on ETR.net for the numbers of people initiating treatment (2004-2016), deaths on treatment (2004-2016), and HIV prevalence in people on treatment (2008-2016). Third, we relied on the National Institute for Communicable Diseases for numbers of microbiological tests performed (2004-2012) and positive tuberculosis diagnoses (2004-2019) (24). Lastly, we used the 2018 national tuberculosis prevalence survey to calibrate the prevalence of active tuberculosis disease (17). For the calibration process, likelihood functions were defined to represent the goodness of fit to each calibration target, allowing for possible under- or over-reporting in the vital register and the ETR.net data.

We simulated posterior distributions numerically using Incremental Mixture Importance Sampling, i.e., using importance sampling to draw a sample of parameter combinations from regions of the parameter space that yield the highest likelihood values (336). The means for the model estimates were calculated over 1000 posterior samples, and 95% confidence

intervals were calculated by taking the 2.5th and the 97.5th percentiles of the posterior sample (Chapter 3).

We performed a sensitivity analysis to assess how the model inputs varied in the calibration process were correlated with the estimated tuberculosis incidence and mortality for 2019.

4.3.2. Model experiments to assess the impact of HIV and programmatic interventions over time

To quantify the effects of HIV, DOTS, increased tuberculosis screening, Xpert MTB/RIF, ART, and IPT on tuberculosis incidence and mortality, we ran the scenarios A to H described in the Table 4-2 below. Each of the counterfactual scenarios B to H was compared to the baseline scenario A to assess the change in tuberculosis incidence and mortality attributable to the relevant factor.

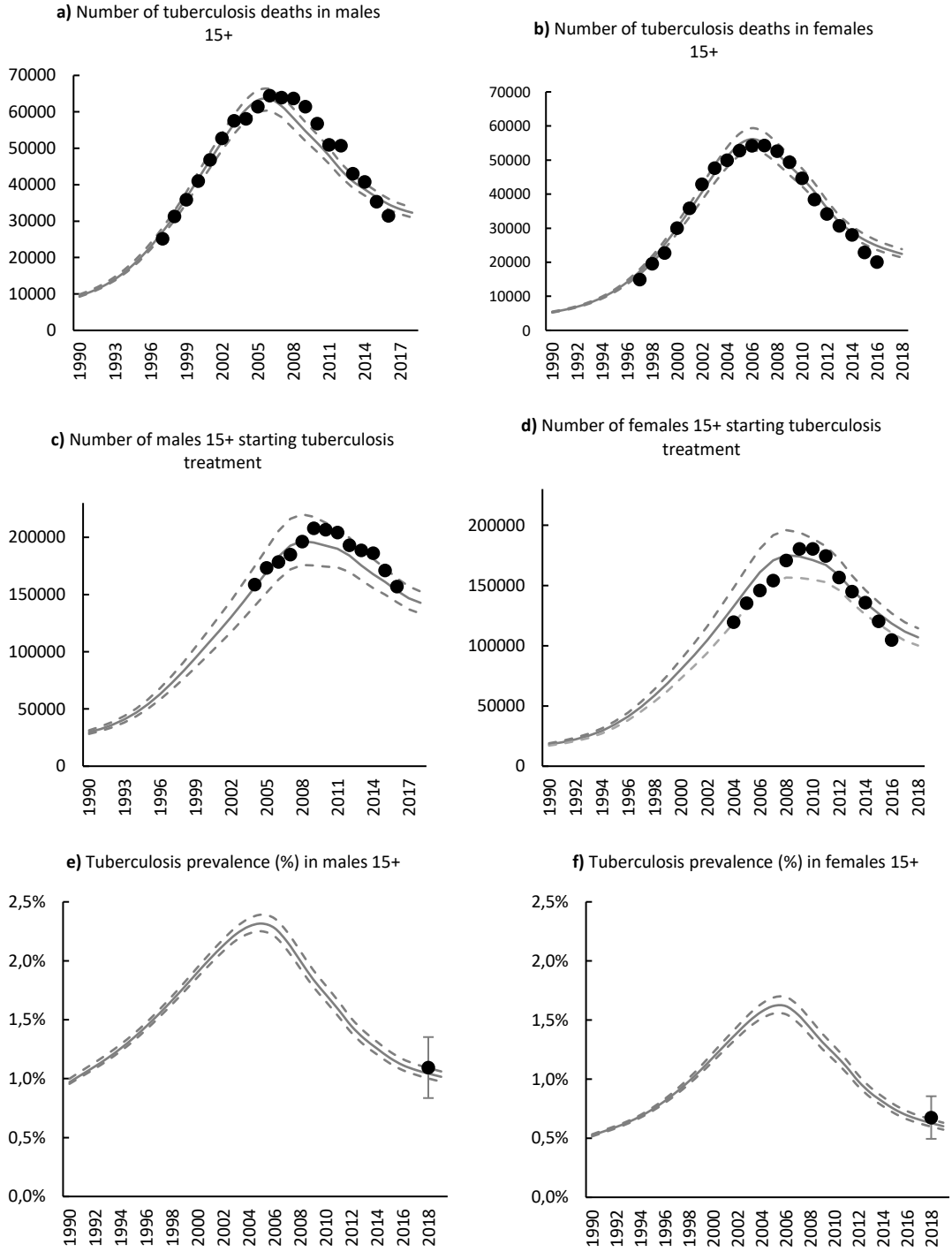
Table 4-2: Model experiments to assess the impact of HIV and programmatic interventions over time

Scenario	Model scenario descriptions	Parameters used
A	The baseline scenario represents the interventions currently in place: DOTS was introduced in 1996, smear-microscopy as the dominant diagnostic tool before 2011, with Xpert MTB/RIF gradually implemented from 2011, public-sector ART scale-up from 2004, implementation of IPT from 2010.	We assumed the relative rate of treatment discontinuation was 0.48 under DOTS (128) Xpert is assumed to be more sensitive than microscopy, but is associated with reduced empirical treatment. ART is assumed to reduce TB incidence and mortality, through both direct effects on viral load, and indirect effects on CD4 count (Table 4-1). IPT is assumed to reduce TB incidence by 52% in latently-infected adults (Ayele 2015).
B	To assess the burden of tuberculosis attributable to HIV, we simulated a scenario with no HIV.	HIV transmission probabilities were set to zero, so that there was no HIV epidemic.
C	To assess the impact of DOTS, we simulated a scenario without DOTS.	Treatment discontinuation rates held constant (no reduction due to DOTS).
D	To assess the impact of IPT, we simulated a scenario where no IPT is implemented.	The number of HIV-positive individuals initiated on isoniazid preventative therapy in each year was set to zero.
E	To assess the impact of ART, we simulated a scenario where there is no ART.	Annual numbers of ART initiations are set to zero.
F	To assess the impact of scaling up tuberculosis screening, we simulated a scenario where testing rates after 2004 remain the same as the 2004 rates.	Screening rates calculated from numbers of microbiological TB tests performed in 2004 are assumed to apply in all subsequent years.
G	To assess the impact of the introduction of Xpert MTB/RIF, we simulated a scenario where Xpert MTB/RIF was not introduced.	Numbers of microbiological TB tests performed by year are unchanged, but all testing is assumed to be based on microscopy.
H	To assess what would have happened without any programmatic changes, we simulated a scenario without any interventions in C) to G).	Including all assumptions described in C-G

4.4. Results

The estimated number of tuberculosis deaths for males and females were consistent with the recorded number of deaths. The estimated deaths rapidly increased from 1994, peaked in 2006, followed by a decline to 31 000 (95% CI 30 000–33 000) and 21 000 (95% CI 21 000–22 000) in 2019, in males and females respectively (Figure 4-2 a and b). The model estimates for the numbers of people starting treatment were slightly inconsistent with the data. Before 2010, the model overestimated the number of females initiating treatment, and after 2008 the model underestimated the number of males initiating treatment (Figure 4-2 c and d). The estimated tuberculosis prevalence was reasonably close to the results of the 2018 tuberculosis prevalence survey; in 2019, the estimated tuberculosis prevalence was 1.02% (95% CI 0.97–1.06%) and 0.6% (95% CI 0.52–0.57%) in males and females respectively (Figure 4-2 e and f).

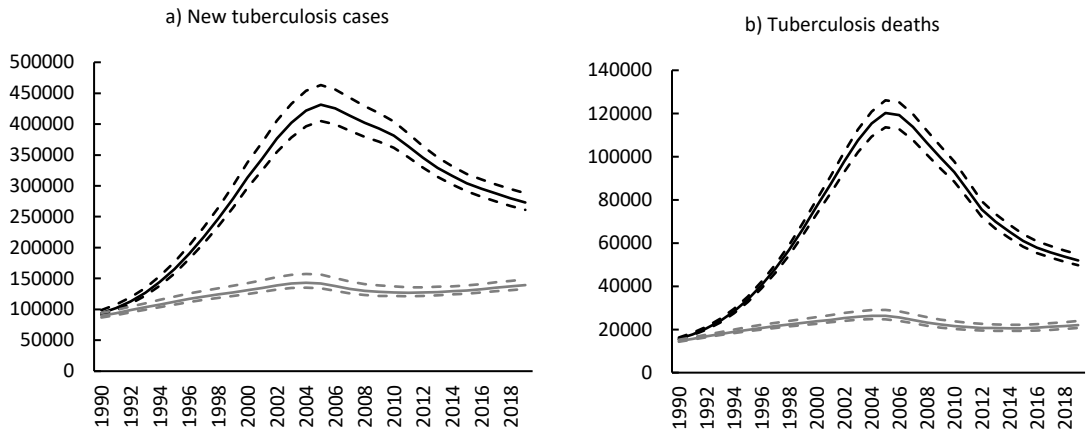
Figure 4-2: Estimated adult tuberculosis trends and calibration data by sex, 1990-2019



Grey solid lines represent model estimates, and dashed lines represent 95% confidence intervals. Black dots represent adjusted recorded mortality in a) and b); people initiating treatment recorded on the electronic tuberculosis treatment register in c) and d), and the national tuberculosis prevalence with 95% confidence intervals around point estimates in e) and f).

In the counterfactual scenario, without HIV, the model estimated that tuberculosis incidence and mortality would have remained relatively low (Figure 4-3), although still high enough for South Africa to be classified a high tuberculosis burden country.

Figure 4-3 Impact of HIV on tuberculosis incidence and mortality, 1990-2019



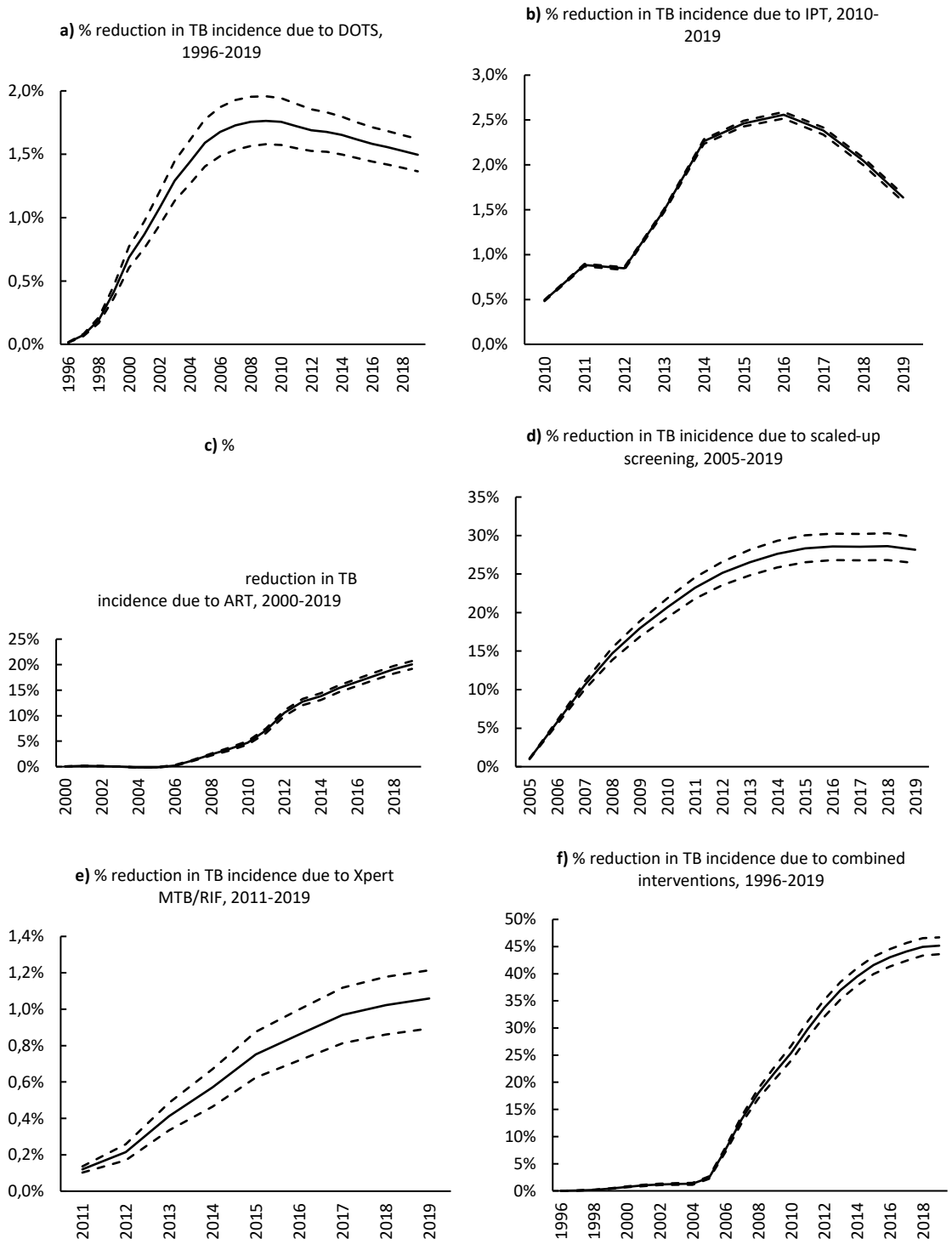
The solid grey line represents the counterfactual scenario where there is no HIV assumed in the model. The solid black line represents the baseline scenario where HIV is present. The dashed lines represent 95% confidence intervals.

In the presence of HIV, the number of incident tuberculosis cases and deaths increased rapidly during the early 1990s and peaked in the mid-to-late 2000s, followed by declines until 2019 (Figure 3). The model estimated 273 000 (95% CI 261 000–288 000) new cases and 52 000 (95% CI 50 000–55 000) deaths in 2019. Over the ten-year period 2009-2019, the percentage reduction in new tuberculosis cases and deaths was 30.4% (95% CI 29.4–31.5%) and 47.7% (95% CI 46.2–49.1%), respectively.

Cumulatively, between 1990 and 2019, there were 8 800 000 (95% CI 8 300 000–9 300 000) new tuberculosis cases and 2 100 000 (95% CI 2 000 000–2 200 000) tuberculosis deaths. Overall, 55.4% (95% CI 54.7–56.1%) of new tuberculosis cases and 68.5% (95% CI 67.0–69.7%) of tuberculosis deaths are attributable to HIV over the 1990-2019 period. 57% of the new TB cases were in HIV-positive individuals, and 69% of TB deaths were in HIV-positive individuals.

Reductions in tuberculosis incidence due to DOTS and IPT were small (<3%) in all years (Figure 4-4 a and b). On the other hand, the reduction in tuberculosis incidence due to ART was evident from 2006, and the impact of ART increased monotonically until 2019 with a reduction of 20.0% (95% CI 19.2–20.7%) in tuberculosis incidence (Figure 4-4 c).

Figure 4-4: The impact of programmatic interventions on tuberculosis incidence



a) DOTS, b) IPT, c) ART, d) scaled-up tuberculosis screening, e) Xpert MTB/RIF, and f) all interventions combined. Solid lines represent the estimated mean reductions in tuberculosis incidence. All dashed lines represent the 95% confidence intervals. ART=antiretroviral therapy. DOTS=Directly Observed Therapy; IPT=isoniazid preventative therapy; TB=tuberculosis.

The reduction in tuberculosis incidence due to screening consistently increased from 2005 to 2019, reaching a maximum of 28.2% (95% CI 26.4–29.8%) (Figure 4d). On the other hand, the reduction in tuberculosis incidence due to Xpert MTB/RIF was very low (<1.3%) for all years (Figure 4-4 e). However, between 2011 and 2019, Xpert MTB/RIF reduced the number of individuals without tuberculosis initiating tuberculosis treatment by 56% (counterfactual: 52 000 vs baseline: 23 000). In addition, Xpert MTB/RIF also reduced the number of individuals starting treatment on an empirical basis by 28% (counterfactual: 65 000 vs baseline: 46 000).

All interventions combined (DOTS, IPT, ART, scaled-up screening, and Xpert MTB/RIF) contributed to a 45.2% (95% CI 43.6–46.7%) reduction in tuberculosis incidence in 2019 (Figure 4-4 f).

Apart from DOTS and IPT, most interventions had a greater impact on tuberculosis mortality than on tuberculosis incidence (Appendix A Figure 1). For example, reductions in mortality in 2019 due to interventions were 37.6% (95% CI 35.8–39.5%) for ART, 37.9% (95% CI 37.1–38.6%) for scaled-up tuberculosis screening, and 3.2% (95% CI 2.4–3.8%) for Xpert MTB/RIF. All interventions combined (DOTS, IPT, ART, scaled-up screening, and Xpert MTB/RIF) led to a to a 63.1% (95% CI 61.1–64.4%) reduction in tuberculosis mortality in 2019.

Most of the model input parameters had the expected relationships with the outcomes (shown by correlation coefficients and scatter plots), but because several parameters were varied simultaneously in the calibration process, some counter-intuitive associations need to be interpreted in terms of correlations between model parameters (for further discussion, see Appendix A, section 8.1.5).

4.5. Discussion

HIV has had a devastating impact on tuberculosis incidence and mortality. Between 1990 and 2019, 8.8 million South Africans developed tuberculosis, and 2.1 million lives were lost. HIV caused 55% (4.8 million) of the tuberculosis cases and 69% (1.4 million) of the tuberculosis deaths. We also showed that interventions implemented by the South African tuberculosis and HIV programmes have led to notable reductions in tuberculosis incidence, with ART and increased screening contributing most of the decline. Our model also showed that the other

interventions – DOTS, IPT, and Xpert MTB/RIF – had modest impacts on tuberculosis incidence. For most of the interventions (increased screening, ART, and Xpert MTB/RIF), the impact on tuberculosis mortality was proportionately greater than the impact on tuberculosis incidence (Appendix Al).

Although HIV is the strongest driver of the tuberculosis epidemic, our model estimated that even in the absence of HIV, tuberculosis incidence in South Africa would remain high. This was demonstrated in the no-HIV counterfactual scenario, in which there were an estimated 235 cases per 100 000 population in 2019. This rate is much higher than the estimated tuberculosis incidence for industrialised regions such as Europe and the America (25). The high tuberculosis burden in the HIV-negative population indicates other underlying factors that drive the epidemic (i.e., low rates of diagnosis and risk factors that increase susceptibility to tuberculosis disease).

The provision of ART substantially impacted tuberculosis incidence; in 2019, it led to a 20% reduction in the model. The benefits of ART on reducing incidence (24,341,342) depend on CD4 count and duration on ART (340) – HIV-positive individuals who initiate ART earlier at higher CD4 counts and stay on ART for longer experience the greatest benefits of ART. In the model, the effect of ART on reducing tuberculosis incidence increased during the mid-2000s when access to ART expanded in South Africa. Over time, the CD4 count threshold at which individuals can start ART has increased (345), and average ART durations have increased, consequently contributing to the substantial reduction in the population-level tuberculosis incidence.

Intensified tuberculosis screening also led to significant declines in tuberculosis incidence. Between 2005 and 2012, South Africa scaled-up efforts to identify tuberculosis cases and testing rates doubled (24). As a result, there were rapid reductions in tuberculosis incidence due to increased tuberculosis screening during this period. In 2019, increased screening led to an estimated 28% reduction in tuberculosis incidence.

The reasons for DOTS having minimal impact on tuberculosis may include high ongoing *Mtb* transmission rates, high prevalence of substantial risk factors such as HIV, which increase progression to disease, and the emergence of resistant tuberculosis (346,347). Lastly, we have only considered one component of the DOTS strategy; considering other aspects may have led to a larger impact. Nonetheless, our findings of the minimal impact of DOTS align with

studies that suggested that DOTS would have minimal impact in settings with a high HIV burden (151,164).

The small population-level impact of IPT on tuberculosis incidence in HIV-positive individuals is consistent with other epidemiological analyses, which attribute the limited impact to the low implementation of IPT in South Africa (342). However, other reasons may be because this HIV-positive population has a high risk of progression to disease or because IPT does not necessarily cure latent *Mtb* infection in HIV-positive individuals (232). In addition, there appears to be minimal protection from IPT after IPT discontinuation or completion, and thus the short duration of IPT protection might explain the relatively modest population-level impact in South Africa (231). Another possible reason may be that ART eligibility criteria have changed over time, and in recent years, more people have started ART at higher CD4 counts. Those starting ART at higher CD4 counts stand to benefit less from IPT.

Our findings regarding the small effect of Xpert MTB/RIF on tuberculosis incidence are in line with studies that found no significant effect of Xpert MTB/RIF on tuberculosis mortality (130). It has been suggested that reductions in empirical treatment offset the positive effect of Xpert MTB/RIF (222). The introduction of Xpert MTB/RIF has increased the number of microbiologically confirmed diagnoses; however, this has not equated to more new diagnoses because many cases were diagnosed empirically prior to adopting Xpert MTB/RIF. In addition, there was more culture testing in those testing negative under microscopy than under Xpert MTB/RIF (281). Another modelling group, which had initially estimated a substantial positive impact of Xpert MTB/RIF on health outcomes, conducted a re-analysis accounting for empirical treatment and the sensitivity and specificity of diagnostic algorithms (227). The revised analysis found a reduction in the benefits, with 70% fewer disability-adjusted life years averted due to Xpert MTB/RIF (227).

We implemented a detailed diagnostic algorithm that estimated true and false positives from microbiological diagnoses. We also considered the proportions of individuals who initiate treatment empirically as informed by South African pragmatic trials and operational studies. As a result, we showed that Xpert MTB/RIF has indeed led to a reduction in the number of people without tuberculosis who start treatment (by 56%) and reduced the number of people who start treatment on an empirical basis (by 28%). Xpert MTB/RIF possibly has other benefits such as reducing the time to diagnosis and time to treatment initiation; we however

did not model the effect of Xpert MTB/RIF on these endpoints. Nonetheless, we assumed that loss to follow-up before treatment initiation was lower when Xpert MTB/RIF compared to smear microscopy testing was used (Chapter 3). We did not model other benefits of Xpert MTB/RIF such as the ability to detect drug-resistant tuberculosis (130) .

This study was subject to several limitations. First, we only considered the adult population (15-year-olds and older). Second, due to the lack of data on the national roll-out of Xpert MTB/RIF, we relied on expert opinion regarding Xpert MTB/RIF implementation. Third, it was difficult to quantify the extent of empirical treatment prior to introducing Xpert MTB/RIF due to data lack of studies to inform our assumptions. Fourth, our model does not distinguish between symptomatic and asymptomatic tuberculosis, although we make assumptions about the prevalence of symptoms for the purpose of modelling screening algorithms. Fifth, our model did not fit the number of treatment initiations data very well, particularly in the earlier years of the ETR data, prior to 2010. The model estimates for treatment initiations peaked earlier than the ETR data, for both males and females, and it overestimated the treatment initiations in males. This may be because, in earlier years, there was greater under-reporting in the ETR data. Lastly, this analysis only focussed on the past impact of interventions implemented in South Africa. Thus, we did not explore the potential impact of new interventions or improvement to current interventions.

To our knowledge, this is the first comprehensive retrospective assessment of the impact of HIV and multiple tuberculosis interventions on the South African tuberculosis burden at a national level. This study demonstrated the tremendous effect HIV has had on tuberculosis incidence and mortality; but even in the HIV-negative population, the tuberculosis incidence remains unacceptably high. The South African tuberculosis programme has made notable efforts that have led to a significant reduction in tuberculosis incidence and mortality. Further modelling studies are needed to identify the changes to current programmes that are required to accelerate these reductions in future.

Chapter 5. Drivers of sex differences in the South African adult tuberculosis incidence and mortality, 1990-2019

Mmamapudi Kubjane, Morna Cornell, Muhammad Osman, Andrew Boulle, Leigh F Johnson. Drivers of sex differences in the South African adult tuberculosis incidence and mortality, 1990-2019.

Publication status: Submitted to Scientific Reports; preprint link DOI:10.21203/rs.3.rs-1908771/v1).

Relevance of this manuscript to the thesis: The analysis in this manuscript addresses the second objective of this thesis.

Author contributions: MK, LJ and AB contributed to the study conceptualisation, analysis and interpretation of the results. LJ and MK wrote the code for the mathematical model. MC contributed to the interpretation of results. MO curated the electronic tuberculosis register data and contributed to interpretation of results. MK wrote the first draft and all authors critically reviewed versions of the manuscript and agreed on the final version to be submitted for publication.

5.1. Abstract

Background: Males have higher tuberculosis incidence and mortality rates than females driven by multiple factors. The objectives of this study were to assess 1) the impact of the HIV epidemic and ART rollout on the sex distribution of tuberculosis incidence and mortality; 2) estimate sex-specific tuberculosis incidence population attributable fractions (PAFs) for smoking, alcohol abuse, undernutrition, diabetes, and HIV; and 3) determine the influence of sex differences in tuberculosis health seeking, HIV testing and ART initiation, social mixing patterns, and tuberculosis treatment retention on tuberculosis incidence and mortality rates.

Methods: We developed an age-sex-stratified dynamic tuberculosis transmission model and calibrated it to South African data. We estimated male-to-female (M:F) tuberculosis incidence and mortality ratios, the effect of the abovementioned factors on the M:F ratios and PAFs for the tuberculosis risk factors.

Results: Between 1990 and 2019, M:F ratios for tuberculosis incidence and mortality remained above 1.0, reaching 1.70 and 1.65, respectively in 2019. In 2019, HIV contributed to more significant increases in tuberculosis incidence among females than males (54.5% vs 45.6%); however, females experienced more reductions due to ART than males (38.3% vs 17.5%). PAFs for tuberculosis incidence due to alcohol abuse, smoking, and undernutrition, in males, were 51.4%, 29.5%, and 16.1%, respectively, higher than in females (30.1%, 15.4%, and 10.7%, respectively); the PAF due to diabetes was higher in females than males (22.9% vs 17.5%). Lower health-seeking rates in males accounted for a 7% higher mortality rate in men.

Conclusion: The higher burden of tuberculosis in men highlights the need to improve men's access to routine screening and ensure earlier diagnosis. Sustained efforts in providing ART is critical in reducing HIV-associated tuberculosis. Additional interventions to reduce alcohol abuse and tobacco smoking are also needed.

5.2. Introduction

Globally, males experience higher tuberculosis incidence and mortality than females (3,7). The estimated male-to-female (M:F) tuberculosis incidence ratio varies by geographic region ranging between 1.1 and 2.5 (3). A meta-analysis of 39 prevalence surveys conducted in 28 countries estimated males to have 2.21 times higher tuberculosis prevalence than females (2). Sex disparities in the burden of tuberculosis are driven by multiple factors, including socio-behavioural and biological differences that directly or indirectly affect the risk of exposure to *Mycobacterium tuberculosis*, acquiring latent infection, or developing active disease (33). Biological hypotheses are that female sex hormones may protect against susceptibility to infection and the development of tuberculosis disease (86).

Males may be more exposed to additional risk factors for tuberculosis such as tobacco smoking and alcohol abuse (69,88,89). Other conditions that increase susceptibility to tuberculosis disease include HIV, diabetes and undernutrition (325,326). These risk factors increase the likelihood of developing tuberculosis by suppressing cell-mediated immunity (90,91) and explain a considerable amount of the global burden of tuberculosis at the population level (7).

HIV, the most potent tuberculosis risk factor, is also distributed differently by sex, with a heavier burden among females than males (348). However, compared to females, males are

less likely to get tested for HIV and have lower antiretroviral therapy (ART) initiation rates (349). In addition, several studies have shown that the age-sex distribution of tuberculosis reflects that of the HIV epidemic (24,350–352). However, limited studies have quantified the effect of the evolving HIV epidemic and the impact of the rollout of ART on the sex distribution of tuberculosis.

Several analyses have explored explanations for the excess burden of tuberculosis in men. Horton *et al*. showed that in Vietnam and Malawi, men had higher rates of tuberculosis incidence and longer delays to treatment (353). Other studies have suggested that the frequent social contacts men have with other men (85), combined with their higher rates of tuberculosis incidence (2), likely amplifies their burden of tuberculosis (83,354). The Global Burden of Disease Study (GBD) 2019 demonstrated the contribution of smoking, alcohol, and diabetes to sex disparities in tuberculosis mortality, showing that eliminating these risk factors would reduce the global tuberculosis mortality M:F ratios from 1.97 to 1.28 (7).

In South Africa, the male tuberculosis prevalence is approximately 1.6 times that in females (17). However, limited analyses have evaluated how modifiable risk factors explain sex disparities at a population level. Understanding the factors that drive sex disparities and the overall burden of tuberculosis is essential for identifying where tuberculosis control efforts need to focus. The specific objectives of this study were to 1) quantify the effect of the evolving HIV epidemic and the impact of the rollout of ART on the sex distribution of tuberculosis incidence and mortality over the period 1990-2019; 2) estimate the sex-specific PAFs for undernutrition, smoking, alcohol, diabetes and HIV (2019); 3) to estimate the impact of sex differentials in a) tuberculosis health seeking b) HIV testing and ART initiation, c) social mixing patterns and d) tuberculosis treatment retention differentials.

5.3. Methods

5.3.1. The tuberculosis model structure

We developed an age-sex-stratified deterministic compartmental model of the tuberculosis and HIV epidemics for the South African adult population (aged 15+ years). The core tuberculosis states were modelled following conventions described by previous studies (353). The risk of infection depends on the mean contact rates, proportions of contacts in each age and sex group (219), the probability of transmission per contact, and the prevalence of

infectious tuberculosis. Transitions between states include tuberculosis infection, progression to tuberculosis disease, natural recovery, diagnosis and treatment initiation, death, and treatment cure (Table 5-1). Following cure by tuberculosis treatment, two post-treatment states are defined: short-term (within six months after cure) and long-term (six or more months after cure). In both states, individuals are at risk of reinfection, whereas in the short-term post-treatment state, individuals are at a greater risk of recurrent TB due to relapse (315).

Table 5-1: Key model parameters

Parameter description	Mean	Standard deviation	Varied / fixed	Section described in supplementary^
The proportion of incident TB cases in HIV-negative adults that were smear-positive	0.51		Fixed	3
TB transmission probability per contact per day (if an infectious individual was smear-positive)	0.0025	0.0025	Varied	4
The annual rate of reactivation in HIV-negative individuals	0.00148		Fixed	5
The proportion of individuals experiencing fast progression	0.112		Fixed	5
Relative rate of TB incidence in previously infected individuals (HIV-negative)	0.79		Fixed	5
Relative rate of immunity to TB per 100-cell increase in CD4	1.1		Fixed	5
Relative rate TB incidence per 100-cell increase in CD4	0.703		Fixed	5
Annual recovery rate in smear-positive TB, HIV-negative individuals	0.075		Fixed	5
Annual recovery rate in smear-negative TB, HIV-negative individuals	0.224		Fixed	5
Relative rate of infectivity: smear-negative compared to smear-positive	0.206		Fixed	5
Annual Smear-negative TB mortality rate (untreated)	0.049		Fixed	5
Annual Smear-positive TB mortality rate (untreated)	0.196		Fixed	5
Relative rate of TB incidence on ART (controlling for CD4)	0.81	0.05	Varied	5
Prevalence of cough >2 weeks duration in individuals with smear-negative TB	0.198		Fixed	6
Ratio of symptom prevalence in patients with smear-positive compared to smear-negative TB	3.03		Fixed	6
The annual rate of health-seeking in males with smear-negative TB	1.07		Fixed	6
The annual rate of health-seeking in males in the general population	1.0		Fixed	6
The annual rate of health-seeking in males due to TB-like symptoms	0.196		Fixed	6
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.271		Fixed	6
The proportion of smear-negative TB cases which ae treated empirically if they initially screened negative on a smear test	0.423		Fixed	6
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.031		Fixed	6
Relative rate empirical treatment if symptoms are not due to TB	0.0014		Fixed	6
Reduction in empiric treatment after a negative screen due to Xpert MTB/RIF	0.50		Fixed	6
Relative rate of health-seeking in women, compared to men	1.55	0.17	Varied	6
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	4.27		Fixed	6
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: initial§	11.10		Fixed	6

Parameter description	Mean	Standard deviation	Varied / fixed	Section described in supplementary^
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: final§	3.84		Fixed	6
Probability of cure if a patient dropped out before completing TB treatment	0.65		Fixed	7
Increase in TB mortality rate per 10-year increase in age	1.4	0.1	Varied	7
The annual mortality rate in HIV-negative individuals receiving TB treatment‖	0.192		Fixed	7
The relative rate of TB mortality per 50 cell increases in CD4 count if HIV+	0.87	0.05	Varied	7
Relative rate of TB mortality if on ART	0.55	0.08	Varied	7
Increase in TB risk if previously experienced TB	3.03		Fixed	8
Annual rate of relapse in short term post-treatment state	0.1		Fixed	8
Increase in TB incidence due to alcohol abuse	1.94†	0.65	Varied	10
Increase in TB incidence due to diabetes (HbA1c > 6.5%)	2.59†	0.83	Varied	10
Increase in TB risk if currently smoking	0.47†	0.39	Varied	10
Increase in TB risk per 10-year increase in the duration of smoking	0.38†	0.12	Varied	10
Increase in TB risk due to low BMI	0.8†	0.25	Varied	10

ART=antiretroviral therapy; BMI=body mass index; HbA1c= Glycated haemoglobin; TB=tuberculosis.
^Additional details and references on the parameter values are provided in the supplementary material / Chapter 3. ‖Applies to when most people get treated in the very advanced stages of disease (i.e., when screening rates are very low, close to zero). †A value of 2.59, for example, is equivalent to an RR of 3.59 when comparing individuals with the exposure to individuals in the baseline category. Similarly, a value of 0.39 is equivalent to an RR of 1.39 when comparing individuals with the exposure to individuals in the baseline category. §This is a time-varying parameter. The initial rate applies up to 2005 (initial), then we estimate a rate that applies from 2012 with linear interpolation over the intervening years (ultimate).

The tuberculosis model was integrated within the Thembisa HIV model (337). The model is also age-sex-stratified, and the HIV epidemic is simulated dynamically from 1985. HIV-positive sub-populations are further stratified by HIV testing history, CD4 count, and duration since ART initiation. This model also captures changes in the ART guidelines over time and is calibrated to South African HIV data (337). HIV is assumed to affect the tuberculosis natural history parameters. These HIV effects are modelled as relative risks, depending on CD4 count and receipt of ART.

To capture age and sex differences in tuberculosis incidence, we applied the cumulative multiplicative effect of selected risk factors (alcohol abuse, smoking, undernutrition, and poorly controlled diabetes) to rates of progression to tuberculosis disease. We defined undernutrition as having a body mass index (BMI) <18.5kg/m² (112), smoking as those currently smoking tobacco products and accounted for the effects of current smoking and duration of smoking (327), alcohol abuse as consuming at least 40g of alcohol on a single day (69), and diabetes as having HbA1c >6.5% or Fasting Blood Glucose >120mg/dl (112).

These risk factors were selected based on evidence for their effect on developing tuberculosis disease and data reflecting their relatively high prevalence in South Africa (Chapter 3). We obtained the age-sex-stratified prevalence of these risk factors from surveys (89,112). Estimates for the relative effect of these risk factors were obtained from published studies (69,90,325–327) and were varied in the calibration process to account for uncertainty around them.

The assumed health-seeking patterns in the model were based on South African studies. We assumed different health facility attendance rates for individuals: 1) with tuberculosis, attending health facilities due to tuberculosis-related symptoms; 2) without tuberculosis, attending due to other health conditions; and 3) without tuberculosis, attending due to tuberculosis-like symptoms. In addition, we assumed that females were more likely to seek care than males (2), HIV-positive individuals had higher health-seeking rates than HIV-negative individuals (216), and smear-positive individuals experienced more tuberculosis symptoms than smear-negative individuals (270). We also modelled the specificity and sensitivity of the diagnostic algorithm implemented in the model.

Once individuals start the six-month tuberculosis treatment course, the following outcomes were considered: cure, failure, discontinuation, and death. Males were assumed to have higher treatment discontinuation rates than females. Although the base rates of tuberculosis mortality on treatment were initially set the same in males and females, these base rates were adjusted to reflect sex differences in health-seeking patterns. We based treatment outcome assumptions on the electronic tuberculosis treatment register (ETR.net) (Chapter 3) (28).

5.3.2. Calibration

We used a Bayesian approach to calibrate the model. Prior distributions were set to represent uncertainty in key model parameters (Table 5-1), and other parameters were fixed at values estimated in earlier model calibrations (Chapter 3) (355). The main data sources used as calibration targets included sex-stratified recorded numbers of tuberculosis deaths from the vital register for 1997–2016; the ETR for sex-stratified numbers of people initiating drug-susceptible tuberculosis treatment (2004–2016), deaths on treatment (2004–2016), and HIV prevalence in treated tuberculosis patients (2008–2016). We also relied on the National Institute for Communicable Diseases for the number of microbiological tests performed (2004–2012) (24). Lastly, we also used the active tuberculosis prevalence data (2018) (17).

For the calibration process, likelihood functions were defined to represent the goodness of fit to these calibration targets, allowing for possible under- or over-reporting in the vital register and the ETR data. We simulated posterior distributions numerically using Incremental Mixture Importance Sampling. Importance sampling was used to draw a sample of parameter combinations from regions of the parameter space that yielded the highest likelihood values to generate posterior estimates (336). The means for the model estimates were calculated from 1000 posterior samples, and 95% confidence intervals were calculated by taking the 2.5^{th} and 97.5^{th} percentiles of the posterior sample (Chapter 3).

5.3.3. Model experiments and outcomes

We estimated M:F ratios for tuberculosis incidence and mortality using the model-estimated rates of new tuberculosis cases and deaths under the baseline scenario (A), representing the actual tuberculosis and HIV epidemic up to 2019, incorporating sex differences. To assess the effect of a specific factor on tuberculosis incidence and mortality and the M:F ratios, we ran individual counterfactual scenarios (B1-11) where each factor was excluded or set equal in males and females in the model, and then compared the model outputs to the outputs obtained in the baseline scenario (A) (Table 5-2).

Table 5-2: Model scenarios to quantify the extent to which various factors contribute to sex differences in tuberculosis

Model scenarios	Description
Baseline scenario (A)	Baseline scenario which represents the actual tuberculosis and HIV epidemic up to 2019, incorporating sex differences.
Counterfactual scenarios (B)	
1. No HIV epidemic	HIV transmission probabilities were set to zero
2. No ART	Annual rates of ART initiations are set to zero
3. Equal ART uptake	Annual HIV testing and ART initiation rates in males and females to be the same
4. No smoking	Prevalence of smoking is zero
5. No alcohol abuse	Prevalence of alcohol assumption is zero
6. No undernutrition	Prevalence of undernutrition is zero
7. No diabetes	Prevalence of diabetes is zero
8. Equal health seeking	Health seeking rates for females are set the same as for males.
9. Equal social mixing	Contact rates and social mixing parameters are set as the average of the baseline male and female parameters
10. Equal treatment discontinuation	Treatment discontinuation in males set the same as for females.
11. All effects equal	Assume no HIV epidemic and all the other parameters for the factors above are set the same for males and females.

ART=antiretroviral therapy; TB=tuberculosis.

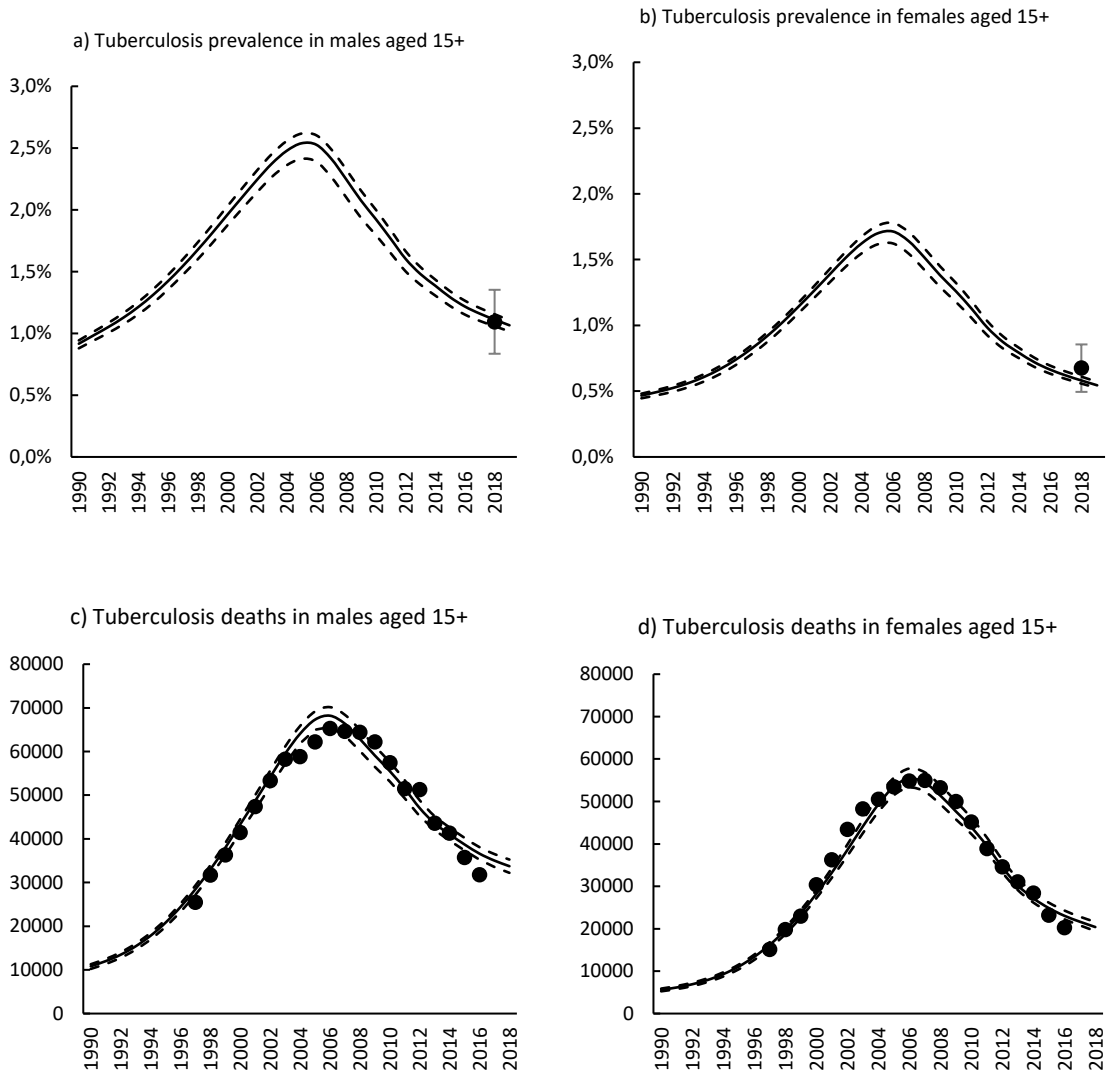
We also calculated sex-stratified percentage increases in tuberculosis incidence and mortality due to HIV; percentage decreases in tuberculosis incidence and mortality due to ART; and tuberculosis incidence PAFs due to smoking, alcohol abuse, undernutrition, diabetes, and HIV. Lastly, we calculated percentage changes in M:F ratios for tuberculosis incidence and mortality under the baseline compared to all counterfactual scenarios.

5.4. Results

Overall, the model estimates for tuberculosis prevalence and mortality were consistent with the sex-stratified observed data, with a higher burden in males than females (Figure 5-1 a-d). Tuberculosis prevalence and deaths rose rapidly during the early 1990s, peaked in the mid-2000s to late-2000s, and subsequently declined until 2019. The 2019 estimated tuberculosis prevalence in males was 1.06% (95% CI 1.0–1.12%) and 0.58% (95% CI 0.56–0.62%) in females. Tuberculosis deaths in 2019 were 32 000 (95% CI 29 000–35 000) in males and 21 000 (95% CI 19 000–22 000) in females.

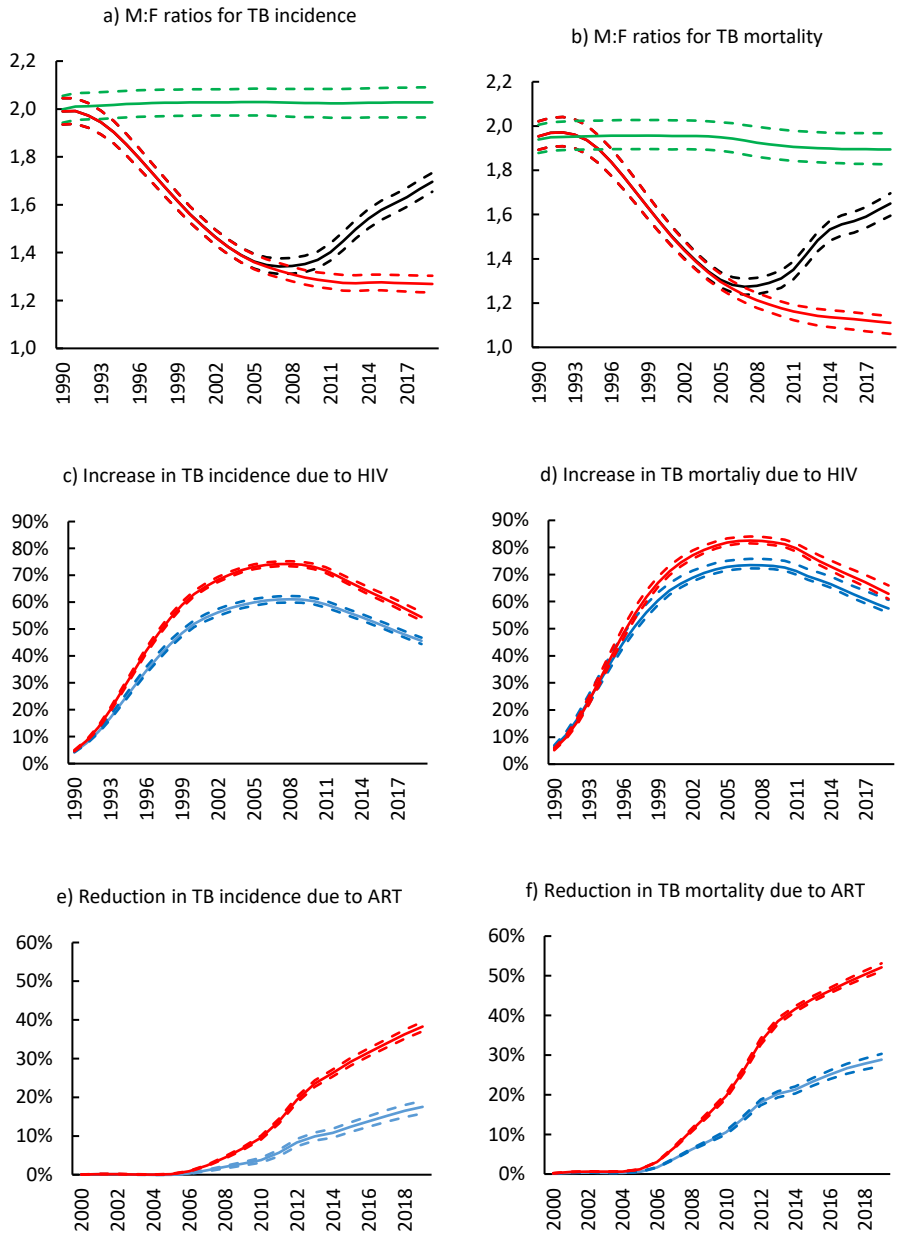
Over the 1990–2019 period, the M:F ratios for tuberculosis mortality and incidence were consistently greater than 1.0. The M:F ratios for tuberculosis incidence and deaths were the highest in the early 1990s (Figure 5-2 a and b, black); if HIV had not been present in South Africa, the M:F ratios would have remained consistently high (Figure 5-2 a and b, green). As the HIV epidemic rapidly grew in the South African population, tuberculosis mortality and incidence for both sexes increased (1996–2002). However, females had a more substantial increase in tuberculosis incidence and mortality due to HIV than males (Figure 5-2 e and f). Consequently, the M:F ratios for tuberculosis incidence and mortality declined and reached their lowest points in the mid-2000s to late-2000s (Figure 5-2 a and b, black).

Figure 5-1: Sex-specific tuberculosis prevalence and mortality in adults, 1990–2019



Solid black lines in (a) and (b) represent model estimates for tuberculosis prevalence in males and females, respectively. Black dots represent the 2018 TB prevalence with 95% confidence intervals. Solid black lines in (c) and (d) represent model estimates for tuberculosis mortality in males and females, respectively. Black dots represent recorded mortality, adjusted for the cause of death misclassification and missing fields. All dashed lines represent 95% confidence intervals.

Figure 5-2: The effect of HIV and ART on male-to-female (M:F) ratios for tuberculosis incidence and mortality, 1990–2019



First row: M:F ratios for tuberculosis incidence (a) and mortality (b) (1990–2019). The solid black lines represent the baseline scenario where the effects of HIV and the rollout of ART from the year 2000 were present in the model. The solid green lines represent the counterfactual scenario where HIV was absent from the model. The solid red lines represent the counterfactual scenario where HIV was present, but ART was not introduced. Second row: Percentage increase in tuberculosis incidence (c) and mortality (d) due to HIV. The solid red lines represent female tuberculosis incidence and mortality, and the solid blue lines represent males. Third bottom row: Percentage reduction in tuberculosis incidence (e) and mortality (f) due to ART. All dashed lines represent 95% confidence intervals. ART=antiretroviral therapy; TB=tuberculosis.

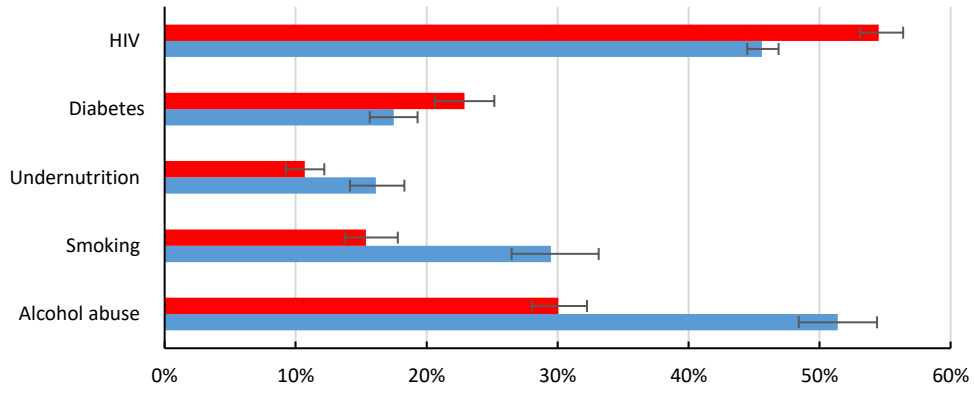
If ART had not been rolled out in South Africa, the M:F ratio for tuberculosis incidence and mortality would have continued to decline (Figure 5-2 a and b, red). However, with the

expansion of ART from the mid-2000s, the M:F ratios increased, reaching 1.70 (95% CI 1.65–1.73) for incidence and 1.65 (95% CI 1.59–1.70) for mortality in 2019.

Over time, HIV led to a greater relative increase in tuberculosis incidence and mortality in females than males. In 2019, HIV contributed to a 54.0% (95% CI 53.1–56.4%) and 62.9% (95% CI 60.9–66.0%) increase in female tuberculosis incidence and mortality, respectively (Figure 5-2 c and d, red). Among males, HIV led to a 45.6% (95% CI 44.5–46.1%) increase in tuberculosis incidence and a 57.4% (95% CI 55.8–60.7%) increase in tuberculosis mortality (Figure 5-2 c and d; blue). However, females benefited more from ART than males. In 2019, ART resulted in 38.3% (95% CI 37.1–39.5%) and 52.1% (95% CI 51.2–53.1%) reductions in tuberculosis incidence and mortality among females, respectively in 2019 (Figure 5-2 e and f, red). For males, ART led to 17.5% (95% CI 15.8–19.1%) and 28.8% (95% CI 27.3–30.3%) reductions in tuberculosis incidence and mortality, respectively, in 2019 (Figure 5-2 e and f, blue).

The PAFs of tuberculosis incidence due to alcohol abuse, smoking, and undernutrition were higher in males than females, estimated at 51.4% (95% CI 48.4–54.4%), 29.5% (95% CI 26.5–33.1%) and 16.1% (95% CI 14.1–18.3%) respectively among males in 2019 (Figure 5-3); among females, the estimated PAFs were 30.1% (95% CI 28.0–32.2%), 15.4% (95% CI 13.8–17.8%) and 10.7% (95% CI 9.3–12.2%) respectively. On the other hand, the PAFs of tuberculosis incidence due to diabetes and HIV were higher in females (22.9% (95% CI 20.6–25.2%) and 54.5% (95% CI 53.1–56.4%) respectively) than in males (diabetes: 17.5% (95% CI 15.7–19.3%) and HIV: 45.6% (95% CI 44.5–46.9%).

Figure 5-3: Population attributable fractions for tuberculosis incidence in 2019 due to alcohol abuse, smoking, undernutrition, diabetes, and HIV



The red bars represent females, and the blue bars represent males.

In the counterfactual scenario where HIV was assumed absent, and all other factors' effects were set equal for males and females, the tuberculosis incidence M:F ratio reduced from 1.7 to 1.01, relative to the baseline scenario (40.7% reduction); for mortality, the M:F ratio reduced from 1.65 to 0.93, (43.6% reduction) (Table 5-3). In the counterfactual scenario where we assumed equal annual rates of HIV testing and ART initiation in males and females, the tuberculosis incidence and mortality M:F ratios reduced by 3.4% and 8.2%, respectively. When we assumed no ART, the tuberculosis incidence and mortality M:F ratios reduced by 25.1% and 32.7%, respectively. In the individual counterfactual scenarios where alcohol abuse, smoking and undernutrition were excluded, the tuberculosis incidence M:F ratios reduced by 30.5%, 16.8% and 6.1%, respectively. On the other hand, excluding HIV and diabetes led to 19.6% and 7.0% increases in the M:F ratios, respectively.

Table 5-3: Male-to-female ratios for TB incidence and mortality in the baseline and counterfactual scenarios, 2019

	TB incidence M:F ratios (95% CI)	% change in M:F ratio, counterfactual vs baseline (95% CI)	TB mortality M:F ratios (95% CI)	% change in M:F ratio, counterfactual vs baseline (95% CI)
Baseline scenario	1.70 (1.65–1.73)		1.65 (1.59–1.66)	
Counterfactual scenarios				
1. No HIV epidemic	2.03 (1.20–2.10)	↑ 19.6 (17.5–21.8)	1.89 (1.83 - 1.97)	↑ 14.8 (12.3–17. 5)
2. No ART	1.27 (1.23–1.30)	↓ 25.1 (24.4–26.1)	1.11 (1.06 - 1.14)	↓ 32.7 (31.5–34.1)
3. Equal ART uptake	1.64 (1.46–1.68)	↓ 3.4 (2.9 –3.9)	1.52 (1.46 - 1.56)	↓ 8.2 (7.6–8.7)
4. No smoking	1.41 (1.37–1.45)	↓ 16.8 (14.7–18.6)	1.36 (1.31 - 1.40)	↓ 17.9 (15.9–20.0)
5. No alcohol abuse	1.18 (1.14–1.22)	↓ 30.5 (28.2–32.7)	1.08 (1.04 - 1.11)	↓ 34.8 (32.7–36.8)
6. No undernutrition	1.59 (1.55–1.63)	↓ 6.1 (5.3–7.0)	1.56 (1.52 - 1.61)	↓ 5.4 (4.6–6.2)
7. No diabetes	1.81 (1.77–1.86)	↑ 7.0 (6.2–7.8)	1.80 (1.74 - 1.85)	↑ 8.9 (7.8–9.9)
8. Equal health seeking	1.75 (1.70–1.78)	↑ 2.9 (2.5–3.4)	1.52 (1.48 - 1.56)	↓ 7.7 (6.8–8.9)
9. Equal social mixing	1.75 (1.70 –1.79)	↑ 3.3 (3.02–3.6)	1.70 (1.64 - 1.75)	↑ 2.9 (2.7–3.2)
10. Equal treatment discontinuation	1.70 (1.65–1.73)	↑ 0.015 (0.004–0.026)	1.66 (1.60 - 1.70)	↑ 0.45 (0.42–0.48)
11. All effects equal[(a)]	1.01 (1.00–1.01)	↓ 40.7 (39.1–42.0)	0.93 (0.92 - 0.94)	↓ 43.6 (41.7–45.2)

ART=antiretroviral therapy. CI=confidence interval. M:F ratio=male-to-female ratio. ↓=decrease. ↑=increase. Under the baseline scenario, all factors were included in the model. Individual counterfactual scenarios were simulated with the exclusion of specific factors (HIV, alcohol, smoking, undernutrition, and diabetes). (3): equal ART scenario = annual rates of HIV testing and ART initiation in males and females are set the same; (8): health-seeking rates for females set the same as for males; (9): contact rates and social mixing parameters set to be the average of the baseline male and female contact rates; (10): rates of treatment discontinuation in males set to be the same as for females. Under the counterfactual scenarios (11): 'All effects equal'= HIV epidemic assumed absent and all the other parameters for the factors above were set the same for males and females, with no effects of alcohol, smoking, undernutrition, and diabetes on TB.

The counterfactual scenario for health-seeking patterns (equal male and female rates) led to a 7.7% decrease in the M:F ratio for TB mortality. When social contact rates were the same in males and females, the M:F ratios for tuberculosis incidence and mortality slightly increased

by 3%. Lastly, in the treatment discontinuation counterfactual scenario (male discontinuation rate set at the same value as female rate), there were minor changes in the M:F ratios for tuberculosis incidence and mortality.

5.5. Discussion

Our model suggests that despite variations in the M:F ratios for tuberculosis incidence and mortality over the 1990–2019 period, overall tuberculosis mortality and incidence were consistently higher in males than females. The higher tuberculosis incidence in males may partly be explained by alcohol abuse and smoking, which are highly prevalent in males and increase the risk of developing tuberculosis through weakening cell-mediated immunity (90,91). Low ART uptake among males compared to females also explains the excess burden of tuberculosis in males. ART substantially reduced the contribution of HIV to tuberculosis incidence in both sexes; however, higher levels of HIV testing and ART initiation among females compared to males (356) led to females experiencing greater relative reductions in tuberculosis due to ART than males. We also showed that health-seeking delays explain the higher mortality among males, while sex differences in social mixing patterns and treatment discontinuation had minor effects on sex disparities in tuberculosis.

In our model, HIV increased tuberculosis incidence and mortality among females by more in than males due to the higher HIV prevalence in females (348). Consequently, the M:F ratios for tuberculosis incidence and mortality declined during the mid-1990s to early 2000s as HIV rapidly increased. However, the expansion of the ART program substantially reduced tuberculosis incidence and mortality, and the higher levels of ART coverage in women compared to men (356) have meant that male tuberculosis rates have not declined to the same extent as those in women. These findings are consistent with other studies demonstrating that although HIV prevalence was higher among females, males still had a higher burden of tuberculosis than females (24,351). Hermans and colleagues showed that HIV led to substantial relative increases in tuberculosis notification rates among females than males between 1993 and 2013; the scale-up of ART led to substantial declines in females' relative tuberculosis notification rates compared to males (351). Altogether, the modelled HIV and ART effects on the sex distribution of tuberculosis support the hypothesis that if HIV removed the protection females have against tuberculosis disease (86), then ART restored this protection (351).

In contrast with our tuberculosis incidence estimates for 2019, the GBD study estimated higher tuberculosis incidence in females than males for South Africa (7). This disparity was attributed to the higher burden of HIV in females than in males (7,348). Differences in methodological approaches and data sources may explain these discrepancies between our estimates and those by the GBD. For instance, the GBD used meta-regression models and relied on mortality data to estimate tuberculosis incidence from mortality-incidence ratios (7). In contrast, we used a dynamic transmission model which accounts for the tuberculosis natural history, impact of HIV and interventions.

Nonetheless, our tuberculosis mortality estimates were consistent with the GBD estimates, with higher mortality in males than females. The GBD suggested that the excess tuberculosis mortality in males was mainly due to alcohol abuse and smoking among HIV-negative individuals (7). We also found alcohol and smoking to be important contributors to the overall tuberculosis incidence and sex differences. Tuberculosis incidence PAFs due to smoking and alcohol abuse were higher in males than females, and we demonstrated that if smoking or alcohol abuse were removed individually, M:F ratios for tuberculosis incidence would reduce by approximately 17% or 30%, respectively. This reflects the increased exposure males have to these risk factors, which are also likely to increase the progression to tuberculosis disease (90,91). On the other hand, because HIV and diabetes are relatively more prevalent in females than males, females had higher PAFs for HIV and diabetes.

In the counterfactual scenario where males' health-seeking rates were increased and set equal to female health-seeking rates, the overall tuberculosis incidence and mortality declined slightly. This counterfactual scenario was associated with a 7% reduction in the M:F ratio for tuberculosis mortality, suggesting that delayed diagnosis and treatment in males may lead to tuberculosis disease severity and death (357). Supporting these findings, other studies suggested that compared to females, males are older and sicker when they seek health care (2); they are more likely to be lost to follow-up and experience poor outcomes, including treatment failure and death (38,353,357). The health-seeking delays in men may be explained by socioeconomic reasons such as the higher rates of employment in men and associated loss of income due to time lost while seeking tuberculosis health care (38).

The assumed social mixing counterfactual scenario modestly influenced the tuberculosis incidence and mortality M:F ratios. In this scenario, social mixing proportions and contact rates were the same in men and women. The model estimated slight increases in tuberculosis

incidence and mortality in females and declines in males, and the M:F ratios increased moderately. This is due to the higher contact rates in women that we assumed in the baseline scenario. However, in other studies where the social mixing patterns were assumed to be highly sex-assortative, sex disparities in tuberculosis increased (85,354). This was mainly due to men having higher rates of social contact with other men who carry a higher tuberculosis prevalence and therefore further increasing the risk of transmission and the burden of tuberculosis among men (85,354).

Our model suggests that removing an individual risk factor or equalising males' and females' health-seeking patterns, social contacts, or treatment outcomes at the current levels is insufficient to eliminate sex disparities. However, assuming the HIV epidemic was absent and all the other factors in males and females were the same, the tuberculosis incidence M:F ratios were reduced to 1.01. For mortality, the M:F ratio reduced to 0.93 (i.e., higher mortality in females). This is because females' 'background' mortality (deaths not related to HIV and tuberculosis, e.g., due to violence) is much lower than in males (28,358); and therefore, more females survive to older ages than males. In our model we assumed tuberculosis mortality rates increase with age (Table 5-1), people in older age groups (55+ years) contribute disproportionately to tuberculosis mortality, and the majority are likely females. The lower female background mortality rates may also explain why in females compared to males, tuberculosis mortality may appear higher relative to background mortality (28), although their absolute tuberculosis mortality risk is low.

Our analysis is strengthened by using a tuberculosis and HIV transmission model calibrated to several South African data sources. This dynamic model allowed us to quantify how HIV and ART affected the sex distribution of tuberculosis incidence and mortality over the 1990–2019 period. However, our study has several limitations. First, we did not include all the factors that may drive sex differences in tuberculosis, such as differences in biological susceptibility to tuberculosis disease (86), occupational exposures such as mining, or incarceration (72,359). Additionally, the results on assessing the effect of the multiple factors we explored on M:F ratios should not be taken as evidence that they fully explain changes in the magnitude of M:F ratios as they are dependent on the model assumption. Second, we did not dynamically model alcohol, smoking, undernutrition and diabetes; their effects depended on their prevalence in the population, with most of the prevalence estimates calculated from 2016 data (89,112). The prevalence of these risk factors may have changed over time.

Hence, the estimated PAFs (for 2019) may not accurately represent the historical effect of these risk factors on tuberculosis incidence. For instance, the prevalence of smoking has been on a declining trend (360), and diabetes has risen over time (361). Lastly, it is unclear whether these risk factors affect tuberculosis transmission, the incidence of tuberculosis disease or mortality. However, for simplicity, we have modelled only the effect of these risk factors on tuberculosis incidence.

In summary, males have consistently had higher tuberculosis incidence and mortality than females. The excess tuberculosis incidence and mortality in males highlights the need to make health services more accessible to males and address the structural barriers to their retention in tuberculosis and HIV care. Additionally, there is a need for effective interventions that reduce excessive alcohol consumption and tobacco smoking.

Chapter 6. Estimating the impact of improving tuberculosis programmatic interventions in South Africa, 2023-2030

Mmamapudi Kubjane, Erika Mohr-Holland, Andrew Boulle, Leigh F. Johnson. Estimating the impact of improving tuberculosis programmatic interventions in South Africa, 2023-2030.

Publication status: In preparation.

Relevance of this manuscript to the thesis: The analysis in this manuscript addresses the third objective of this thesis.

Author contributions: MK, LJ and AB contributed to the study conceptualisation, analysis, and interpretation of the results. LJ and MK wrote the code for the mathematical model. LJ and AB were the study supervisors. EM gave insights on implemented TB programmatic interventions and interpretation of the results. MK wrote the first draft, and all authors critically reviewed versions of the manuscript and agreed on the final version to be submitted for publication.

6.1. Abstract

Background: The Global End tuberculosis (TB) Strategy aims to achieve TB incidence and mortality reductions of 80% and 90%, respectively, by 2030 relative to 2015. This study sought to assess the impact of improving rates of health attendance and TB screening, improving linkage to TB care and retention, increasing preventative therapy uptake, and reducing antiretroviral therapy interruptions on TB incidence and mortality in South Africa.
Methods: We used an age-sex-stratified dynamic TB transmission model to estimate the impact of implementing improvements to existing interventions on TB incidence and mortality between 2023 and 2030.
Results: Between 2023 and 2030, we estimated that reductions in cumulative TB incidence and mortality due to all intervention improvements combined, compared to no changes in policy would be 21.7% (95% confidence interval (CI) 19.5–24.4%) and 33.1% (95% CI 31.5–35.1%), respectively. Improving screening would lead to the greatest reductions. By 2030 relative to 2015, combined interventions would reduce TB incidence by 43.5% (95% CI 41.3–45.2%) and mortality by 55.7% (95% CI 51.8–58.4%).

Conclusion: Improving existing interventions can potentially reduce the burden of TB in South Africa, with increased screening likely being the most impactful. Without further innovations and improvements to the current TB management approaches, the 2030 End TB milestones are unlikely to be met.

6.2. Background

Tuberculosis (TB) remains an important health problem in South Africa. In 2019, approximately 273 000 (95% confidence interval (CI) 261 000–288 000) persons (15+ years) developed TB disease and 52 000 (95% CI 50 000–55 000) died due to TB (355). While HIV is the main TB driver in South Africa (4,6), other contributing factors include under-diagnosis and incomplete treatment, which drive TB transmission and mortality (2,20). Recurrent TB is also a problem among individuals with a history of previous TB treatment (21,22). Additionally, risk factors such as undernutrition, alcohol misuse, tobacco smoking, and diabetes contribute substantially to the burden of TB (3,7).

South Africa has made considerable efforts to manage the TB epidemic by adopting and implementing global TB strategies through the National Strategic Plan (NSP) for HIV, TB, and Sexually Transmitted Infections (138). The NSP for 2016-2022 has also adopted the End TB Strategy, which aims to reduce the global TB incidence by 80% and global TB mortality by 90% by 2030 (relative to 2015 levels) (11). Additionally, the NSP has adopted the 90-90-90 targets of the Stop TB Partnership Global Plan to End TB (138). These targets aimed to ensure that by 2020 90% of all persons who need TB treatment or TB preventative therapy (TPT) are identified and provided with treatment as required; 90% of persons in high risk populations are diagnosed and initiated on the appropriate treatment; and lastly, that successful treatment is achieved for at least 90% of all persons diagnosed with TB (138). However, very few formal analyses have estimated and assessed South Africa's progress towards meeting these 90-90-90 TB targets.

In the context of HIV, the 90-90-90 targets aimed to ensure that by 2020, 90% of persons living with HIV (PLWHIV) were tested and knew their status; 90% of persons diagnosed with HIV received treatment; and that 90% of the individuals on treatment were virally suppressed (356). HIV epidemiological data and modelling analyses suggested that South Africa has met the first and third 90% targets but lags behind on the second target to ensure persons with HIV initiate and remain on antiretroviral therapy (ART) (356). These 90-90-90

HIV targets were recently updated to 95-95-95 by 2025 (362), and this progress in HIV care is also beneficial to the TB control programme.

Existing TB programmatic interventions have led to reductions in the burden of TB in South Africa. These interventions include a standard six-month TB treatment course, scaled-up microbiological testing, Xpert MTB/RIF roll-out to replace smear microscopy, TPT, and ART for persons with HIV (23,24). However, TB incidence and mortality remain high in the country. Additionally, the COVID-19 pandemic and COVID-19-related interventions caused disruptions to TB care-seeking patterns (3,13). Previous modelling studies have suggested that scaling up existing interventions can substantially reduce TB incidence and mortality (141,172,174,180,237) and may be cost-effective (178,181). However, it remains uncertain whether South Africa will meet the End TB goal.

Several reports, including the South African prevalence survey and our previous modelling analysis, have shown that men carry the greatest TB burden (17,363). Men are likely to have delayed diagnosis and treatment (2,353) and experience worse treatment outcomes than women (364). Additionally, men are tested for HIV and initiated on ART at a lower rate than women (349,356). Another group that experiences high TB morbidity and mortality is persons with a history of previous TB treatment (21,22). This group could be targeted for TPT, but the potential impact has not been assessed at a national level. Evaluating the impact of scaling up existing interventions and South Africa's potential to meet the End TB Strategy is vital for policymakers to decide where investment is required to achieve the greatest gains.

This study aimed to evaluate the impact of scaling up existing interventions on South African TB incidence and mortality and the potential to attain the 2030 End TB goals (132). The interventions considered in this study included improving rates of health attendance and TB screening, reducing initial loss to follow-up (ILTFU), reducing treatment discontinuation, increasing TPT for PLWHIV and persons previously treated for TB, and meeting the HIV 90-90-90 targets. Lastly, we aim to assess South Africa's progress towards the 90-90-90 TB targets.

6.3. Methods

6.3.1. The baseline model

We previously developed an age-sex-stratified compartmental model of TB and HIV for adults (15+ years) in South Africa. In the baseline model, we considered only interventions that were introduced up to 2018; these have been described previously (355). To this baseline model, we added the implementation of Xpert Ultra (from mid-2018) and the switch to a three-month isoniazid-rifapentine preventative therapy course (3HP) (from mid-2021). We also considered the effect of COVID-19-related disruptions on the rate of TB screening.

We briefly describe the TB transmission model here; further descriptions of the model and key parameters are provided elsewhere (355). We modelled movement between states, including TB infection, progression to TB disease, natural recovery, diagnosis and treatment initiation, death, and treatment cure (355). Age and sex differences in TB risk factors were captured by applying age-sex-specific relative risks to rates of progression to TB disease. Following cure by TB treatment, individuals move to post-treatment states – first, to short-term (≤ 6 months after cure); and then long-term (6+ months after cure) (355). In both states, individuals are at risk of reinfection, however, in the short-term state, individuals are also assumed to have a high chance of relapse (315). The risk of infection is a function of the mean contact rates, age-sex-mixing patterns (83), the probability of transmission per contact, and the prevalence of infectious TB.

The Thembisa HIV model – a compartmental model of the South African HIV epidemic designed to answer policy questions relating to HIV prevention and treatment (337) – forms the HIV component of the model. The model is age-sex-stratified, and the HIV is simulated from 1985. HIV-positive cohorts are further divided into HIV testing history, CD4 count, and duration since ART initiation categories. The model also captures changes in the ART guidelines over time and was fitted to multiple South African data (337). The HIV effects on the TB natural history are modelled as relative risks, which depend on CD4 count and duration since ART initiation.

We modelled the uptake of TPT for people with latent TB infection (LTBI) who are HIV-positive and eligible as per the prevailing guidelines at the time (317). The uptake of TPT depended on CD4 count and ART duration. Between 2010 and 2021, we modelled isoniazid

preventative therapy (IPT) use (described previously); from mid-2021, we modelled the use of the three-month isoniazid-rifapentine preventative therapy course (3HP). For the use of 3HP, we assume a treatment duration of 3 months and protection to last 12 months, (similar to the 12 month IPT) because there is no evidence suggesting that 3HP effectiveness is significantly different from IPT (365).

We considered smear microscopy and Xpert MTB/RIF as the main tools for diagnosing TB, accounting for the phased implementation of Xpert MTB/RIF from 2011; from 2018 onwards, we assumed the use of Xpert Ultra (287,366,367). For individuals on the 6-month TB treatment course, the possible outcomes include cure, failure, discontinuation, and death. These treatment outcome assumptions were based on the electronic TB treatment register (ETR) data for drug-susceptible TB, and have been described previously (28,355).

South African data suggested that COVID-19-related interventions that restricted movements have decreased Xpert Ultra testing (26,27). Therefore, to account for the effects of COVID-19-related disruptions on TB diagnosis, we assumed that between mid-2019 to mid-2020, screening rates dropped by 10%, and from mid-2020 to mid-2021, there was a 20% reduction in the rate of TB screening.

6.3.2. Calibration

The model was previously calibrated to South African data, including sex-stratified recorded numbers of TB deaths from the vital register, numbers of people initiating drug-susceptible TB treatment, deaths on treatment, HIV prevalence in persons treated for TB, the number of microbiological tests performed (24) and TB prevalence data (17). Since the calibration data related only to the period up to 2018, we did not re-calibrate the model in the current paper. To generate uncertainty ranges in this current analysis, we used the posterior distributions estimated in a previous calibration analysis (363).

6.3.3. Intervention scenarios

We focused on interventions that 1) increase the proportions of persons presumed to have TB who get screened at health facilities; 2) increase male TB health-seeking rates, HIV testing and ART initiation rates to be the same as those for females; 3) reduce ILTFU; 4) reduce treatment discontinuation; 5) increase the uptake of TPT in HIV-positive individuals, and 6)

provide TPT to previously treated persons with TB (Table 6-1). We also estimated the impact of meeting the 90-90-90 targets for HIV (scenario 7). Finally, in the last scenario (8), we included the combined effect of all interventions (1) to (7).

Table 6-1: Summary of the interventions implemented between 2023 and 2030

Interventions and targeted parameters	Examples of interventions activities
1) Double screening Double the proportion of persons tested among those presenting with TB symptoms to 0.4.	Screen all individuals visiting health care facilities; and encourage those with symptoms to be tested microbiologically (368).
2) Engage men in care Equalise male and female health facility attendance rates, HIV testing and ART initiation and ART interruptions rates.	Distribute self-testing kits to men through their pregnant partners (369); mobile HIV testing campaigns (370); peer-delivered U=U messaging to encourage men to test for HIV (371); introduce male ART clinics (372).
3) Halve initial loss to follow-up Improved linkage to care after diagnosis by halving initial loss to follow-up when Xpert is used to 0.047.	Trace or send reminders (i.e., via text messages) to persons who were screened and received a positive TB diagnosis to ensure treatment initiation (368,373)
4) Halve discontinuation Improved TB care and retention in care Halve annual treatment discontinuation rate in males to 0.151. Halve treatment discontinuation rate in females to 0.118.	Provide patients with support and reminders by health care workers to adhere to and complete treatment as required (368,373,374).
5) Double TPT in HIV+ Double the monthly rates of preventative therapy initiation in eligible persons with HIV to 0.024.	Nurse-centered interventions to promote TPT uptake to eligible patients attending health facilities and educate patients on TPT (375); give health facility managers leadership and management training to increase the uptake of up-to-date information and positive attitudes towards TPT, and improve health worker's skills to enable TPT use (376).
6) TPT post treatment Provide preventative therapy to 80% of persons who completed treatment.	
7) Reduce ART interruptions Meeting the HIV 90-90-90 targets in 2019. Targeting the second HIV indicator, as the first and third 90 are met (11): the annual rate of ART interruption (0.2318) is reduced by 80% to 0.046.	Text message appointment reminders and peer support (377,378).
8) All interventions The combined impact of all interventions.	

ART=antiretroviral therapy. ILTFU=initial loss to follow-up.TPT=tuberculosis preventative therapy, which is 3HP (isoniazid and rifapentine for three months).

6.3.4. Outcomes

The model estimated TB incidence and mortality rates for the baseline scenario (no changes to existing TB policy) and under each scenario (1 to 8). We then calculated the cumulative (2023-2030) TB incidence and mortality in each scenario and the percentage reductions by comparing the baseline and intervention scenarios (1 to 8). Lastly, we report on the progress towards meeting the TB 90-90-90 targets (8,379) as defined in Table 6-2: 90% of all persons who need TB treatment or TPT are identified and provided the treatment as required; 90% of persons in key populations are diagnosed and receive the appropriate treatment, and lastly, that there is treatment success for at least 90% of all persons diagnosed with TB (138).

Table 6-2: 90-90-90 TB target definitions

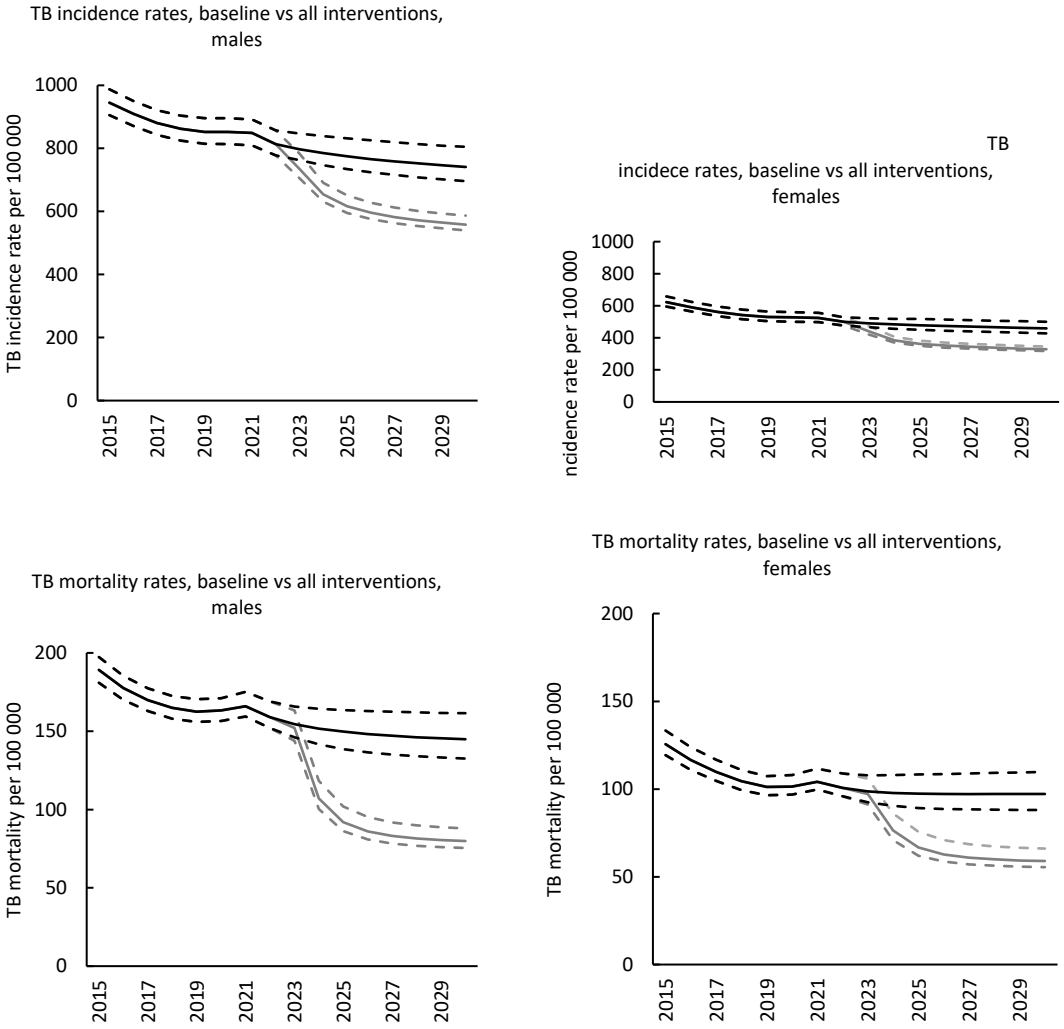
The 90-90-90 TB targets (as per WHO (8,379))	Definition in the model
Preventative therapy coverage 90% of all eligible persons (PLWHIV and child contacts) provided preventative therapy.	Ratio of the number of HIV-positive persons initiating preventative therapy to the number of PLWHIV starting ART and/or entering HIV care.
Case detection (90% of persons with TB are notified and treated)	Ratio of modelled persons newly treated for TB (excluding false positive TB) to estimated incident TB.
TB treatment success rates 90% of notified persons with TB are successfully treated (where treatment success is defined as a combination of cure and completion)	Ratio of number of persons completing treatment (net of deaths during treatment) to those who have started treatment (excluding false positive).

ART=antiretroviral therapy. LTBI=latent TB infection. People living with HIV=PLWHIV. TB=tuberculosis

6.4. Results

In the continuation of the baseline scenario (with no changes to current policy) (Figure 6-1, black), TB incidence and mortality rates are estimated to be on a gradual downward trend over 2015-2030, although with a slight reversal of the trend over 2020-2021 (due to COVID-19- related interruptions). Over time, the TB incidence and mortality rates were higher in males than females.

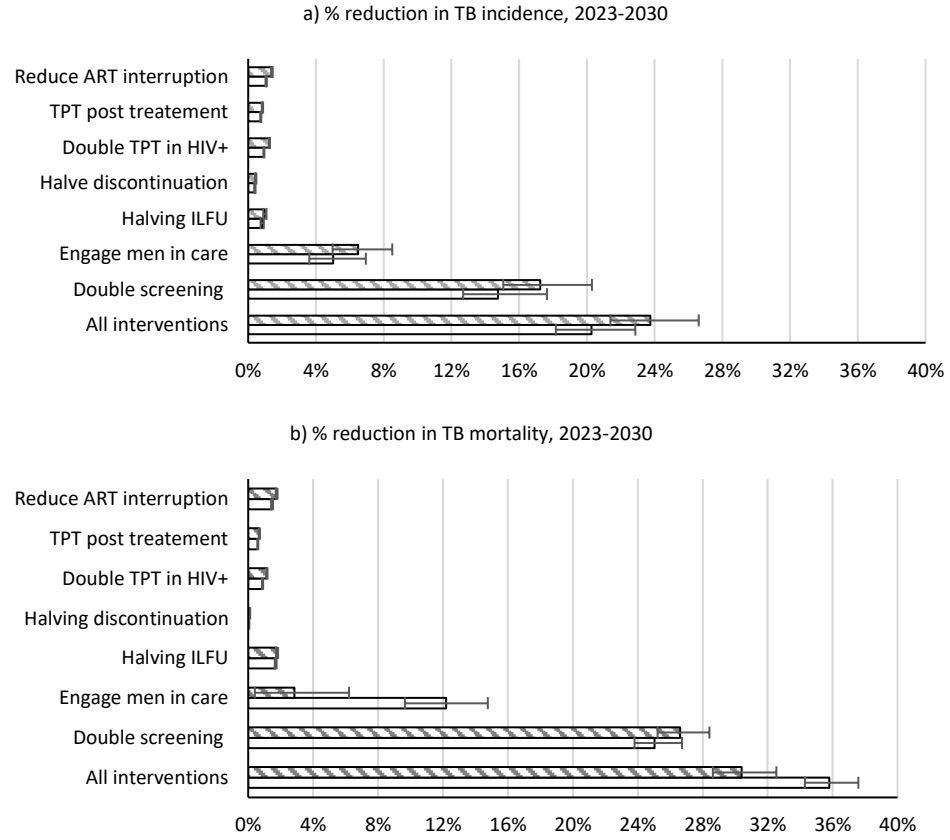
Figure 6-1: Tuberculosis incidence and mortality rates, 2015-2030, by sex



Black lines represent the continuation of the baseline scenario without any improvement to existing interventions. The grey lines represent the scenario with all intervention improvements combined. Dashed lines represent 95% confidence intervals.

Under the scenario with all intervention improvements combined, between 2023 and 2030, the overall cumulative TB incidence would be reduced by 21.7% (95% CI 19.5–24.4%), with a 20.3% (95% CI 18.2–22.9%) reduction in males and a 23.8% (95% CI 21.4–26.4%) reduction in females (Figure 6-2 a). The impact of doubling the proportion of individuals screened was higher in females than males, with estimated reductions in the cumulative TB incidence between 2023 and 2030 of 14.7% (95% CI 12.7–17.6%) in males and 17.2% (95% CI 15.1–20.3%) in females. Improving male engagement in care would contribute to TB incidence reductions of 5.0% (95% CI 3.6–6.9%) in males and 6.5% (95% CI 5.0–8.5%) in females.

Figure 6-2: Projected percentage reduction in cumulative tuberculosis incidence and mortality rates between 2023 and 2030, compared to the baseline scenario, by sex and intervention



Intervention improvements were assumed to be implemented from 2023 to 2030. The baseline represents a scenario where we assumed the continuation of the existing control programme interventions (with no improvements). Bars with grey shades represent females; unshaded bars represent males. ART=antiretroviral therapy. ILTFU=initial loss to follow-up.TPT=tuberculosis preventative therapy, which is 3HP (isoniazid and rifapentine for three months).

Interventions to improve retention in HIV and TB care also had relatively small impacts and showed a slightly higher impact in females than males. Reducing ART interruptions in HIV-positive individuals between 2023 and 2030 would reduce TB incidence by 1.06% (95% CI 1.02–1.10) in males and 1.41% (95% CI 1.35–1.45%) in females. On the other hand, halving ILTFU would contribute to TB incidence reductions of 0.82% (95% CI 0.73–0.92%) in males and 0.98% (95% CI 0.89–1.08%) in females. Halving treatment discontinuation would reduce the cumulative TB incidence between 2023 and 2030 by 0.39% (95% CI 0.36–0.44%) in males and 0.44% (95% CI 0.39–0.48%) in females.

Similarly, TPT would also have a slightly greater impact on females than males. Doubling the TPT provision to HIV-positive individuals with LTBI would contribute to TB incidence reductions of 0.93% (95% CI 0.9–0.96%) in males and 1.26% (95 CI 1.23–1.28%) in

females. Providing 80% of persons who have completed TB treatment with TPT would lead to TB incidence reductions of 0.75% (95 CI 0.72–0.77%) in males and 0.84% (95% CI 0.81–0.88%) in females.

Assuming improvements in all interventions combined would lead to overall TB mortality reductions of 33.1% (95% CI 31.5–35.1%) (35.8% (95% CI 34.3–37.6%) in males; 30.4% (95% CI 28.6–32.5%) in females). The higher impact in males is driven by improved male engagement in care (Figure 6-2 b). By itself, improved male engagement in care would lead to TB mortality reductions of 12.2% (95% CI 9.7–14.8%) in males and 2.8% (95% CI 0.4–6.2%) in females. Doubling TB screening would lead to greater TB mortality reductions: 25.0% (95% CI 23.8–26.7%) in males and 26.5% (95% CI 25.2–28.3%) in females.

Similar to impacts on TB incidence, all other interventions would have relatively modest impacts on mortality, with estimated TB mortality reductions of <2%. Reducing ART interruptions would reduce TB mortality by 1.47% (95% CI 1.41–1.53%) in males and 1.75% (95% CI 1.69–1.81%) in females. Improving linkage to care by halving ILTFU would contribute to TB mortality reductions of 1.70% (95% CI 1.64–1.76%) in males and 1.79% (95% CI 1.72–1.85%) in females (Figure 6-2 b). However, halving treatment discontinuation showed no significant positive impact on mortality. Doubling TPT provision to HIV-positive persons with LTBI could contribute to TB mortality reductions of 0.89% (95% CI 0.85–0.92%) in males and 1.16% (95% CI 1.13–1.19%) in females. Lastly, providing TPT to 80% of individuals who completed TB treatment would reduce TB mortality by 0.60% (95% CI 0.56–0.62%) in males and 0.69% (95% CI 0.65–0.72%) in females.

Between 2015 and 2020, the estimated reductions in TB incidence in males and females were 9.8% (95% CI 8.8–10.7%) and 15.4% (95% CI 14.1–16.4%), respectively (Table 6-3). For mortality, the reductions were 13.7% (95% CI 12.2–15.0%) and 19.3% (95% CI 17.6–20.7%) in males and females, respectively. In the continuation of the baseline scenario (with no improvements in TB programmatic interventions), the model suggested that the reduction in TB incidence rates between 2015 and 2030 would be 21.8% (95% CI 14.9–26.0) and 26.5% (95% CI 19.2–31.2%), among males and females respectively.

Table 6-3: Reductions in TB incidence and mortality rates compared to 2015

	Baseline 2020 vs 2015 % (95% CI)	Continuation of baseline 2030 vs 2015 % (95% CI)	All intervention improvements 2030 vs 2015 % (95% CI)
Tuberculosis incidence			
Male	9.8 (8.8 – 10.7)	21.6 (14.6 – 25.8)	40.9 (38.7 – 42.5)
Female	15.4 (14.1 – 16.4)	26.3 (18.9 – 31.31.0)	47.2 (44.9 – 48.9)
Total	12.1 (11.1 – 13.1)	23.5 (16.4 – 27.9)	43.5 (41.3 – 45.2)
Tuberculosis mortality			
Male	13.7 (12.2 – 15.0)	23.4 (12.3 – 30.0)	57.7 (54.1 – 60.2)
Female	19.3 (17.6 – 20.7)	22.5 (10.7 – 30.0)	53.0 (48.6 – 56.0)
Total	16.0 (14.4 – 17.4)	23.0 (11.6 – 30.0)	55.7 (51.8 – 58.4)

CI=confidence interval

For mortality, the reductions in 2030 relative to 2015 would be 24.0% (95% CI 13.0–30.5%) in males and 22.5 (95% CI 10.7–30.0%) in females. In the scenario with all intervention improvements combined, the reduction in TB incidence in 2030 relative to 2015 would be 40.9% (95% CI 38.7–42.5%) in males and 47.2% (95% CI 44.9–48.9%) in females; the mortality reduction in 2030, relative to 2015, would be 57.7% (95% CI 54.1–60.2%) in males and 53.0% (95% CI 48.6–50.0%) in females.

In 2022, the estimated TPT coverage was 0.31 (9% CI 0.31–0.32), the treatment coverage ratio was 0.86 (95% CI 0.82–0.91), and treatment success proportion was 0.79 (95% CI 78.9–79.4) and (Table 6-4). Under the continuation of the baseline scenario, without any improvement of interventions, the indicators in 2030 would be similar to 2022. However, if all the interventions were introduced, the indicators would improve substantially, with TPT coverage ratio in eligible HIV-positive individuals at 0.59 (95% CI 0.58–0.61), treatment coverage at 1.22 (95% CI 1.12–1.32), and TB treatment success at 0.869 (95% CI 0.863–0.872).

Table 6-4: Progress towards the 90-90-90 TB targets

The 90-90-90 TB targets	Baseline, 2022 (95% CI)	Baseline, 2030 (95% CI)	All interventions, 2030 (95% CI)
Preventative therapy coverage (LTBI treatment coverage, HIV+ adults only) Ratio of new TPT to new entrants to HIV care	0.31 (0.31 – 0.32)	0.30 (0.29 – 0.31)	0.59 (0.58 – 0.61)
Case detection ratio Ratio of persons with TB on treatment to incident TB	0.86 (0.82 – 0.91)	0.85 (0.8 – 0.98)	1.22 (1.12 – 1.32)
TB treatment success rates TB treatment completion proportion	0.792 (0.789–0.794)	0.790 (0.786 – 0.793)	0.869 (0.863 – 0.872)

CI=confidence interval; LTBI=latent TB infection.

6.5. Discussion

Our model suggests that improvements to the current TB programme would substantially reduce TB incidence and mortality by 2030. However, the estimated 44% incidence and 56% mortality reductions in 2030 relative to 2015 fall short of the End TB milestones to reduce TB incidence and mortality by 80% and 90%, respectively, by 2030 (1). Among the interventions we explored, increasing TB screening rates had the most potential to significantly reduce TB incidence and mortality, while all other interventions would have minimal impact. Our results further suggest that despite the higher burden of TB in men, most interventions would have a greater impact on females than males, highlighting the need for interventions to improve men's engagement in care.

Consistent with our results, previous modelling studies have also suggested that scaling up screening would be one of the most effective interventions in reducing the burden of TB in South Africa (174,180,190,237). Additionally, our earlier modelling analysis has shown that historically, increased microbiological testing, in addition to the provision of ART, explained most of the declines in the burden of TB in South Africa over the period 2005-2019 (355). Our results further suggest that increasing the proportion of persons screened may have a higher impact on females than males. These sex differences in impacts could be because we have assumed that females are more likely to seek TB care than their male counterparts (2). Thus, doubling the proportions of individuals screened further reduced transmission among women (due to assortative mixing) and led to more significant reductions in mortality among females.

The model also suggests that doubling the provision of TPT to persons with HIV in care and reducing ART interruptions would have a higher impact in females than males. These findings may be explained by the observation that females are more likely to be tested for HIV and initiate ART than males (356). As a result, the persons who have entered HIV care services would be more likely to benefit from these interventions. In addition, our previous analysis has also shown that compared to males, females experienced more significant reductions in TB incidence and mortality due to ART (363). These observations highlight the need to address the sex differences in accessing and engaging in TB and HIV care services. We further implemented an intervention scenario where we assumed the TB health facility attendance rates, HIV testing rates and ART initiations for males and females were equal. This scenario would lead to greater reductions in mortality among males (12% in males and

3% in females), suggesting that addressing men's barriers to care seeking would have a major impact on mortality.

Although there is evidence to support the individual-level effectiveness of TPT in preventing TB disease (324), our model suggests TPT would have a small population-level impact. This small impact of TPT may be due to the short duration of protection (170,231). Also, in the model we did not consider all other high-risk groups recommended to be provided with TPT such as childhood household contacts, health care workers, prisoner and mineworkers. Additionally, the coverage of preventative therapy is low in South Africa, and there is therefore a need for more efforts to reduce barriers for the implementation of TPT (233,375,380). More research should evaluate the effectiveness of interventions to improve and promote TPT uptake.

A previous modelling study projected that the provision of TPT combined with active case-finding in previously treated individuals in a community with a high burden of TB in the Western Cape would avert approximately 40% of persons with incident TB and 41% of TB deaths between 2016 and 2025 (184). A plausible reason for the difference between our projected impact and that reported in the Marx *et al.* study, is that they assumed that the TPT intervention was lifelong and that on average, a person will be on TPT for 6.6 years and remain protected over this period (184). We assumed that people on 3HP are only protected for approximately one year. In addition, Marx *et al.* considered the impact of increased active case finding as well as TPT but did not report the impact of TPT alone.

Our results also suggest that halving the rates of treatment discontinuation would have minimal impact on TB incidence and mortality. In the model, we assumed that most unrecorded deaths are incorrectly classified as treatment discontinuations (299). To account for this misclassification, we doubled the proportions of the deaths recorded in the ETR (355). Therefore, we are potentially overstating mortality rates in treated TB patients, and this might explain why we do not predict substantial reductions in mortality if patients are retained in TB treatment. In addition, our model assumes that some patients who discontinue treatment are nevertheless cured (298). Studies that have assessed the effectiveness of the interventions to increase retention in TB care (i.e., supporting patients and sending them text messages as reminders) have had mixed successes in improving retention (368,381). There is also limited empirical evidence regarding the effect of these treatment retention interventions on mortality. Therefore there is a need for more empirical studies to evaluate the

effectiveness of treatment retention interventions (368,382) and their impact on other endpoint outcomes such as mortality.

Similarly, we estimated that reducing ILTFU by 50% would lead to minimal (<2%) reductions in TB incidence and mortality. Law *et al*. reported that interventions such as tracing patients and sending reminders (i.e. via text messages) to patients attending an urban clinic in KwaZulu Natal could increase treatment initiations by approximately 10% (368). In our model, the baseline ILTFU was 9.4% and we assumed that in the intervention scenario ILTFU reduced to 4.7%, which translated to a 5.2% increase in the number of treatment initiations (slightly lower than the increases reported by Law *et al.* (368)). These increases in treatment initiations are nonetheless encouraging, and suggest investment in such interventions to improve linkage to care (368).

The global and South African TB trends have been declining; however, these declines have not been fast enough to reach the End TB milestones. In addition, South Africa's progress towards the 90-90-90 TB care and prevention targets is still lagging, particularly in providing TPT. Even before the emergence of the COVID-19 pandemic, the slow progress towards attaining the specified milestones was apparent (174,383). However, COVID-19 may have further slowed the decline. There is still limited data to inform mathematical models on the effects that the COVID-19 pandemic had on other aspects of TB, such as transmission and the TB natural history, and a limitation of our model is that we have only considered the effect of COVID-19 on rates of TB screening. Nonetheless, available data suggested that COVID-19-related interventions have led to interruptions in TB care – specifically resulting in declines in the number of TB tests performed (26). Consistent with the WHO estimates, we estimated that these COVID-19-related interruptions led to relatively constant TB incidence rates and slightly increased TB mortality rates between 2019 and 2020 (1).

There are several limitations to this analysis. First, we did not model any human or fiscal constraints associated with these intervention improvements; we note that the South African health system may be constrained to implement the highly optimistic intervention scenarios. For instance, increasing the proportion of individuals who get screened for TB or reducing ART interruptions would lead to increases in the numbers of Xpert Ultra tests performed or increase ART coverage (i.e., require more resources) (Appendix C). Also, previous studies have shown that increased screening interventions require intensive human resources (209). Also, we did not model other interventions such as active case finding, TPT for other high-

risk populations such as household contacts, targeted universal testing for TB, urine lipoarabinomannan test, or potential TB vaccines. Another limitation is that we did not model any interventions to address other TB risk factors (i.e., diabetes, alcohol use, and smoking), which contribute significantly to TB incidence and mortality (3,7). Another limitation is that we projected the model using calibration data up to 2018; therefore, there is uncertainty regarding recent TB trends. Altogether, within the context of these limitations and specified model assumptions, these projections are not definitive but are indications of which aspects of the current TB programme require the most attention to achieve significant future TB reductions.

Existing TB management interventions need to be complemented by innovative approaches to fast-track the progress towards ending TB. Some of the priorities needed to accelerate the progress would include the development of vaccines to reduce the risk of TB disease, new low-cost point-of-care diagnostic tools, and a shorter regimen for TB disease. In addition, it may also be worth addressing broader determinants of TB disease, such as diabetes, alcohol use and smoking; and socioeconomic barriers to better TB care and management such as lack of money and transport.

Chapter 7. Discussion

7.1. Overview

The research in this thesis focused on understanding the South African TB epidemiology using a mathematical model. This discussion chapter aims to highlight and discuss the methodological approach, key findings and their contribution to the body of research, implications for the policy and future research, and the strength and limitations.

7.2. Thesis aims

This research contributed to developing an age-sex-stratified TB transmission dynamic model to represent the South African TB epidemic at a population level. The model was used to address three specific objectives. The first objective (Chapter 4) was to quantify TB incidence and mortality attributable to HIV and to evaluate the past impact on TB incidence and mortality of programmatic interventions implemented in South Africa (DOTS, ART, intensified TB screening, IPT and the implementation of Xpert MTB/RIF as a first-line diagnostic tool). This first analysis was restricted to the years from 1990 to 2019.

To understand the sex distribution of TB and factors that drive sex differences in South African TB incidence and mortality, the second objective (Chapter 5) was to quantify the extent to which various factors contribute to sex differences in TB incidence and mortality. These factors included HIV, ART uptake, smoking, alcohol abuse, undernutrition, diabetes, health-seeking patterns, social contact rates and TB treatment discontinuation. Similarly, this analysis was restricted to the years 1990-2019.

Finally, the third objective (Chapter 6) was to estimate the future impact on TB incidence and mortality of interventions to increase TB screening, improve linkage to TB care and retention, increase preventative therapy, and reduce ART interruptions. The projection period for the study was from 2023, the assumed year of intervention implementation, to 2030, which marks the End TB milestone endpoint.

7.3. Methodological approach

Chapter 3 described the methodological approach to developing the model with detailed descriptions of the model parameterisation and data sources. This methodological chapter supports the three primary analyses (Chapter 4 to Chapter 6). To briefly summarise, the developed model is a deterministic model with components including transmission dynamics, diagnostic pathway, and effects of HIV. To dynamically model the impact of HIV and ART on TB incidence and mortality, the TB model was combined with the Thembisa model, a previously-developed South African HIV and demographic model. To capture age and sex differences in TB incidence, age- and sex-specific relative risks were applied to rates of progression to TB disease. The model also incorporated a diagnostic pathway representing health-seeking patterns and the sensitivity and specificity of the diagnostic algorithm. A Bayesian approach was used to calibrate the model to the numbers of people starting treatment from the electronic TB register (2004-16), deaths from the vital register (1997-2016), microbiological tests (2004-19), and the national TB prevalence survey (2018). This ensured that the model produced credible estimates representing the South African TB epidemic. The calibrated model addressed the three key study objectives in Chapter 4 to Chapter 6. The results of these three analyses are discussed in the following sections of this chapter.

7.4. Discussion of findings

7.4.1. South African tuberculosis incidence and mortality trends and the impact of HIV

Model results from the first analysis showed that tuberculosis incidence and mortality increased rapidly during the 1990s, peaking in the mid-to-late 2000s, followed by declining trends until 2019. The peaks of the TB epidemic reflected the rapidly growing and maturing HIV epidemic. This research quantified the contribution of HIV to the estimated TB burden. Of the estimated eight million new cases that developed between 1990 and 2019, half were attributable to HIV; of the two million deaths that occurred, two-thirds were attributable to HIV. The contribution of this analysis was quantitatively and dynamically demonstrating how the HIV epidemic affected the TB trajectory.

In running the counterfactual model scenarios, it was possible to estimate what the TB trajectory could have been without HIV. The model suggested that even in the absence of HIV, the TB burden would have been unacceptably high in South Africa. In 2019, there would have been approximately 102 000 new TB cases and 19 700 TB deaths, still making South Africa a high-burden country (25). Consistent with these findings, results from the South African TB prevalence survey have shown a high prevalence of TB in the HIV-negative population, with only 29% of TB patients with known HIV status being HIV-positive (384). This high burden of TB in the HIV-negative population highlights the need also to consider this group for interventions such as intensified screening. In addition, there is a need to address other divers of the TB epidemic such as smoking, alcohol abuse, diabetes and undernutrition. These TB risk factors were explored in the second analysis (Chapter 5).

7.4.2. Retrospective impact of South African TB programmes on tuberculosis incidence and mortality

Chapter 4 also gave a comprehensive assessment of the impact of the various interventions implemented by the South African TB programme from 1990 to 2019. The interventions explored in the analysis reflected the evolution of control strategies recommended by the global TB community and their respective implementation in the country. Among all these interventions examined (DOTS, IPT in eligible HIV-positive individuals, intensified TB screening, ART, Xpert MTB/RIF to replace smear microscopy), ART and intensified TB screening contributed the most to declines in TB incidence and mortality. Besides DOTS and IPT in HIV-positive individuals, all the other interventions had a more significant impact on TB mortality than on TB incidence.

i. *Intensive TB screening, 2004-2019*

An important contribution of this was quantifying the effect of South Africa's efforts in intensifying TB screening – with the observed doubling of the number of tests performed between 2004 and 2012 (24). Previous TB models for South Africa have not shown this past impact of intensified screening. Intensified screening activities are beneficial in reducing TB incidence and mortality because increased diagnosis is likely to lead to treatment initiations and a reduced transmission pool. In addition, prompt TB treatment initiation would reduce severe TB disease and death (357). In 2019, increased screening contributed to 28% and 38% reductions in incidence and mortality, respectively (355). These results affirm South Africa's

efforts to intensify TB screening, mainly over 2004-2012 (24) and reaffirm that finding TB cases is a crucial TB control intervention.

ii. *Antiretroviral therapy, 2000-2019*

Since the scale-up of ART in the mid-2000s (23,340), ART has substantially impacted TB incidence and mortality; leading to a 20.0% reduction in TB incidence and a 37.6% reduction in TB mortality in 2019. The steady increase in population-level impact reflects improvements in ART coverage (partly due to progressive changes in HIV policy to increase the CD4 count threshold at which individuals can start ART (345)), as well as an increase in the average ART durations, with greater immune recovery at longer ART durations (24,340–342). Given that HIV accounts for a substantial amount of the incidence of TB in South Africa, these findings highlight that the ART programme is essential to TB care and prevention.

iii. *Xpert MTB/RIF 2011-2019*

From the implementation of Xpert MTB/RIF in 2011 to 2019, the estimated reductions in incidence and mortality were low (1.1% and 3.2%, respectively, in 2019). This low impact is consistent with a meta-analysis of clinical trials which assessed the effect of Xpert MTB/RIF on mortality as an outcome and found an insignificant effect (small effect and the confidence interval was wide and included the null, see paper) (130). Some of the reasons for the estimated low impact on incidence and mortality were discussed (Chapter 4). In brief, they included that the effect of Xpert MTB/RIF may have been offset by empirical treatment (222) – providing patients with TB medication without microbiological confirmation of TB disease. Also, under Xpert MTB/RIF, there is less culture testing in people who test Xpert-negative than in people who test smear-negative (281). Although Xpert MTB/RIF has increased the number of microbiologically confirmed diagnoses, this did not necessarily lead to more new diagnoses and treatment initiations because many patients were diagnosed and treated empirically before adopting Xpert MTB/RIF.

Our model incorporated a detailed diagnostic algorithm that estimated true and false positives from microbiological diagnoses; it also considered the proportions of individuals who initiate treatment empirically as informed by South African pragmatic trials (224,281). However, it was challenging to quantify the level of empirical treatment with a high degree of confidence; also, no specific counterfactual scenario was run to show the effect of no reduction in

empirical treatment. Therefore, there is uncertainty with the model estimates on the level of empirical treatment. Nevertheless, the model showed that although Xpert MTB/RIF did not lead to substantial declines in TB incidence and mortality, it nonetheless led to a 56% reduction in the number of people without TB who start treatment and a 28% reduction in the number of people who start TB therapy on an empirical basis.

iv. ***Directly observed therapy short course, 1996-2019***

The low impact of DOTS on TB incidence and mortality (<2%) shows that curative interventions alone, particularly in a high TB prevalence setting with other prevalent TB risk factors, such as HIV, are not sufficient (346,347). Previous modelling studies have also projected that DOTS are less impactful in settings with high HIV burdens (151,164).

v. ***Isoniazid preventative therapy, 2010-2019***

IPT has been shown to protect against TB disease (324). However, in the model, these benefits did not translate to substantial reductions in the population-level TB incidence and mortality over time. For example, in 2019, the provision of IPT to HIV-positive individuals only led to 1.6% and 1.9% reductions in incidence and mortality, respectively. Some of the reasons explaining the low population impact of IPT in the HIV-positive population were discussed in chapter 4. Briefly, the possible reasons were: a) low coverage of IPT; b) there is already a high risk of progression to TB disease in HIV-positive individuals; c) the short duration of protection offered by IPT (170,231); and d) in recent years, as individuals start ART at higher CD4 counts (345), and remain on ART for longer durations, average CD4 counts in ART patients have increased, which implies that there is less reduction in TB risk due to IPT (in absolute terms).

7.4.3. The South African tuberculosis trends by sex, effects of HIV and ART

Existing research and data show that the burden of TB is higher in males than in females, and several factors drive this skewed distribution (2,7,25). Our study provides additional insights regarding how HIV and the provision of ART influence the sex distribution of TB by conducting counterfactual experiments to show what the trajectory would have been without HIV and ART between 1990 and 2019.

The model results showed that over this period, 1990-2019, females experienced more significant relative increases in TB incidence (54.0% vs 45.6% in 2019) and mortality (62.9%

vs 57.4% in 2019) due to the higher HIV prevalence in females than in males (348). Conversely, the results showed that females experienced more reductions in TB incidence (38.3% vs 17.5% in 2019) and mortality (52.1% vs 28.8% in 2019) due to ART. This is likely because females are more likely to be tested for HIV and initiate ART than males (356). Over the 1990-2019 period, TB incidence and mortality remained higher for males than females; the estimated M:F ratios of TB incidence and mortality in 2019 were 1.7 and 1.65, respectively. Altogether, the model results are consistent with other empirical studies (351) and support the hypothesis that if HIV removes the protection females have against TB disease (86), then ART restores this protection.

7.4.4. Factors driving sex differences in the tuberculosis burden

i. *Contribution of smoking, alcohol, diabetes and undernutrition to sex differences in TB*

The second analysis further quantified TB incidence attributable to smoking, alcohol abuse, diabetes and undernutrition, stratified by sex. The estimated PAFs of TB incidence due to alcohol abuse, smoking, and undernutrition were higher in males (51%, 30% and 16%, respectively) than in females (30.1%, 15.4%, and 10.7, respectively). These higher PAFs of TB incidence in males are explained by the high prevalence of alcohol abuse, smoking and undernutrition in males, and the role of these factors in developing TB by suppressing cell-mediated immunity (90,91). On the other hand, the PAFs of diabetes were higher in females (22.9%) than in males (17.5%). In the analysis to quantify the extent to which these risk factors contribute to the higher TB incidence in males than females, the model suggests smoking and alcohol abuse contributed more. If smoking or alcohol abuse were eliminated, the M:F ratios for TB incidence would reduce by approximately 17% or 30%, respectively.

The WHO Global TB report has also identified these risk factors (smoking, alcohol, diabetes and undernutrition) as important due to the considerable amount of TB incidence they contribute to and therefore need to be given attention (3). Furthermore, consistent with our findings, the Global Burden of disease study also showed that smoking and alcohol contributed significantly to TB mortality in men and explained the majority of the observed higher burden of TB in men (7).

These results, therefore, highlight the need for the TB control programme to consider broader interventions addressing the high prevalence of alcohol abuse and smoking. For example, for

alcohol, interventions to reduce hazardous drinking include minimum unit pricing for alcohol (385), increased tax on alcoholic products, limiting alcohol marketing on media platforms and improved enforcement of existing alcohol-related regulations in South Africa (386). For smoking, interventions are needed to support smoking cessation, although evidence for their effectiveness is mixed (387), and price controls/taxation to increase the price of cigarettes may also be required (388,389). There is a need for more research to evaluate the effectiveness of these interventions and whether they are cost-effective.

ii. *Health seeking patterns*

Delays in health-seeking have a direct effect on TB mortality. This is because health-seeking delays often imply delays in diagnosis and treatment initiation. Delays in health-seeking also impact the likelihood of transmission and, therefore, TB incidence. This study suggested that if males' health-seeking rates were increased and set equal to female health-seeking rates, TB mortality would reduce and the M:F TB mortality ratios would reduce by 7%. Some possible reasons explaining delays in men's health facility attendance include higher rates of employment in men and associated concern about the loss of income due to time lost while seeking tuberculosis health care (38). Another barrier may be that very few health care services are dedicated to men, and the common perceptions are that public health clinics are spaces for women, children and the elderly (38,390). Therefore, interventions need to address these socioeconomic barriers to attending health care facilities (i.e., mobile clinics at workplaces or places of leisure) and create male-friendly health services, i.e., male clinics (390).

iii. *Social mixing patterns*

Social mixing patterns did not have major effects on TB incidence and mortality M:F ratios. This was mainly because, in the baseline/default parameters, the model assumed slightly higher contact rates among women. Nonetheless, other studies have shown that males have higher rates of social contact with other males (37,38), and because of the higher prevalence of TB among males, assortative mixing further increases the risk of TB transmission and the burden of TB among men; therefore, it further increases sex differences (85,354).

This study suggested that removing a single risk factor or equalising males' and females' health-seeking patterns, social contacts, or treatment outcomes at the current levels would not completely remove all sex disparities TB. In this scenario, the TB incidence and mortality

M:F ratios were reduced to 1.01 and 0.93. These residual sex differences in mortality were probably because for females, deaths that are not due to HIV and TB, e.g., due to violence, are much lower than in males (28,358). Therefore, more females live longer to older ages than males. In our model, we assumed that mortality rates are higher in older TB patients than in younger TB patients, and therefore the older female age distribution implies a higher TB mortality rate on average.

7.4.5. The impact of improving existing interventions

The third analysis of this thesis went further to project the future impact of improving existing interventions between 2023 and 2030. This also involved modelling changes and events affecting South African TB control in recent years. These include shifting to shorter preventative therapy regimens, scaling up TB preventative therapy uptake, and shifting from Xpert MTB/RIF to Xpert Ultra (287,366,367). Another significant event incorporated in the model was the emergence of the COVID-19 pandemic, which substantially reduced TB testing rates (26,27). The specific interventions explored in this analysis were to:

a) Improve case findings by doubling the proportion of individuals screened for TB.
b) Improve men's engagement in care by equalising male and female health facility attendance rates, HIV testing and ART initiation and interruption rates.
c) Improve linkage to care after diagnosis by halving rates of initial loss to follow-up.
d) Improve TB care and retention in care by halving treatment discontinuation rates.
e) Increase the uptake of preventative therapy in eligible HIV-positive individuals.
f) Provide preventative therapy to 80% of individuals who completed TB treatment.
g) Improve ART retention by reducing the rates of ART interruptions by 80%.

The results of the second analysis (Chapter 5) demonstrated the factors that contributed to sex differences in TB and provided a strong motivation for reporting epidemiological estimates and the intervention impacts by sex to show if there would be any sex differences. To that end, in this third analysis, results and intervention impacts were also reported by sex. The findings of this analysis suggested that there would be sex differences in the impacts of interventions, with reductions in TB incidence and mortality generally proportionately greater in females than in males. The differences were particularly evident in the interventions related to TB health seeking and HIV care, i.e., a) improving case finding; and HIV care-

related interventions, including e) doubling the provision of TPT to HIV-positive individuals in HIV care; and g) reducing ART interruptions.

i. *Tuberculosis screening*

In this third analysis, the model estimated that over the 2023-2030 period, doubling the proportion of individuals screened would lead to the greatest reductions in TB incidence (20.3% in males, 23.8% in females) and mortality (25.0% in males, 26.5% in females) compared to the other interventions explored. These findings are consistent with the first analysis, which showed that intensified screening explained most of the declines in the burden of TB in South Africa over the period 2005-2019. In addition, previous modelling analyses have also suggested that scaling up TB screening can potentially be an effective intervention in reducing the burden of TB in South Africa (174,180,190,237).

Furthermore, this third analysis suggests that females would experience more reductions than males. This is because females are more likely to seek TB care than their male counterparts (5). Therefore, doubling the proportions of individuals screened further reduces transmission among women (assuming females mix more with females) and leads to more significant reductions in TB incidence and mortality among females.

ii. *Tuberculosis preventative therapy (TPT)*

Similar to the low impact of TPT (IPT) estimated in the first analysis (Chapter 4), the model's projections also suggest a relatively low population-level impact of future improvements in TPT uptake. The possible reasons for the low impact of TPT have been discussed; the South African TB control programme needs to address these issues. In particular, there is a need to simplify the guidelines (375) for implementing TPT (60). Furthermore, to create environments that allow the implementation of existing TPT guidelines, leadership and management training of health facility managers may also be needed (61). While there is increasing support and advocacy to improve the implementation of the use of 3HP in South Africa, there is a need for enhanced data recording of both TPT uptake and completion through existing or new registries (i.e., the TB treatment registry) (376). Additionally, there is a need for more research and clinical trials to show the durability of protection against TB disease due to 3HP in settings such as South Africa.

iii. *HIV-associated interventions: preventative therapy in HIV-positive individuals and ART interruptions*

HIV care-related interventions, including doubling the provision of TPT to HIV-positive individuals in HIV care and reducing ART interruptions, would have a higher impact on females than males. These findings are possibly explained by the observation that HIV is more prevalent in women than in men, and females are more likely to be tested for HIV and initiate ART than males (356). Women are thus more likely to benefit from these interventions because they are more likely to have entered HIV care.

Given that South Africa has the largest HIV epidemic in the world, with approximately 8 million people living with HIV, and at least 5 million of these are receiving ART (19) (19,391), ART will remain vital for preventing HIV-associated TB disease risk and deaths. The first analysis (Chapter 4) showed that ART was responsible for most TB incidence and mortality declines from 2000 to 2019. Moreover, it will be critical to retain individuals on ART.

This analysis suggested that between 2023 and 2030, interventions to reduce ART interruptions would lead to minimal (<2%) TB incidence and mortality reductions for both males and females. However, despite this estimated low impact, it would be worth investing in interventions to improve ART retention (for example, by providing text message appointment reminders and peer support to HIV-positive individuals receiving ART (377,378)), perhaps in combination with other interventions to improve engagement in care.

iv. *Improving men's engagement in care*

This third analysis went further to assess the potential impact of increasing males' engagement in care by increasing and setting male TB health facility attendance rates, HIV testing rates and ART initiations to the same level as their female counterparts. The model suggested that this scenario would lead to more significant reductions in mortality among males (12% in males and 3% in females), suggesting that addressing men's barriers to care seeking would significantly impact mortality. These findings suggest that the TB programme should invest in interventions to increase men's engagement in TB and HIV care. These may include distributing HIV self-testing kits to men through their pregnant partners (369), mobile HIV testing campaigns (370), peer-delivered messaging to encourage men to test for HIV (371), and introducing health facilities that provide general health services to men (i.e., male clinics) (372).

7.4.6. The contribution of the COVID-19 pandemic to TB control challenges

The COVID-19 pandemic has contributed to interruptions in TB care – specifically resulting in declines in the number of TB tests performed (26). However, there is still limited data to inform mathematical models on the effects that the COVID-19 pandemic had on other aspects of TB, such as transmission and the natural history of TB. As a result, the model only considered the effect of COVID-19 on rates of TB screening. The model suggested that between 2019 and 2020, TB incidence rates were relatively constant, and mortality slightly increased (Chapter 6). Also, we assumed that after 2020 South Africa had recovered to regular screening rates, but this may not be accurate. These estimates were consistent with the WHO (1). Therefore, to keep South Africa on track in controlling the burden of TB, there is a need for sustained implementation of the plans to recover the regressive effects of COVID-19 (392,393).

7.4.7. Progress towards the 2030 end TB milestone targets

The third analysis (Chapter 6) also aimed to assess South Africa's potential to achieve the 2030 End TB milestones to reduce TB incidence and mortality by 80% and 90%, respectively, by 2030 (1) by scaling-up existing interventions. Concerning the progress toward TB prevention and care, South Africa is still behind on preventative therapy targets but doing well on the other targets. For 2022, the model estimated TPT coverage, calculated as the ratio of HIV-positive individuals initiating preventive therapy to the number of people with HIV starting ART and entering HIV care, was only 0.31. The case detection ratio, estimated as the ratio of modelled newly treated TB cases (excluding false positive TB) to estimated incident TB, was 0.86. Treatment success, defined as the ratio of the number of individuals completing treatment (net of deaths during treatment) to those who started treatment (excluding false positive), was 0.79.

Altogether, the model suggested that improvements to the current TB programme, implemented between 2023 and 2030, would reduce TB incidence and mortality by 44% and 56%, respectively, by 2030 compared to 2015 levels. However, these estimated reductions are insufficient to meet the 2030 End TB milestones to reduce TB incidence and mortality by 80% and 90%, respectively, by 2030 relative to 2015 (1).

There is a clear and urgent need to implement additional innovative interventions to fast-track the progress towards the 2030 End TB milestones. Some of the priorities needed to accelerate the progress would include the development of vaccines to reduce the risk of TB disease, new low-cost point-of-care diagnostic tools, and a shorter regimen for TB treatment. In addition, it may also be worth addressing broader determinants of TB disease, such as diabetes, alcohol abuse and smoking.

7.5. Strengths and limitations

This thesis was strengthened by using a dynamic-transmission model calibrated to multiple South African-specific data sources. Using this dynamic model has allowed us to capture the evolutions of both the TB and HIV epidemics. Calibration to sex-stratified data has allowed the model to capture the sex distribution of TB in South Africa. As a result, it was also possible to assess, for the first time, the effect HIV and ART had on sex differences in the South African TB epidemic over the 1990–2019 period and to quantify the contribution of other risk factors to TB mortality. This approach also allowed the estimation of the future impact of interventions.

Currently, South Africa mainly relies on the WHO (3) and IHME (7) as the leading agencies to produce TB incidence and mortality estimates. The work of this thesis has contributed to one of the few South African-led TB modelling initiatives (394,395). This model also has the potential to address ongoing TB policy questions and assess progress toward the evolving TB control targets.

However, this study is subject to several limitations, and all interpretations results need to be contextualised in light of these limitations. First, although the model was age and sex-stratified, calibration was only to sex-specific data and did not include the age-specific data. As such, it was not possible to gain more insights into the age distribution of TB or understand what factors account for the age distribution of TB incidence and mortality. Also, our model only focused on adults TB – 15 years and older. As a result, it was not possible to directly compare our model estimates with IHME and WHO. Additionally, we could not evaluate the impact of specific programmes on children, such as IPT for household TB contacts aged <5 years.

Third, the model did not include drug-resistant TB. As a result, it was not possible to produce estimates of the burden of drug-resistant TB and assess the impact of diagnostic tools to identify drug-resistant TB. Third, the model did not include data on TB patients treated in private health care facilities, although it is estimated that approximately 8% of symptomatic TB cases seeking TB care are in the private sector (17).

Fourth, the model does not distinguish between symptomatic and asymptomatic TB, although assumptions were made about the prevalence of symptoms for modelling screening algorithms. Fifth, for this research, we did not consider additional interventions such as candidate TB vaccines (i.e., the M72/AS01E vaccine (134), BCG re-vaccination in adolescents (135), active case finding (i.e. screening household contacts) and other diagnostic tests such as digital chest x-rays, urine Lipoarabinomannan, and biomarkers to identify individuals at risk of TB disease. Future modelling analysis would need to explore the impact of these interventions.

Also, the model did not incorporate the effects of the COVID-19 pandemic on TB transmission and the TB natural history, due to the lack of robust data regarding these effects. Also, the projections made in the last analysis (Chapter 6) were based on the previous model calibration, which relied only on data up to 2018. Thus, all the estimates need to be interpreted cautiously, and readers should bear in mind the uncertainty associated with the recent TB trends.

Lastly, we acknowledge the limitations of our uncertainty analysis. First, we did not vary all parameters simultaneously because the calibration process would be very intensive computationally (i.e., due to many model compartments, populations stratifications and many parameters). Instead, we performed a three-stage calibration approach. In the first stage we varied parameters related to the TB natural history; in the second stage we varied parameters related to TB interventions; and in the third stage we varied those parameters related to sex differences in TB. The same calibration targets and respective likelihood function definitions were used in all these stages. We acknowledge that in the calibration process, our decisions on prior distributions are subjective, as are our likelihood definitions and the assumed standard deviations in the likelihood calculations. We also note that the data we use may have biases we cannot adjust, and in addition, we also acknowledged that it is possible that our model estimates may not be fully accurate. Given these limitations, our model results may have underestimated the uncertainty, and therefore our results need to be interpreted with

caution. Nonetheless, to improve the credibility of our model estimates, we have used multiple data sources (prevalence, testing data, mortality data and treatment initiations) to calibrate the model.

There are other broader avenues which were not covered in this research and therefore need to be considered in the future. There is a need for subnational (district-level and provincial-level) models to help understand variations in the burden of TB in South Africa and investigate the factors that account for the geographical variations in TB. Such models would help in identifying where gaps in the treatment cascade are the most significant, by province and district. There is also a need for more detailed models which help understand the level of TB transmission occurring in indoor spaces such as households, prisons, schools, and health care facilities. Furthermore, such studies would be beneficial in identifying where infection control interventions in health facilities and active case finding targeted at high-risk populations would yield the most benefits (396,397).

In recent years increasing research has highlighted the long-term disability and the increased risk of death in individuals who have survived TB disease (398–400). Menzies *et al*. estimated that about half of the TB disease burden is due to long-term complications after TB treatment (399). This suggests that future South African modelling studies would need to also account the post-TB health losses, quantify the morbidity and mortality, and inform TB control policies to invest in providing care to this previously treated population.

7.6. Conclusion

This thesis has demonstrated that HIV is responsible for a significant fraction of the South African TB incidence and mortality, and intensified TB screening and the provision of ART contributed substantially to the observed declining trends in TB trends in recent years. Therefore, to sustain the declining TB trends, finding active TB individuals, and ensuring that HIV-positive individuals are diagnosed, initiated on ART and retained in care will remain critical. In addition, the higher burden of TB in males than females highlights the need for males to be targeted for routine screening to ensure earlier diagnosis, improved management and retention in TB and HIV care.

There is a need for additional innovative interventions to fast-track progress toward significant reductions in TB incidence and mortality. In addition, improving the provision of

TB preventative therapy in HIV-positive individuals and other TB risk groups would be essential. Furthermore, research and innovation toward finding a vaccine that effectively prevents TB disease are critical. Also, broader interventions are required to reduce exposure to additional TB risk factors such as alcohol abuse and smoking. Finally, there is a need for cost-effectiveness studies to assess the cost and health benefits of the interventions that the national TB programme plans to implement and to inform policy decisions.

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Chapter 8. Appendices

There is a vast overlap between Chapter 3 (the model development and calibration chapter) and the supplementary material supporting Chapters 4 to 6. Therefore, in this appendix chapter are the additional tables and figures supporting the analyses in Chapters 4 to 6, but not included in Chapter 3. These include the posterior estimates for the parameters varied in the analysis for Chapters 4 and 5, and additional inputs and outputs for the all the respective analysis.

8.1. Appendix A: Supplementary material for Chapter 4

The full supplementary materials for Chapter 4 are also accessible with the publication: https://doi.org/10.1016/j.ijid.2022.07.047.

8.1.1. Parameters varied in Chapter 4

We used a Bayesian approach to calibrate the model and estimate various parameters. Because our model is slow to run, and because the Bayesian calibration process is particularly slow to converge when there are many parameters being included in the uncertainty analysis, we calibrated the model through a series of steps. We first (in a previous calibration analysis) estimated the TB transmission and natural history parameters that gave the best fit to South African TB data, using the same likelihood definitions as given below. In this present analysis, we considered the parameters that determine the impact of TB interventions. The prior means and standard deviations are summarized in Appendix A Table 1, with the posterior means and 95% confidence intervals for the parameters varied and estimated in the previous calibration analysis. We also indicate the parameters varied in this present analysis.

Appendix A Table 1: Summary of model parameters with prior means and standard deviations, posterior means and 95% confidence intervals from the previous calibration analysis, and summary of those varied in this present analysis

Parameter description	Mean	Standard deviation	Posterior means (95% CI) from previous calibration	Parameters varied in the current analysis
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.0025	0.0025	0.0030 (0.0026–0.0034)	✓
The annual rate of reactivation in HIV-negative individuals	0.0024	0.0012	0.00148 (0.0014–0.00155)	
Relative rate of TB incidence per 100 cell increase in CD4	0.71	0.085	0.703 (0.693–0.712)	
Annual recovery rate in smear-positive TB, HIV-negative individuals	0.09	0.02	0.075 (0.067–0.081)	
Annual recovery rate in smear-negative TB, HIV-negative individuals	0.24	0.05	0.224 (0.198–0.247)	
Relative infectivity of smear-negative TB compared to smear-positive individuals	0.22	0.03	0.206 (0.196–0.218)	
Increase in TB risk if previously experienced TB	3.50	1.5	3.03 (2.55–3.53)	
Smear-negative TB mortality (untreated)	0.061	0.012	0.049 (0.046–0.052)	
Smear-positive TB mortality (untreated)	0.212	0.042	0.196 (0.174–0.221)	
The relative rate of TB mortality per 50 cell increase in CD4 count if HIV+	0.87	0.05	0.949 (0.944–0.954)	
Proportion with cough >2 weeks in individuals with smear-negative TB	0.2	0.1	0.198 (0.149–0.263)	
The proportion of incident TB cases in HIV-negative adults that are smear-positive	0.52	0.1	0.51 (0.48–0.54)	
Relative ratio of symptoms in patients with smear-positive TB, compared to smear-negative TB	2.2	0.5	3.03 (2.74–3.23)	
Relative rate of TB incidence for those on ART (controlling for CD4)	0.81	0.05		✓
Relative rate of TB mortality if on ART	0.55	0.08		✓
The annual rate of health-seeking in males with smear-negative TB	2.14	0.49		✓
The annual rate of health-seeking in males in the general population	1.15	0.5		✓
The annual rate of health-seeking in males due to TB-like symptoms	0.22	0.15		✓
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.125	0.144		✓
The proportion of smear-negative TB cases which are treated empirically if they initially screened negative on a smear test	0.33	0.236		✓
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.5	0.289		✓
Relative rate of empirical treatment if symptoms are not due to TB	0.5	0.289		✓
Relative rate of health-seeking in women, compared to men	1.55	0.17		✓
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	3	1		✓
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions				✓
Initial (up to 2005)	8.71	2.5		✓
Ultimate (after 2012)	4	1.2		✓

ART = antiretroviral therapy; TB=tuberculosis. Ticks indicate the parameters which were varied in the respective steps.

8.1.2. Comparison of prior and posterior distributions

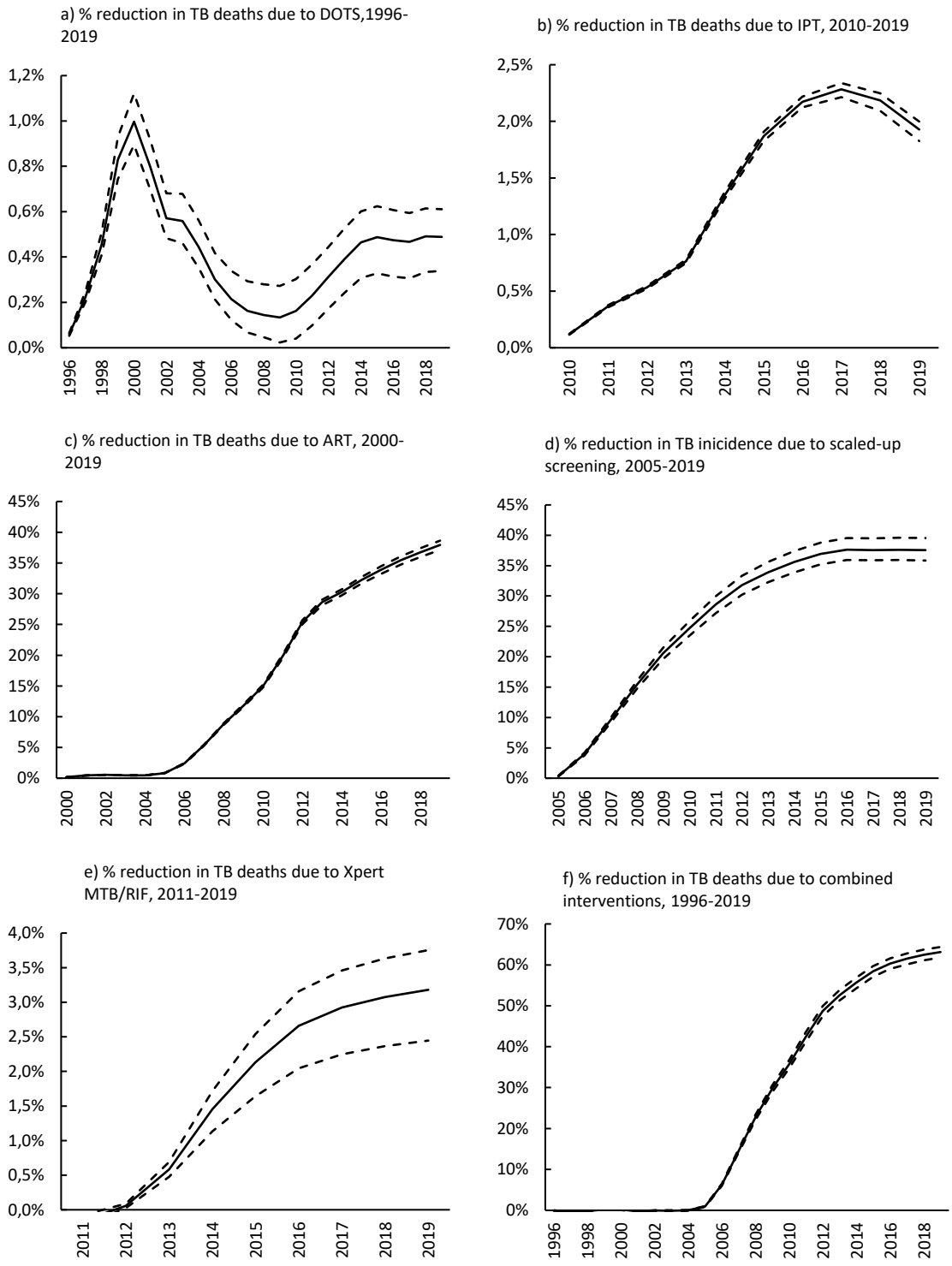
As indicated in Appendix A Table 1, most of the TB natural history parameters were estimated in a separate analysis and fixed in this current analysis. Appendix A Table 2 below shows the prior and posterior distributions for parameters varied in this current analysis. Most of the prior and posterior distributions means are similar and the 95% confidence intervals overlap. However, there were some differences with other parameters, in particular the parameters representing empirical treatment and relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions (in earlier years). This reflects the uncertainty associated with the parameter due to limited empirical evidence to inform the prior distributions.

Appendix A Table 2: Comparison of prior and posterior distributions for model parameters

Parameter description	Prior mean (95% confidence interval)	Posterior mean (95% confidence interval)
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.0025 (0.00013 – 0.0184)	0.0034 (0.0031 - 0.0037)
Relative rate of TB incidence for those on ART (controlling for CD4)	0.81 (0.703 - 0.898)	0.840 (0.822 - 0.862)
Relative rate of TB mortality if on ART	0.55 (0.392 - 0.703)	0.498 (0.469 - 0.536)
The annual rate of health-seeking in males with smear-negative TB	2.14 (1.29 - 3.202)	1.07 (0.903 - 1.212)
The annual rate of health-seeking in males in the general population	1.15 (0.389 - 2.317)	1.0 (0.76 - 1.3)
The annual rate of health-seeking in males due to TB-like symptoms	0.22 (0.030 - 0.596)	0.196 (0.163 - 0.224)
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.125 (0.00625 - 0.244)	0.068 (0.046 - 0.092)
The proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test	0.33 (0.0168 - 0.653)	0.28 (0.222 - 0.353)
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.5 (0.0 - 1.0)	0.031 (0.017 - 0.051)
Relative rate empirical treatment if symptoms are not due to TB	0.5 (0.0 - 1.0)	0.0014 (0.0005 - 0.0029)
Relative rate of health-seeking in women, compared to men	1.55 (1.235 - 1.901)	1.376 (1.2884 - 1.475)
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	3 (1.372 - 5.254)	4.27 (3.72 - 5.12)
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions		
Initial (up to 2005)	8.71 (4.520 - 14.248)	11.10 (9.73 - 12.47)
Ultimate (after 2012)	4 (2.005 - 6.671)	3.84 (3.27 - 4.52)

ART = antiretroviral therapy; TB=tuberculosis. The ratio of model the estimated ('true') tuberculosis cases to the number of recorded deaths classified as TB (described in section 11.1)) was estimated at 1.26 (95% CI 1.22 – 1.29).

Appendix A Figure 1: The impact of programmatic interventions on tuberculosis deaths.



a) DOTS, b) IPT, c) ART, d) scaled-up screening, and e) Xpert MTB/RIF. Solid lines represent the estimated mean reductions in tuberculosis deaths. f) The impact of combined interventions on tuberculosis deaths. The black lines represent the estimated mean tuberculosis deaths in the baseline scenario with all existing interventions included, and the grey represents the counterfactual scenario with no intervention included. All dashed lines represent the 95% confidence intervals.

Appendix A Figure 2: The effect of Xpert MTB/RIF on laboratory diagnoses and treatment initiations

	False positive laboratory diagnoses in adults	Adults without TB starting TB treatment	Adults starting TB treatment without a positive lab diagnosis
Baseline			
2011	41886	38317	89683
2012	35361	32932	74313
2013	27724	26436	63470
2014	25376	24445	57424
2015	22826	22240	52607
2016	22418	21897	50578
2017	22984	22440	48811
2018	23390	22836	47130
2019	23071	22568	46005
Counterfactual, No Xpert MTB/RIF			
2011	50163	45113	97887
2012	52179	46899	88527
2013	54062	48577	82904
2014	56024	50323	78265
2015	57000	51206	73975
2016	55979	50341	70929
2017	57393	51603	68782
2018	58408	52516	66597
2019	57614	51844	64578

8.1.3. Sensitivity analysis for latent TB prevalence assumptions

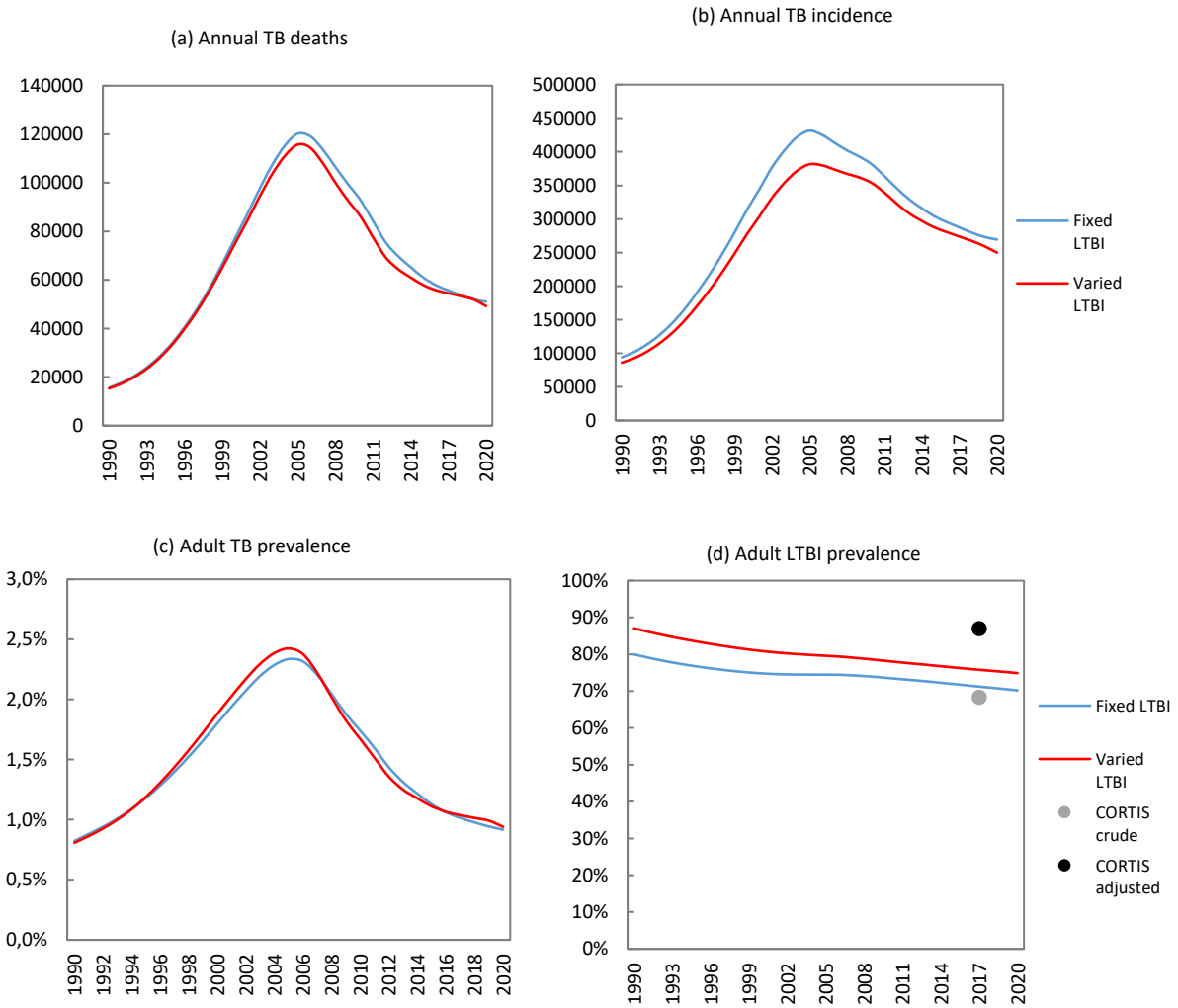
- There is substantial uncertainty around the initial LTBI prevalence in 1985, and using the CORTIS data to set the age-specific initial assumptions in 1985 might not be ideal. There are two important sources of bias in the CORTIS data. The first is that the data relate to 2016-2018 (250) whereas we are trying to set assumptions for the population in 1985. Although we use age-specific data to avoid problems with the sampled age distribution not matching the true age distribution in 1985, our model simulations suggest that the prevalence of LTBI has been declining over time (see Figure 19 pane d below), in line with international trends (59). This would suggest that the age-specific CORTIS data may understate the true LTBI prevalence estimates in 1985.

- The second source of bias is that the CORTIS data are collected from five sites in low-income communities with high TB prevalence, and these are unlikely to give us a nationally-representative picture of LTBI prevalence. This would suggest the CORTIS data may overstate the true LTBI prevalence at a national level. It is likely that these two sources of bias offset one another to some extent, and in the absence of better data, the CORTIS data are probably a reasonable starting point when setting the initial LTBI prevalence in the model.

- To assess the sensitivity of the model results to this parameter, we re-calibrated the model allowing for the uncertainty in the effect of age on the initial LTBI prevalence. (This parameter accounts for most of the variation in initial LTBI prevalence.) We assigned a gamma prior with a mean of 0.064 (the same as the value used in the original model calibration) and a standard deviation of 0.016. After refitting the model, the posterior mean for this parameter was 0.090 (95% CI: 0.082-0.099), i.e., substantially higher than the prior mean, and implying a much higher initial LTBI prevalence than previously estimated. Appendix A Figure 3 (panels a-d) below compares the model outputs in the original calibration ('Fixed LTBI') with the model outputs when we vary the LTBI age parameter in the calibration ('Varied LTBI'). Although the higher initial LTBI prevalence estimate does not appear to have much impact on the modelled trends in TB prevalence and mortality (panels a and c), the modelled annual number of new TB

cases in adults are substantially lower when the initial LTBI prevalence is higher (panel b), and as expected, overall prevalence of LTBI prevalence is also higher (panel d).

Appendix A Figure 3: Adult TB trends under different assumptions about the effect of age on initial LTBI prevalence



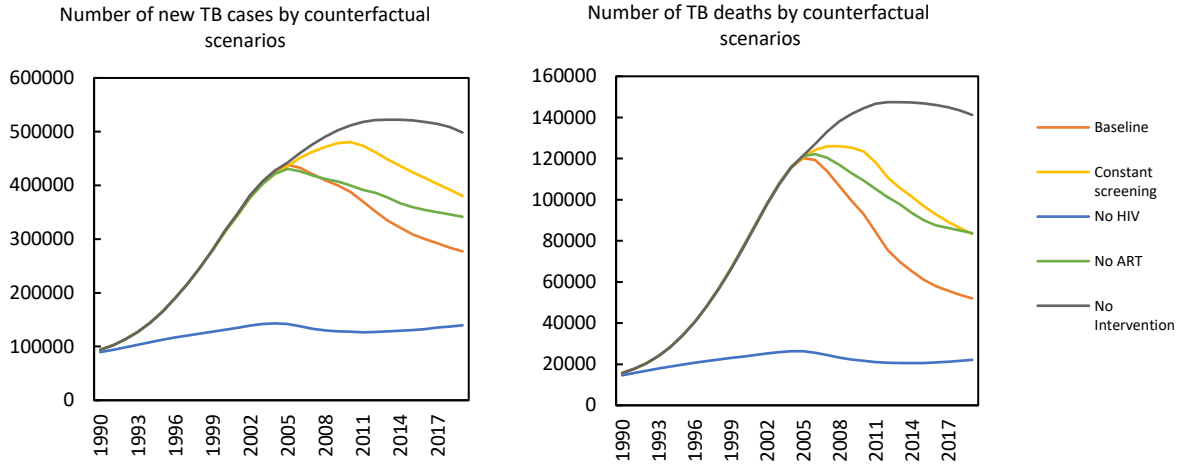
In panel (d), the 'crude' CORTIS data are the prevalence estimates for South African adults (15+) after re-weighting the age-specific prevalence estimates using the 2017 South African population age distribution. The 'adjusted' CORTIS data are based on the same age standardization, but in addition we adjust for the sensitivity and specificity of the IGRA assay used in the CORTIS trial (assumed to be 0.78 and 0.96 respectively (251)).

- There are a number of reasons to be suspicious of the results obtained in this sensitivity analysis, when allowing the age effect of the initial LTBI to vary in the calibration process. Firstly, the annual TB incidence in adults is implausibly low; in most of the posterior simulations, the modelled number of treated TB cases is *less* than the number of cases recorded in the ETR. (As discussed earlier, we would

expect the ETR to understate the true number of treated TB cases.) Secondly, the estimated LTBI prevalence estimates seem extremely high when compared against regional averages (59). We therefore do not consider these as an acceptable 'alternative' set of model outputs, but present them here for the sake of understanding the sensitivity of the model outputs to the initial LTBI assumptions.

8.1.4. TB incidence and mortality by different model experiments

Appendix A Figure 4: TB incidence and mortality by different counterfactual scenarios



- With the removal of the DOTS, Xpert MTB/RIF and IPT interventions, the TB incidence and mortality trends remain roughly the same as in the baseline scenario, so these trends in these scenarios are not shown here.

- Without increased screening and ART, the TB incidence and mortality would have peaked much later, and would have declined much more slowly than in the baseline scenario.

8.1.5. Sensitivity analysis – correlation coefficients for model input parameters and model outcomes

We assessed the correlation between each parameter varied in the calibration process, and the model estimated new TB cases and deaths in 2019 (Appendix A Table 3); we also assessed the correlation between the input parameters (Appendix A Table 4). The model outputs (new TB cases and deaths) were generated for each of the 1000 parameter combinations in the

posterior sample. We then generated scatter plots to show the relationship between the model parameters and new TB cases and deaths for 2019 (Appendix A Figure 5 and 6, respectively).

- As expected, the TB transmission probability was positively associated with incidence (r=0.82) and mortality (r=0.45).
- The negative association (r=-0.43) between the relative rate of TB mortality on ART and TB mortality is unexpected. However, we also see that the parameter is negatively associated with other parameters that likely influence mortality (e.g., health-seeking rates in HIV-positive individuals (r=-0.34) and women (r=-0.19)). We also observed that the change in the relative rates of symptom screening between 2005 and 2012 were positively correlated with the relative rate of TB mortality on ART (r=-0.42 in 2005 and 0.30 in 2012). This may be because there is a trade-off in how much of the observed TB mortality reduction up to 2019 can be explained by ART versus increased TB screening. That is, if a lot of the reduction is due to ART (low relative rate of TB mortality on ART), then a relatively small amount of the change is attributable to changes in screening (i.e., low values of the change in the relative rate of symptom screening between 2005 and 2012).
- If empirical treatment were beneficial, we would expect a negative correlation between the empirical treatment parameters and TB incidence and mortality. However, we observed a positive association between 1) the proportions of empirical treatment in active TB cases who are treated empirically before any microbiological test is done (r=0.76 for incidence; r=0.35 for mortality), and 2) those treated empirically if they initially screened negative smear test (r=0.38 for incidence; r=0.22 for mortality). We fitted our model to the total number of people treated in the South African electronic treatment register (ETR) to estimate these parameters. The positive associations with the empirical treatment parameters suggest that more people were likely misdiagnosed (i.e., empirical treatment is not as impactful in reducing incidence and mortality due to treating false-positive individuals).
- If a particular health-seeking parameter (rate) is beneficial, we expect a negative relationship between TB incidence and mortality outcomes. We observed a positive association between the outcomes and the relative rate of

health-seeking in HIV-positive individuals (r=0.55 for incidence; r=0.42 for mortality). This is possibly because as this parameter increases, the fraction of treated TB cases who are HIV-positive cases increases. As HIV-positive individuals are less infectious than HIV-negative individuals, increasing the proportion of treated active TB individuals who are HIV-positive increases the level of TB transmission. We also observed that the health-seeking relative rate in HIV-positive versus HIV-negative parameter is positively correlated with the transmission probability, r=0.41.

Appendix A Table 3: Correlation coefficients for model input parameters varied in the calibration process, and specified outcomes

Model parameters	TB incidence, 2019	TB mortality, 2019
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.82	0.45
Relative rate of TB incidence for those on ART (controlling for CD4)	0.48	0.30
Relative rate of TB mortality if on ART	-0.28	-0.43
The annual rate of health-seeking in males with smear-negative TB	-0.13	-0.15
The annual rate of health-seeking in males in the general population	-0.07	-0.21
The annual rate of health-seeking in males due to TB-like symptoms	0.11	0.10
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.76	0.35
The proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test	0.38	0.22
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	-0.21	-0.27
Relative rate empirical treatment if symptoms are not due to TB	-0.17	-0.16
Relative rate of health-seeking in women, compared to men	0.12	0.05
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	0.55	0.42
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions*		
Initial (up to 2005)	-0.20	0.09
Ultimate (from 2012)	-0.29	-0.26

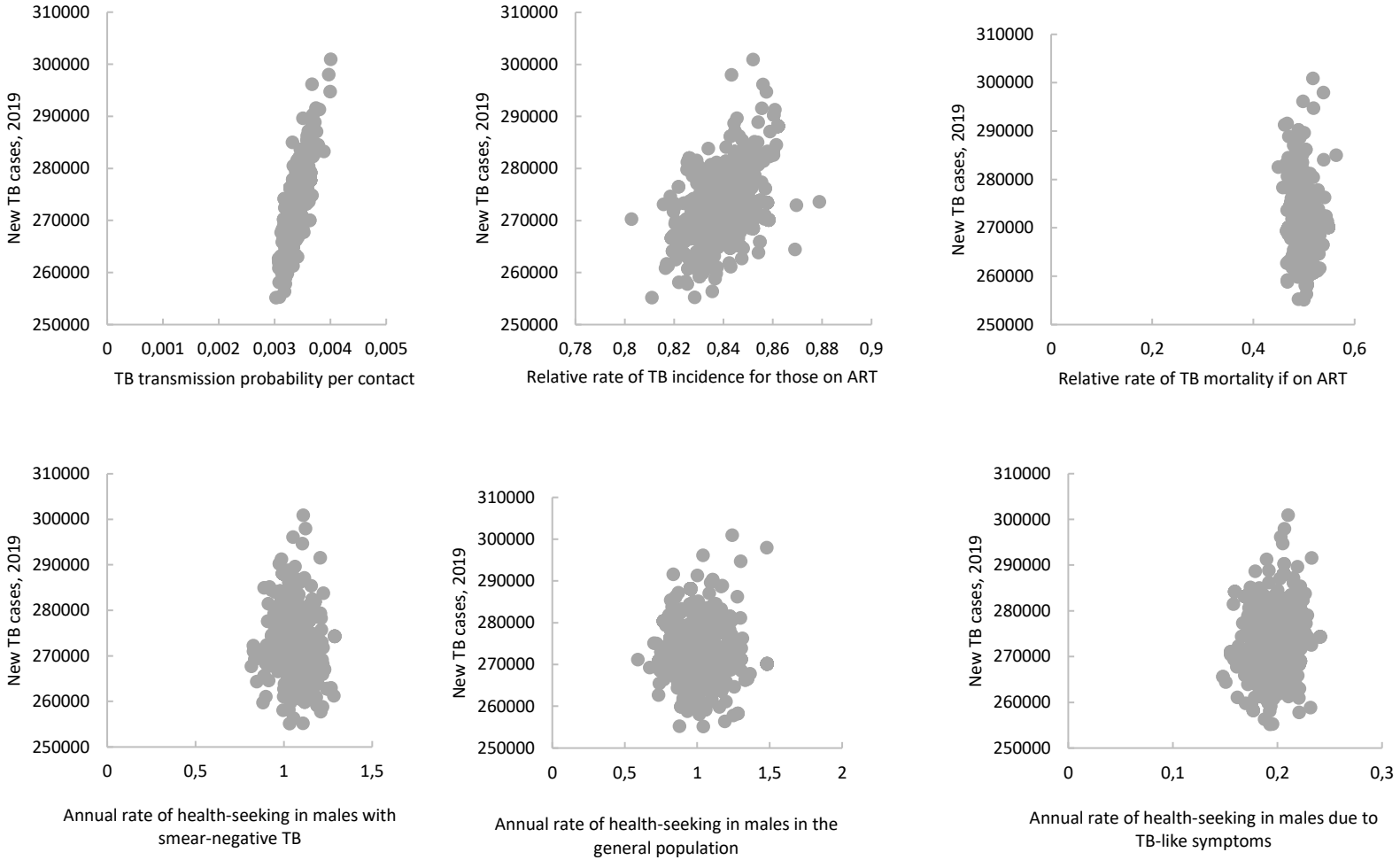
ART=antiretroviral therapy. TB=tuberculosis. *The initial rate applies up to 2005, the ultimate rate applies from 2012, with linear interpolation over the intervening years (2006-2011).

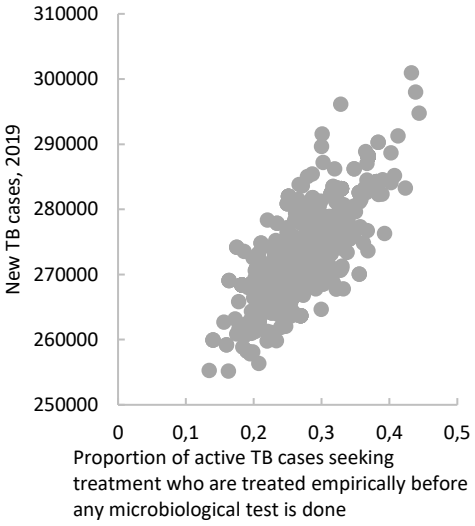
Appendix A Table 4: Pair-wise correlation coefficients between model parameters

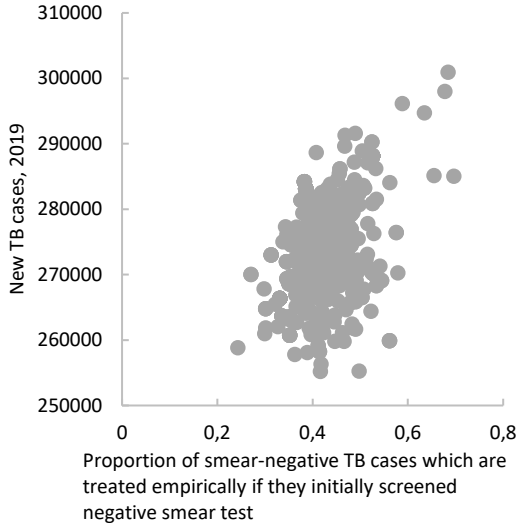
	Transmission probability	RR TB on ART	RR TB mort on ART	Health seeking active	Health seeking general population	Health seeking TB-like symptoms	Empirical treatment, no screen	Empirical treatment, negative screen	RR empiric, no symptoms	RR empiric, no TB	RR health seeking in women	RR health seeking in HIV+ vs HIV-	RR screening symptomatic initial	RR screening symptomatic ultimate
Transmission probability	1.00													
RR TB on ART	0.52	1.00												
RR TB mort on ART	-0.43	-0.24	1.00											
Health seeking active	0.08	-0.34	-0.19	1.00										
Health seeking general population	0.01	-0.01	0.38	-0.32	1.00									
Health seeking TB-like symptoms	0.10	-0.08	-0.06	0.76	-0.44	1.00								
Empirical treatment, no screen	0.88	0.53	-0.16	-0.32	0.21	-0.20	1.00							
Empirical treatment, negative screen	0.25	0.29	0.18	-0.41	0.28	-0.15	0.31	1.00						
RR empiric, no symptoms	-0.12	0.06	0.19	0.35	-0.41	0.24	-0.21	-0.38	1.00					
RR empiric, no TB	-0.23	-0.02	0.31	-0.49	0.21	-0.40	0.04	0.13	-0.13	1.00				
RR health seeking in women	0.21	0.26	-0.19	-0.03	0.02	0.17	0.15	0.27	-0.15	0.16	1.00			
RR health seeking in HIV+ vs HIV-	0.41	0.50	-0.34	-0.20	-0.39	0.10	0.37	0.30	-0.15	-0.12	0.21	1.00		
RR screening symptomatic initial	-0.18	-0.33	-0.42	0.32	-0.32	0.29	-0.35	-0.21	-0.01	-0.11	0.06	-0.12	1.00	
RR screening symptomatic ultimate	-0.30	0.04	0.30	-0.18	0.44	-0.26	-0.15	-0.20	-0.11	0.37	-0.43	-0.22	-0.16	1.00

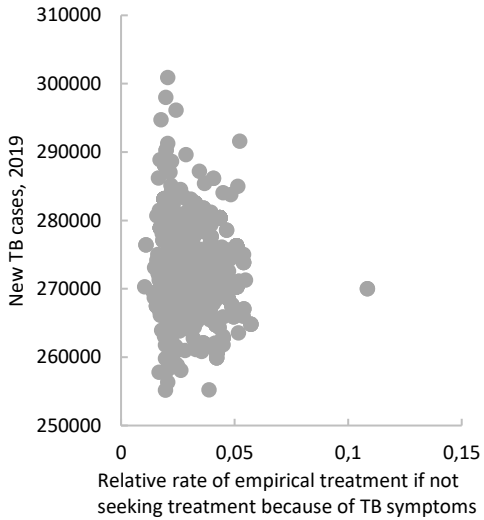
RR=relative rate. TB=tuberculosis.

Appendix A Figure 5: Scatter plots to show the relationship between estimated new TB cases and model parameters




New TB cases, 2019
310000
300000
290000
280000
270000
260000
250000
0
0,1
0,2
0,3
0,4
0,5
Proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done


New TB cases, 2019
310000
300000
290000
280000
270000
260000
250000
0
0,2
0,4
0,6
0,8
Proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test


New TB cases, 2019
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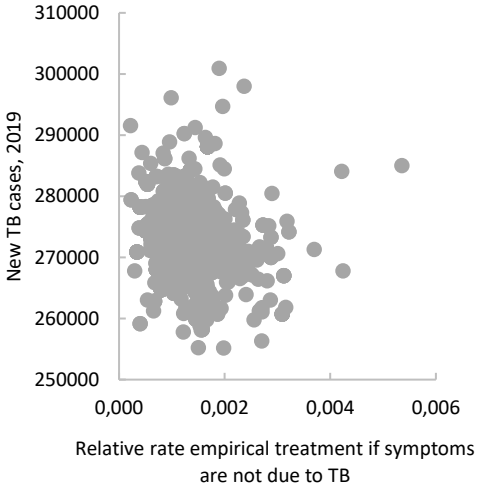
300000
290000
280000
270000
260000
250000
0
0,05
0,1
0,15
Relative rate of empirical treatment if not seeking treatment because of TB symptoms


New TB cases, 2019
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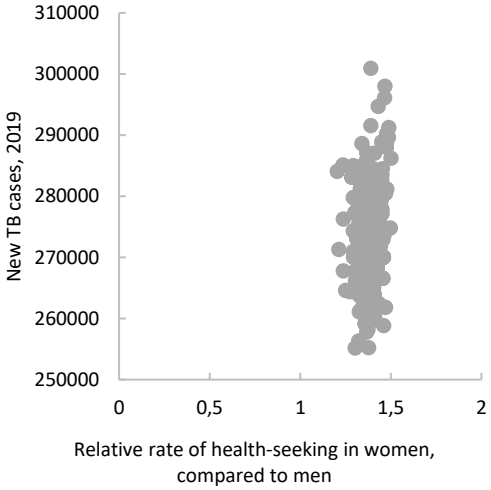
290000
280000
270000
260000
250000
0,000
0,002
0,004
0,006
Relative rate empirical treatment if symptoms are not due to TB


New TB cases, 2019
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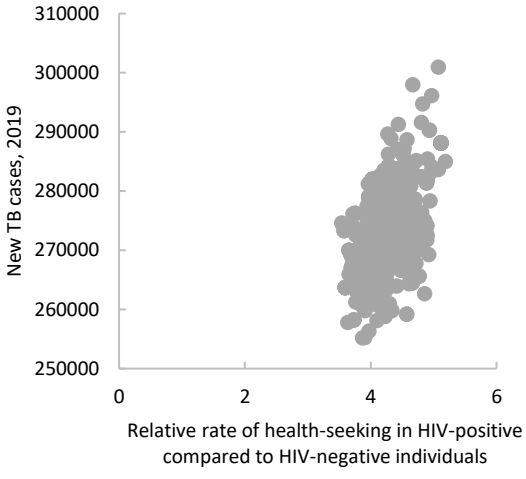
290000
280000
270000
260000
250000
0
0,5
1
1,5
2
Relative rate of health-seeking in women, compared to men


New TB cases, 2019
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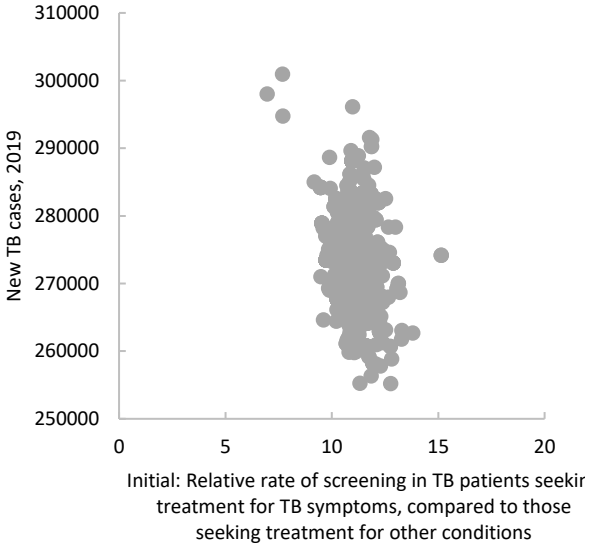
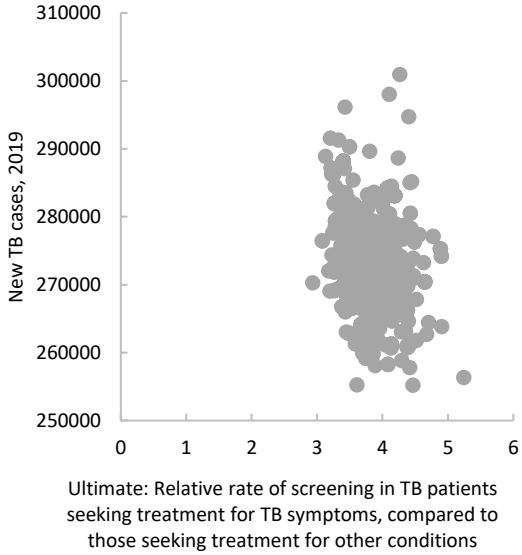
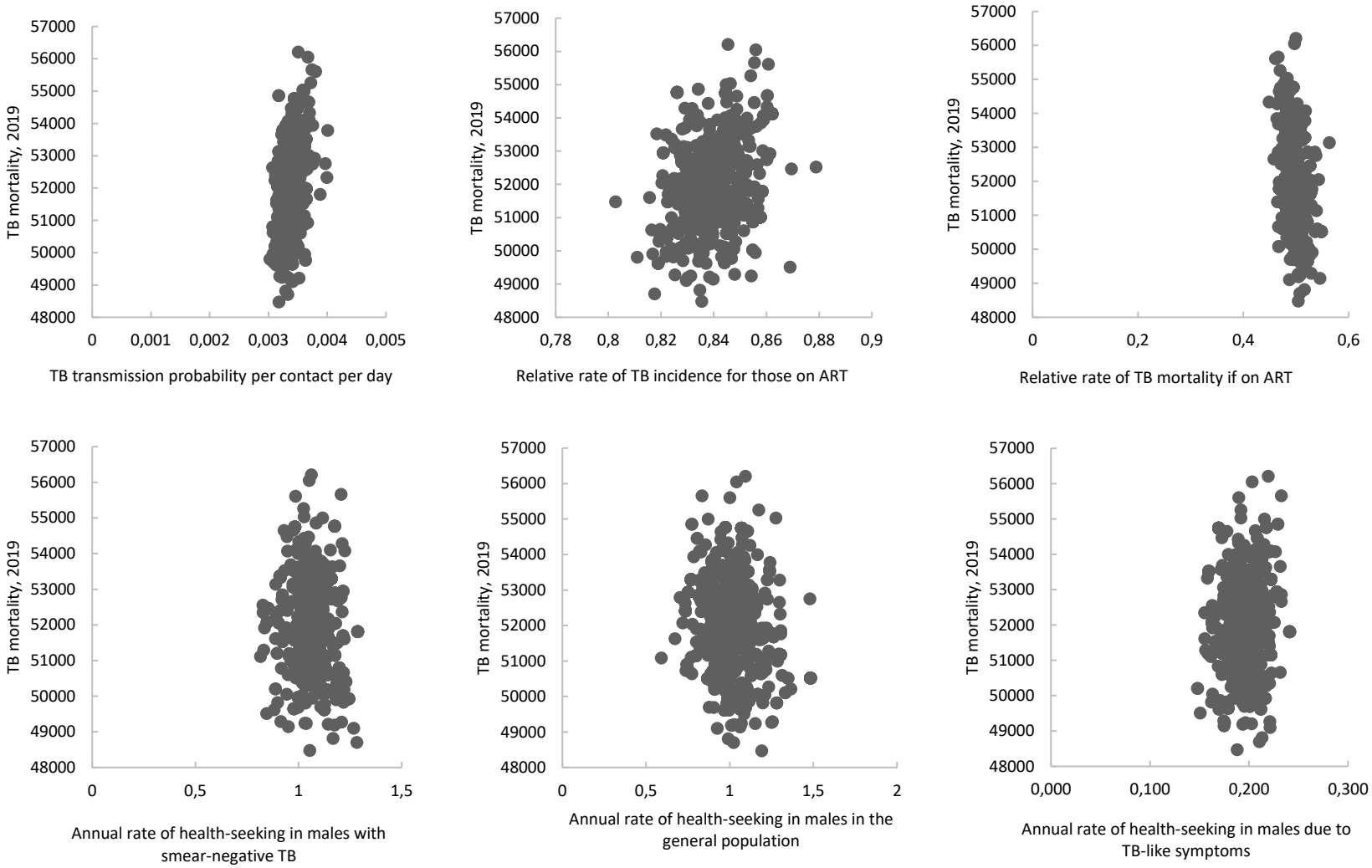
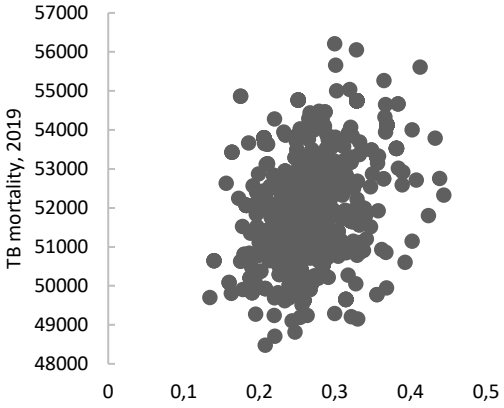
290000
280000
270000
260000
250000
0
2
4
6
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals

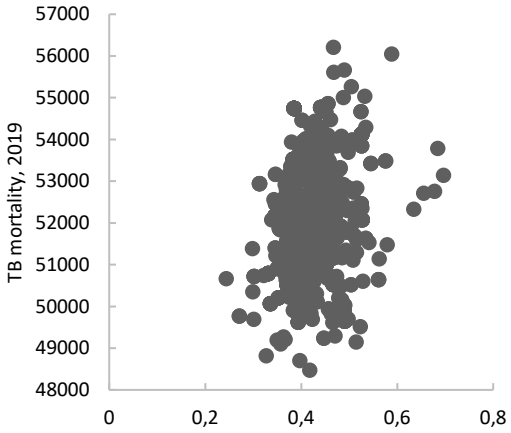

310000
300000
290000
280000
270000
260000
250000
New TB cases, 2019
0
5
10
15
20
Initial: Relative rate of screening in TB patients seekir treatment for TB symptoms, compared to those seeking treatment for other conditions


310000
300000
290000
280000
270000
260000
250000
New TB cases, 2019
0
1
2
3
4
5
6
Ultimate: Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions

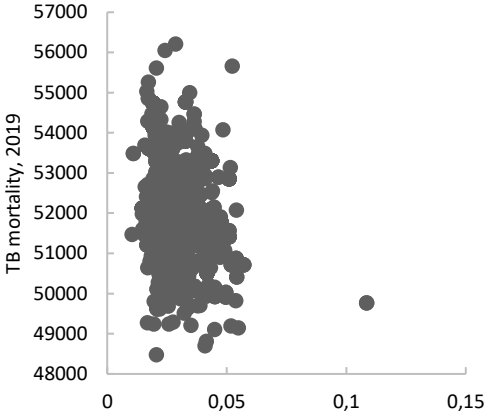
Appendix A Figure 6: Scatter plots to show the relationship between estimated TB mortality and model parameters





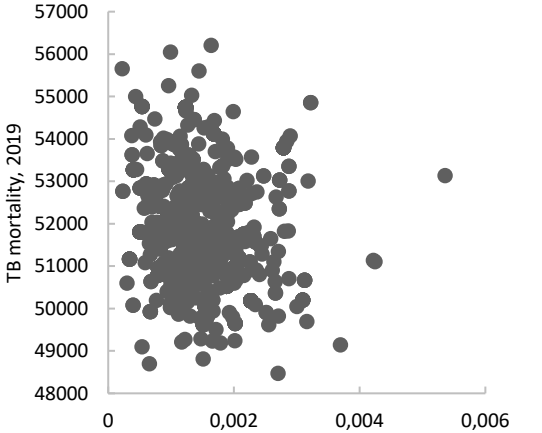


The proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test

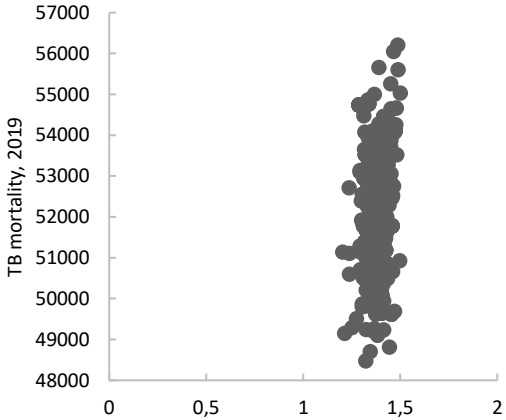


Relative rate of empirical treatment if not seeking treatment because of TB symptoms

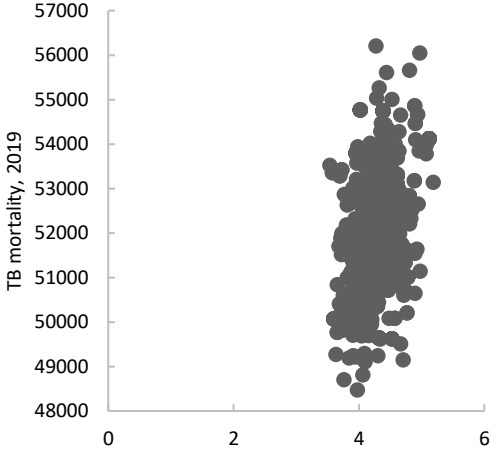
...



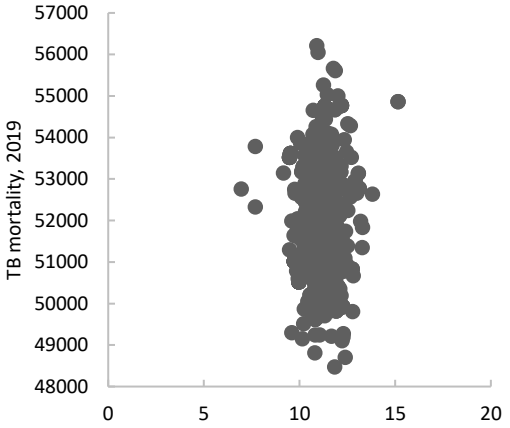
Relative rate empirical treatment if symptoms ar not due to TB



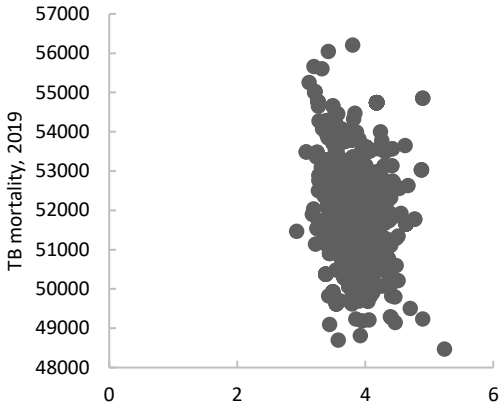
Relative rate of health-seeking in women, compared to men



Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals



Initial: Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions



Ultimate: Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions

8.2. Appendix B: Supplementary material for Chapter 5

The full supplementary materials for Chapter 5 are also accessible with the pre-print: https://doi.org/10.21203/rs.3.rs-1908771/v1.

8.2.1. Parameters varied in Chapter 5

We used a Bayesian approach to calibrate the model and estimate various parameters. Because our model is slow to run, and because the Bayesian calibration process is particularly slow to converge when there are many parameters being included in the uncertainty analysis, we calibrated the model through a series of steps. We first (in a previous calibration analysis, step 1) considered TB transmission and natural history parameters (355). Then we considered the parameters (previous calibration analysis, step 2) that determine the impact of TB interventions (355). In this present analysis, we focus on the parameters that are most influential in explaining the male-female differences in TB incidence. The prior means and standard deviations are summarized in (Appendix B Table 1), with the posterior means and 95% confidence intervals for the parameters varied and estimated in the previous calibration analysis. We also indicate the parameters varied in this present analysis. In each step we use the same likelihood definitions as given in this section below.

Appendix B Table 1: Summary of model parameters (with prior means and standard deviations) that are varied and estimated through calibration

Parameter description	Mean	Standard deviation	Uncertainty analysis		
			Previous step 1	Previous step 2	Current step 3
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.0025	0.0025	0.0030 (0.0026–0.0034)	0.0034 (0.0031 - 0.0037)	✓
The annual rate of reactivation in HIV-negative individuals	0.0024	0.0012	0.00148 (0.0014–0.00155)		
Relative rate of TB incidence per 100 cell increase in CD4	0.71	0.085	0.703 (0.693–0.712)		✓
Annual recovery rate in smear-positive TB, HIV-negative individuals	0.09	0.02	0.075 (0.067–0.081)		
Annual recovery rate in smear-negative TB, HIV-negative individuals	0.24	0.05	0.224 (0.198–0.247)		
Relative infectivity of smear-negative TB compared to smear-positive individuals	0.22	0.03	0.206 (0.196–0.218)		
Increase in TB risk if previously experienced TB	3.499	1.5	3.03 (2.55–3.53)		
Smear-negative TB mortality (untreated)	0.061	0.012	0.049 (0.046–0.052)		
Smear-positive TB mortality (untreated)	0.212	0.042	0.196 (0.174–0.221)		
The relative rate of TB mortality per 50 cell increase in CD4 count if HIV+	0.87	0.05	0.949 (0.944–0.954)		✓
Proportion of cough >2 weeks in individuals with smear-negative TB	0.2	0.1	0.198 (0.149–0.263)		
The proportion of incident TB cases in HIV-negative adults that are smear-positive	0.52	0.1	0.51 (0.48–0.54)		
Relative ratio of symptoms in patients with smear-positive TB, compared to smear-negative TB	2.2	0.5	3.03 (2.74–3.23)		
Relative rate of TB incidence for those on ART (controlling for CD4)	0.81	0.05		0.840 (0.822 - 0.862)	✓
Relative rate of TB mortality if on ART	0.55	0.08		0.498 (0.469 - 0.536)	✓
The annual rate of health-seeking in males with smear-negative TB	2.14	0.49		1.07 (0.903 - 1.212)	✓
The annual rate of health-seeking in males in the general population	1.15	0.5		1.0 (0.76 - 1.3)	
The annual rate of health-seeking in males due to TB-like symptoms	0.22	0.15		0.196 (0.163 - 0.224)	
The proportion of active TB cases seeking treatment who are treated empirically before any microbiological test is done	0.125	0.144		0.068 (0.046 - 0.092)	
The proportion of smear-negative TB cases which are treated empirically if they initially screened negative smear test	0.33	0.236		0.28 (0.222 - 0.353)	
Relative rate of empirical treatment if not seeking treatment because of TB symptoms	0.5	0.289		0.031 (0.017 - 0.051)	

Parameter description	Mean	Standard deviation	Uncertainty analysis	Parameter description	Mean
			Previous step 1		
Relative rate empirical treatment if symptoms are not due to TB	0.5	0.289		0.0014 (0.0005 - 0.0029)	
Relative rate of health-seeking in women, compared to men	1.55	0.17		1.376 (1.2884 - 1.475)	✓
Relative rate of health-seeking in HIV-positive compared to HIV-negative individuals	3	1		4.27 (3.72 - 5.12)	
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: initial	8.71	2.5		11.10 (9.73 - 12.47)	
Relative rate of screening in TB patients seeking treatment for TB symptoms, compared to those seeking treatment for other conditions: ultimate	4	1.2		3.84 (3.27 - 4.52)	
Increase in TB mortality rate per 10-year increase in age	1.4	0.1			✓
Increase in TB incidence due to alcohol misuse	1.94	0.65			✓
Increase in TB incidence due to diabetes (HbA1c > 6.5%)	2.59	0.83			✓
Increase in TB risk if currently smoking	0.47	0.39			✓
Increase in TB risk per 10-year increase in duration of smoking	0.38	0.12			✓
Increase in TB risk due to low BMI	0.8	0.25			✓

ART=antiretroviral therapy; BMI=body mass index. TB=tuberculosis. Ticks indicate the parameters which were varied in the respective steps

8.2.2. Comparison of prior and posterior distributions

Appendix B Table 2 below shows the prior and posterior distributions for parameters varied in this current analysis. Most of the prior and posterior distributions means were similar and the 95% confidence intervals overlap. However, there were slight differences between the prior and posterior distributions for the parameters for effects of risk factors (alcohol abuse, diabetes, smoking, and low BMI). This reflects the uncertainty associated with the effects of these risk factors on developing tuberculosis disease.

Appendix B Table 2: Comparison of prior and posterior distributions for model parameters

Parameter description	Prior mean (95% confidence interval)	Posterior mean (95% confidence interval)
TB transmission probability per contact per day (if infectious individual is smear-positive)	0.0025 (0.0001 – 0.0184)	0.003 (0.0027 - 0.0032)
Reduction in TB incidence per 100 increases in CD4	0.71 (0.531 – 0.860)	0.72 (0.71 - 0.73)
Relative rate of TB mortality per 50 cells increases in CD4 count, in HIV-positive adults	0.87 (0.758 – 0.951)	0.92 (0.91 - 0.93)
Relative rate of TB incidence on ART (controlling for CD4)	0.81 (0.758 - 0.951)	0.74 (0.71 - 0.77)
Relative rate of TB mortality if on ART	0.55 (0.392 - 0.703)	0.71 (0.67 - 0.74)
Increase in TB mortality rate per 10-year increase in age	1.4 (1.211 - 1.603)	1.39 (1.34 - 1.45)
Annual rate of health seeking in males with smear-neg TB	2.14 (1.29 - 3.202)	1.04 (0.95 - 1.13)
Relative rate of health seeking in females	1.55 (1.235 - 1.901)	1.47 (1.40 - 1.57)
Increase in TB incidence due to alcohol misuse	1.94 (0.883 - 3.408)	2.56 (2.28 - 2.86)
Increase in TB incidence due to diabetes	2.59 (1.228 - 4.453)	1.51 (1.32 - 1.69)
Increase in TB risk if currently smoking	0.47 (0.031 - 1.482)	0.18 (0.14 - 0.27)
Increase in TB risk per 10-year increase in duration of smoking	0.38 (0.182 - 0.649)	0.23 (0.2 - 0.26)
Increase in TB risk if experiencing low BMI	0.8 (0.388 - 1.359)	1.18 (1.02 - 1.35)

ART = antiretroviral therapy; TB=tuberculosis.

8.3. Appendix C: Supplementary material for Chapter 6

Appendix C Table 1: Assumed sensitivity and specificity of Xpert Ultra tests by smear-status from mid-2017

	Value	Source
Sensitivity of Xpert Ultra ($Se_{Ul}(a)$)		(286,367)
Smear-positive ($Se_{Ul}(1)$)	0.99	
Smear-negative ($Se_{Ul}(0)$)	0.77	
Specificity of test		
Xpert Ultra (Sp_{Ul})	0.99	(287,366)

Appendix C Table 2: Changes in ART coverage when ART interruptions are reduced between 2023 and 2030

	2023	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Baseline								
ART coverage in males age 15+	0.692	0.704	0.714	0.722	0.729	0.734	0.738	0.741
ART coverage in females age 15+	0.747	0.751	0.754	0.756	0.758	0.760	0.761	0.763
Reduced ART interruptions								
ART coverage in males age 15+	0.692	0.841	0.858	0.872	0.883	0.892	0.899	0.905
ART coverage in females age 15+	0.747	0.897	0.905	0.911	0.916	0.920	0.923	0.925

Appendix C Table 3: Changes in the numbers of adults screened microbiologically when the proportion of screening is doubled

	2023	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Baseline	2906720	2945680	2981440	3016240	3050520	3083980	3116340	3146920
Doubling screening	5813440	5711540	5789040	5857650	5924550	5989710	6052830	6112580

Appendix C Table 4: Changes in the numbers of preventative therapy initiations when the rates of initiations are doubled

	2023	2024	2025	2026	2027	2028	2029	2030
Baseline	359817	356958	355429	354530	353902	353400	352893	352289
Doubled TPT initiations	692631	674597	668816	666940	666185	665752	665266	664538

8.4. Appendix references

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