Mathematical modelling of tuberculosis in South Africa: investigating the impact of interventions on population-level incidence and mortality

by
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DECLARATION

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ABSTRACT

Background. Tuberculosis (TB) remains a major public health threat in South Africa. Substantial additional efforts are therefore needed to prevent, find, and successfully treat the disease. An increasing number of mathematical modelling studies have investigated the population-level impact of TB prevention and care interventions; however, this evidence has not yet been assessed in the South African context. Of particular concern for TB care in South Africa is the high proportion of initial loss to follow-up (ILTFU), defined as loss to follow-up of individuals who were diagnosed with TB but who did not (yet) initiate TB treatment. The aim of this thesis was to review existing literature on TB mathematical modelling research to determine the most effective intervention strategies to reduce TB burden in South Africa, to identify potential gaps in TB modelling research, and further, to conduct a mathematical modelling study to estimate the impact of reducing ILTFU in South Africa.

Methods. A systematic review of studies that used transmission-dynamic models of TB in South Africa was conducted. PubMed, Scopus, and Web of Science databases were searched. Target populations, types of interventions, and estimates of impact on outcomes related to the End TB strategy targets were summarized. For country-level studies, average annual percentage declines (AAPDs) in TB incidence and mortality were estimated to compare the impact of interventions. Additionally, an existing TB transmission-dynamic model was adapted to estimate the impact of reducing ILTFU in South Africa. Data from the LINKEDIn study, a large quasi-experimental study that was conducted in three South African provinces, were used to inform model scenarios and intervention parameter estimates. The impact of scaling-up the LINKEDIn intervention to country level was specified as the number of incident cases and deaths averted over a 13-year period (2023-2035).

Results. Twenty-nine studies were identified in the systematic review, of which seven modelled TB preventive interventions, 12 considered interventions along the TB care cascade, and 10 modelled combinations of both. One study considered reductions in TB-related catastrophic costs. The highest impact of a single intervention was estimated in studies of TB vaccination, preventive treatment among people living with HIV, and scale up of antiretroviral treatment. For preventive interventions, AAPDs for incidence varied between 0.06% and 7.07%, and for care-cascade interventions between 0.05% and 3.27%. In the modelling study, reducing ILTFU by 50% in the population was projected to avert 49,812 (95% uncertainty interval [UI]: 21,258-84,644) incident TB cases and 21,479 (UI: 9,500-32,661) deaths between 2023 and 2035. Sensitivity analyses showed that population-level impact would depend on rapid implementation and maximum effect of the intervention.

Conclusion. This thesis describes a body of mathematical modelling research with focus on TB prevention and care in South Africa. Higher estimates of impact reported in studies of preventive interventions were found, highlighting the need to invest in TB prevention in South Africa. The population-level impact of reducing ILTFU was projected to be modest. Combinations rather than single interventions, such as the LINKEDIn intervention, are likely needed to reach the End TB Strategy targets in South Africa.

Keywords: Tuberculosis; South Africa; systematic review; interventions; transmission-dynamic model; initial loss to follow-up

OPSOMMING

Agtergrond. Tuberkulose (TB) bly 'n groot bedreiging vir openbare gesondheid in Suid-Afrika. Aansienlike bykomende pogings is dus nodig om die siekte te voorkom, op te spoor en suksesvol te behandel. 'n Toenemende aantal wiskundige modelleringstudies het die bevolkingsvlakimpak van TB-voorkoming en sorgintervensies ondersoek; hierdie werk is egter nog nie in die Suid-Afrikaanse konteks beoordeel nie. Van besondere kommer vir TB-sorg in Suid-Afrika is die hoë proporsie van aanvanklike verlies tot opvolg (ILTFU), gedefinieer as verlies aan opvolg van individue wat met TB gediagnoseer is, maar wat (nog) nie TB-behandeling begin het nie. Die doel van hierdie tesis was om bestaande literatuur oor TB wiskundige modelleringsnavorsing te hersien om die mees doeltreffende intervensiestrategieë te bepaal om TB-las in Suid-Afrika te verminder, om potensiële leemtes in TB-modelleringsnavorsing te identifiseer, en verder om 'n wiskundige modelleringstudie uit te voer om die impak van die vermindering van ILTFU in Suid-Afrika te beraam.

Metodes. 'n Sistematiese oorsig van studies wat oordrag-dinamiese modelle van TB in Suid-Afrika gebruik het, is uitgevoer. PubMed-, Scopus- en Web of Science-databasisse is deursoek. Teikenpopulasies, tipes intervensies en ramings van impak op uitkomste wat verband hou met die eind-TB-strategie-teikens is opgesom. Vir studies toepaslik tot die hele Suid-Afrikaanse bevolking is gemiddelde jaarlikse persentasie dalings (AAPDs) in TB-voorkoms en mortaliteit beraam om die impak van intervensies te vergelyk. Daarbenewens is 'n bestaande TB-oordrag-dinamiese model aangepas om die impak van die vermindering van ILTFU in Suid-Afrika te beraam. Data van die LINKEDIn-studie, 'n groot kwasi-eksperimentele studie wat in drie Suid-Afrikaanse provinsies uitgevoer is, is gebruik om modelscenario's en intervensie parameter beramings in te lig. Die impak van die uitbreiding van die LINKEDIn-invensie na die hele Suid-Afrika is gedefinieer as die aantal TB gevalle en sterftes wat oor 'n tydperk van 13 jaar (2023-2035) afgeweer is.

Resultate. Nege-en-twintig studies is in die sistematiese oorsig geïdentifiseer, waarvan sewe TB-voorkomende intervensies, 12 intervensies tot die TB-sorgkaskade, en 10 kombinasies van beide gemodelleer het. Een studie het verlagings in TB-verwante katastrofiese koste oorweeg. Die grootste impak van 'n enkele intervensie is beraam in studies van TB-inenting, TPT vir mense wat met MIV leef, en opskaal van antiretrovirale behandeling. Vir voorkomende intervensies het AAPD's vir insidensie tussen 0.06% en 7.07% gewissel, en vir sorg-kaskade intervensies tussen 0.05% en 3.27%. In die modelleringstudie, is die vermindering van ILTFU met 50% in die bevolking geprojekteer om 49 812 (95% onsekerheidsinterval [UI]: 21 258-84 644) TB-gevalle en 21 479 (UI: 9 500-32 661) TB-sterftes tussen 2023 en 2035 te voorkom. Sensitiwiteitsanalises het getoon dat bevolkingsvlak impak sal afhang van vinnige implementering en die maksimum effek van die intervensie.

Afsluiting. Hierdie tesis beskryf 'n geheel van wiskundige modelleringsnavorsing met die fokus op TB-voorkoming en -sorg in Suid-Afrika. Hoër ramings van impak wat in studies van voorkomende intervensies gerapporteer is, is gevind, wat die behoefte beklemtoon om in TB-voorkoming in Suid-Afrika te belê. Die impak op bevolkingsvlak van die vermindering van ILTFU is geprojekteer om beskeie te wees. Kombinasies eerder as enkele intervensies, soos die LINKEDIn-intervensie, is waarskynlik nodig om die eind-TB-strategie-teikens in Suid-Afrika te bereik.

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Publications, presentations, and dissemination plan

This work has been presented at SACEMA research days for which I won runner-up best presenter in 2021 and best presenter in 2022, as well as on multiple occasions in an informal setting to colleagues at SACEMA and Stellenbosch University.

We plan to disseminate findings of this thesis through two publications. The first (presented in Chapter 2) is a systematic review of TB transmission-dynamic mathematical modelling studies, focusing on the impact of different interventions on population-level outcomes in South Africa (objective 1). The second (presented in Chapter 3) is focused on implementing an intervention to reduce initial loss to follow-up in South Africa using an existing transmission-dynamic mathematical model (objective 2).

The first study (Chapter 2) has been accepted for publication at the South African Medical Journal:

"Impact of interventions on tuberculosis prevention and care in South Africa – a systematic review of mathematical modelling studies" (https://doi.org/10.7196/SAMJ.2023.v113i3.16812, March 2023 issue)
Brown, L; van Schalkwyk, C; de Villiers, A; Marx, F

My contributions as first author to the systematic review:

I developed and wrote the study protocol with the help of Dr Florian Marx and Dr Cari van Schalkwyk which was published in the international prospective register for systematic reviews (PROSPERO; CRD42021276526). I conducted all literature searches, extracted, and synthesized data from included studies, wrote the first draft, finalized, and submitted the manuscript to SAMJ. Dr van Schalkwyk and Dr Marx provided input during the methods and results design as well as the write up of the manuscript. With help from Abigail de Villiers, I conducted a risk of bias assessment on all included studies of the systematic review. All authors reviewed the manuscript and approved its final version for submission.

We plan to publish the second study (Chapter 3), a mathematical modelling study which aims to estimate the impact of reducing initial loss to follow-up in South Africa, following submission of this thesis.

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Key abbreviations

Abbreviation	Description
AAPD	Average annual percentage decline
ACF	Active case finding
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BCG	Bacille Calmette-Guérin vaccine
CICF	Community-based active case finding
DS-/DR-TB	Drug-susceptible/ drug-resistant TB
DST	Drug susceptibility testing
HIV	Human immunodeficiency virus
I(LTFU)	(Initial) loss to follow-up
IPT	Isoniazid preventive therapy
M.tb	*Mycobacterium Tuberculosis*
MDR-/XDR-TB	Multidrug-resistant/ extensively drug-resistant TB
NTP	South Africa's National Tuberculosis Programme
PHC	Primary health-care facility
PLWH	People living with HIV
PRCC	Partial rank correlation coefficient
RS-/RR-TB	Rifampicin-susceptible/ rifampicin-resistant TB
TB	Tuberculosis
TB MAC	TB Modelling and Analysis Consortium
TPT	TB preventive treatment
WHO	World Health Organization

1 Introduction

1.1 Background on tuberculosis

1.1.1 Epidemiology of tuberculosis

Tuberculosis (TB) is a curable and preventable infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*). The bacterium was isolated more than 140 years ago (1), however the disease continues to affect approximately 10 million people yearly with 1.5 million deaths recorded each year (2). *M.tb* is predominantly transmitted by airborne infectious aerosol through coughing, sneezing, singing, and talking. Characteristic symptoms of TB disease may include prolonged coughing, chest pain, weakness or fatigue, weight loss, fever, and night sweats (3).

There are different aspects of TB that make the disease difficult to diagnose, treat, and control (4). TB can evolve from a contained infection, known as latent TB, to active disease at which point an individual may develop symptoms. TB can manifest as subclinical (without symptoms) or clinical disease in an infected person, in the lungs (pulmonary TB) or other parts of the body such as in bones (extrapulmonary TB). The disease can become resistant to the drugs used for treatment which is one of the most difficult challenges in TB control. Increased resistance often results in unsuccessful treatment outcomes (5). Some individuals are more at risk of developing active TB than others. These include, but are not limited to, immunocompromised individuals such as people living with HIV (PLWH) or diabetes, people living in high populous areas which are associated with malnutrition and increased air pollution, adults in their most productive years (although TB can affect all age groups), and people with increased intake of alcohol and tobacco use (6).

1.1.2 Major factors influencing the TB epidemic in South Africa

Together with growing drug resistance of TB, the HIV epidemic is said to be the cause of the rapid increase in TB burden in the 1990s which has negatively impacted TB control in South Africa (7). In 2021, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated an HIV prevalence in adults aged 15-49 of 18.3% (15.6 – 20.5%) in the country which highlights the major contribution towards TB burden (8). It has been estimated that 55% of TB cases and 69% of TB deaths between 1990 and 2019 were due to HIV, consistent with the idea that HIV has a substantial population-level effect on TB (9).

Since 2019, SARS-CoV-2 has also largely contributed to an increase in TB burden across the globe due to substantial disruptions in TB health services (10). A recent review found that COVID-19 negatively impacted TB and HIV control in South Africa due to diversion of key resources from TB and HIV control to COVID-19 response, lack of patient access to health care, and suspension of TB and HIV research (11). The WHO's Global TB report for 2022 states that COVID-19 continues to negatively impact TB diagnosis and treatment, stalling progress towards the End TB strategy targets. The main outcome of TB impacted by the COVID-19 pandemic was the large decrease in case notifications reported in 2020. There was, however, partial recovery from this decrease in 2021 (2).

1.1.3 The World Health Organization's End TB strategy targets

In 2014, the World Health Assembly adopted the WHO's post-2015 End TB strategy to eliminate TB globally through targets for prevention, care, and control by 2035 (12). The targets include a reduction in TB incidence rates by 90%, the number of TB deaths by 95%, and ensuring zero catastrophic costs are incurred by TB-affected households, compared to 2015 levels. According to WHO data, for South Africa to reach these goals the country requires a reduction in the TB

incidence rate from 988 to 98.8 per 100,000 population and the number of TB deaths to decrease from 65,000 to 3,250 by 2035 (2). Although South Africa has reached the first milestone of the End TB strategy to reduce TB incidence by 20% compared to 2015 levels (2), the country is unlikely to reach the 2035 targets with current strategies (13,14).

1.1.4 TB prevention and care strategies

Several pharmaceutical and non-pharmaceutical interventions for TB control exist in South Africa and elsewhere. Current preventive strategies include vaccination with the Bacille Calmette-Guérin (BCG) vaccine, antiretroviral treatment (ART) among PLWH, treating latent TB infection and screening initiatives among high-risk groups, as well as TB preventive treatment (TPT) such as isoniazid preventive therapy (IPT) and rifampicin, among others (15).

In addition to preventative measures, interventions along the TB care cascade are vital in reducing losses between TB diagnosis, initiating treatment, and successful treatment completion (13,16). These interventions may include targeted case finding initiatives, introduction of novel diagnostic tools (e.g., using more sensitive diagnostic tools such as Xpert Ultra, or drug susceptibility testing), improving linkage to care (e.g., through better communication between patients and health care workers), and treatment interventions (e.g., novel or shorter treatment regimens, improving treatment adherence), among others (17).

Estimating which of these interventions have had the greatest impact on TB incidence and mortality in South Africa in recent years will provide guidance on resource allocation for future research. I consider this research gap through a systematic review of transmission-dynamic mathematical modelling papers in Chapter 2.

1.1.5 The care cascade and initial loss to follow-up in South Africa

Individuals with presumptive TB may be lost along the care cascade anywhere between accessing health care services, receiving test results, initiating TB treatment, and successfully completing their treatment. Identifying and quantifying these losses is useful for highlighting gaps in health systems, and planning strategies to improve the quality of care (18). Care cascades have been widely used in HIV research in South Africa (19–21), and are being increasingly used to evaluate TB control (16,22). In 2013, it was estimated that ~53% of individuals who accessed care in South Africa were successfully treated (13). This estimate was updated to ~47% in 2020, presented by the TB Think Tank during a meeting titled “Finding the missing people with TB” in May of 2022 (correspondence: South African TB Think Tank). This highlights the need for increased efforts to improve existing measures and close the gaps along the cascade.

Initial loss to follow-up (ILTFU), defined by the WHO as a “TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more” (23), is an important gap in the South African TB care cascade (24–26). Individuals who are ILTFU are a concern for TB programmes as they are associated with poor patient outcomes (24,27) and are expected to contribute to onward transmission. An estimated 21% of diagnosed TB patients in South Africa are initially lost to follow-up (13). Several studies have reported underlying reasons and risk factors for ILTFU in South Africa. Healthcare-related factors identified include poor communication and lack of counselling by health care workers, misinterpretation of diagnostic results, under-resourced facilities, and negative staff attitudes (26,28). Patient-level factors include poor knowledge on TB treatment, stigma surrounding TB (especially its linkage to HIV), and other socioeconomic factors (such as poverty and lack of transport to primary health care facilities) (24). Various interventions to avert ILTFU have been proposed. These include more attention to keep track of, register, and report TB patients who did not timely initiate treatment (29), ensuring that correct contact information is recorded upon registration of a patient, in case follow-up is

necessary, clear communication of diagnostic results to patients, interventions to support treatment initiation such as registration of TB patients in hospitals (30), and early interaction with TB patients to facilitate timely registration and treatment initiation (31).

1.2 Different models used in infectious disease modelling

Infectious disease models are important tools for evaluating the effect of intervention strategies and assisting policymakers in making informed decisions. There are a vast range of models that are used to predict, assess, and control potential infectious disease outbreaks which fall under statistical models (e.g., spatial models and regression techniques) and mathematical/ mechanistic models (e.g., deterministic compartmental and stochastic Markov Chain models) (32). A key distinction between the model types, is that mathematical models simulate transmission and other biological processes, while statistical models assume a distributional shape of the epidemic (33). Within the mathematical model group, further comparisons can be made including dynamic versus static models, individual-based versus compartmental models, and deterministic versus stochastic models.

Approaches to mathematical modelling of diseases can be static or dynamic. Static models assume that, over time, the probability of disease exposure is constant in the population or varying in a pre-defined way (34), while dynamic models allow the risk of infection to depend on the time-varying prevalence of infectious individuals (35). A further distinction that can be made are individual-based vs. compartmental models which can either be static or dynamic. In summary, compartmental models aggregate individuals in a population according to common characteristics where they, in essence, lose their individuality. Individual-based models, however, track each member of the population independently where they experience events tailored to their demographics and behaviour (36). Distinguishing between deterministic models and stochastic models is also important when considering different modelling techniques. When given an input parameter set, deterministic outcomes will be the same for each model run. Alternatively, as a result of the intrinsic randomness in events simulated by stochastic models, outcomes will be different each time the model is run (36,37).

In this thesis, I focus on transmission-dynamic compartmental TB models in South Africa which are being increasingly used to estimate the impact of different interventions on population-level outcomes such as incidence and mortality (38–40).

1.3 Problem statement

South Africa remains one of five high TB burden countries to have more than 500 cases per 100,000 population in 2021 (2). Recently, considerable declines in individuals accessing healthcare services, TB testing and diagnosis have occurred in conjunction with lockdown measures implemented to contain SARS-CoV-2 transmission (10). Consequently, TB incidence, prevalence and mortality are expected to rise which will impact South Africa's progress towards achieving the End TB strategy targets.

To mitigate these adverse consequences, substantial efforts are required to prevent, find, and successfully treat TB in the country. Through the systematic review in Chapter 2, I extract data from existing TB modelling studies in South Africa to determine which types of interventions could result in the largest reduction in TB burden. Additionally, the review identifies gaps in mathematical modelling research that should be addressed to better inform policy making in South Africa. Using findings from the review, Chapter 3 implements a modelling approach to fill one of these gaps – to estimate the impact of reducing ILTFU in the South African population, a key loss in the TB care cascade. Having estimated which interventions could be most successful in reducing

TB burden in South Africa, as well as filling a knowledge gap in TB research, allows for a better understanding of where resources could be best allocated in this high-burden country.

1.4 Justification

Identifying which types of interventions should be focused on for TB prevention and control, and estimating the impact of these useful interventions, will aid in reducing TB burden in South Africa. Many systematic reviews focusing on mathematical modelling of TB control measures exist (41–43), but none have considered the impact of different types of interventions in the South African context specifically. With regards to reducing ILTFU, several mathematical models have estimated the impact of related interventions in the South African population (44–46), however, to my knowledge, none involve the use of data from a study that has been implemented in the country, and none has simulated ILTFU within the detailed TB care cascade.

Toward this thesis, I conducted a systematic review of mathematical modelling studies in South Africa to determine the most impactful interventions for TB control in the country. The systematic review is especially relevant in the context of the 2023-2028 National TB programme (NTP) Strategic plan and will highlight important research gaps for further modelling studies for South Africa. Additionally, I addressed an important gap, estimating the impact of reducing ILTFU in South Africa through a mathematical modelling study. I used data and expert opinion provided by researchers from the LINKEDIn study, a large quasi-experimental study that was conducted in three South African provinces, to estimate population-level impact of scaling-up their intervention countrywide.

The combination of the systematic review and modelling study will add to the existing body of TB research in South Africa and has implications for TB decision making.

1.5 Research questions

This thesis aims to answer the following research questions:

1. “In South Africa, what is the population-level impact of different types of interventions for tuberculosis prevention and care towards the targets of the End TB strategy projected by mathematical modelling research?”

2. “What is the estimated impact of reducing initial loss to follow-up at country-level on TB incidence and mortality in South Africa?”

1.6 Aims and objectives

The aim of this project was to systematically review existing mathematical modelling research to determine the most effective intervention strategies to reduce TB burden in South Africa, to identify gaps in this research, and further conduct a mathematical modelling study to estimate the impact of reducing initial loss to follow-up in South Africa. The following objectives were used to complement this aim:

1. Conduct a systematic review of mathematical modelling studies in South Africa that estimated the impact of prevention and care interventions on population-level outcomes linked to the WHO’s End TB strategy Targets (TB incidence, mortality, and TB-affected households facing catastrophic costs), and determine which interventions had the most promising impact towards reducing TB burden.

2. Adapt an existing transmission-dynamic mathematical model of TB to estimate the population-level impact of reducing initial loss to follow-up on TB incidence and mortality in South Africa using data and estimates from a large implementation study conducted in three South African Provinces.

1.7 Ethical considerations

This thesis includes a systematic review (Chapter 2) and a mathematical modelling study (Chapter 3). The systematic review involved a search of publications using three online databases (Scopus, PubMed, and Web of Science) accessible through Stellenbosch University, as well as the TB Modelling and Analysis Consortiums' (TB MAC) publicly available list of publications. Our search resulted in 29 publications which were obtained from online database searches (n = 27), the TB MAC public database (n = 1) and reference list searches (n = 1). No individual patient-level data was accessed during this review.

The modelling study simulated population-level tuberculosis incidence, and mortality at country-level in South Africa. No individual patient-level data was used. Additional data required, such as parameter estimates for the baseline level of initial loss to follow-up in South Africa was obtained through review of the published literature (the systematic review conducted as well as recent epidemiological studies on tuberculosis) and expert opinion. The mathematical model used in this study was developed as part of another project and has been previously calibrated for the South African context.

An application for exemption from ethical clearance (Project ID: 26464, HREC reference number X22/09/023) was approved by the Health Research Ethics Committee (HREC) on 12/10/2022.

1.8 Thesis overview

The outline of this thesis is as follows: Chapter 1 consists of relevant background information on TB and describes interventions and strategies used to prevent and treat the disease. The purpose, justification and objectives of the study are also outlined in the first chapter. Chapter 2 acts as the first paper in the thesis. It is a systematic review of mathematical models used to determine which existing interventions for TB prevention and care are most promising in reducing TB incidence and mortality in South Africa. The review is used to highlight important gaps in TB modelling research in South Africa. Chapter 3 describes findings from a mathematical modelling study. I used an existing transmission-dynamic mathematical model to estimate the number of incident TB cases and TB deaths that could be averted if an intervention to reduce ILTFU in the South African population was scaled up country wide. The study uses data and estimates from the LINKEDin study, a large implementation study to reduce ILTFU in three South African provinces. Chapter 4 includes the discussion of the research conducted towards this thesis as a whole and provides recommendations for future research.

2 Impact of interventions for tuberculosis prevention and care in South Africa – a systematic review of mathematical modelling studies

This chapter presents a study that has been accepted for publication in the peer-reviewed scientific journal, the South African Medical Journal. The manuscript is titled "*Impact of interventions for tuberculosis prevention and care in South Africa – a systematic review of mathematical modelling studies"* (https://doi.org/10.7196/SAMJ.2023.v113i3.16812) and will be published in the March 2023 issue. The study aims to systematically review TB transmission-dynamic mathematical modelling studies specific to South African populations at national and sub-national level that estimated the impact of interventions on outcomes that link to one of the three End TB strategy targets. This chapter also aims to identify gaps in TB modelling research.

2.1 Introduction

South Africa remains one of the countries with the highest TB burden in the world (2). In 2020, an estimated 328,000 people developed TB, and 61,000 people died from the disease (2); TB thus remains the leading infectious disease cause of death in the country (47). Recent measures to contain the spread of SARS-CoV-2 (10) have led to considerable declines in individuals accessing health care services, TB testing and individuals diagnosed with TB (48); resulting in an expected increase in TB prevalence and mortality. These developments have also seriously affected South Africa's progress towards the milestones and targets set for the World Health Organization (WHO)'s End TB strategy that aims to reduce the number of TB deaths by 95%, the TB incidence rate by 90% (relative to 2015), and the percentage of TB-affected families facing catastrophic costs due to TB to zero by 2035 (49).

To mitigate these adverse consequences on TB epidemiology and to restore progress towards the End TB strategy targets, substantial additional efforts are needed to prevent, find and successfully treat TB in South Africa. A comprehensive consultation process, coordinated by the TB Think Tank of the National Department of Health, is currently under way to define additional interventions to be implemented as part of South Africa's upcoming 2023-2027 National Tuberculosis Programme (NTP) Strategic Plan.

For policy makers to identify and implement strategies for optimal outcomes towards the End TB strategy targets, evidence must be collected to inform decisions (40). Generating this evidence directly through empirical research poses considerable challenges. Cluster-randomized trials to estimate the population-level impact of interventions on TB incidence, mortality and catastrophic costs demand considerable resources and time. They often focus on a limited set of (e.g., one or two) interventions, yielding limited insights into how these interventions will compare with alternatives (50).

Mathematical models for infectious diseases are valuable tools for evaluating the effect of intervention strategies and assisting policymakers in making informed decisions (51). Transmission-dynamic models of TB are increasingly used to estimate the impact of interventions on population-level outcomes in high-burden countries, including South Africa (38,39,52). To date, the evidence from mathematical modelling research on interventions to reduce TB incidence, mortality and catastrophic costs in South Africa has not been systematically assessed.

In an effort to support decision making for TB in South Africa, I reviewed mathematical modelling studies that estimated the population-level impact of interventions towards the End TB strategy targets for TB incidence and mortality, and catastrophic costs associated with TB. I aimed to describe the types of interventions, intervention designs and target populations considered, and the

impact estimated through modelling. I also aimed to highlight gaps in TB modelling research that could be addressed in future research to inform TB policy making in the country.

2.2 Methods

The PICOS (Population, Intervention, Control, Outcomes and Study design) tool (53) was employed to define the research question and the design of this systematic review. Table 2.1 outlines the application of the PICOS methodology. The review protocol is registered with the international prospective register for systematic reviews (PROSPERO; CRD42021276526). I adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for 2020 (54). The PRISMA checklist can be found in the appendix (Table A1).

Table 2.1: PICOS framework for the research question and the limit applied on each criterion

PICOS criterion	Definition	Limit management
Population	South Africa (country or subpopulations)	Search limit
Intervention	Any interventions reducing the impact of population-level outcomes (e.g., case finding, vaccination, TB preventive treatment, diagnosis, treatment)	No limit applied
Comparator	Current status quo of each modelled intervention	No limit applied
Outcome	Reduction in number of TB deaths, reduction in TB incidence rate, reduction in number of households facing catastrophic costs	Inclusion/exclusion criteria
Study Design	Transmission-dynamic, mathematical models	Search terms and Inclusion/exclusion criteria

2.2.1 Search strategy and selection criteria

I conducted a systematic search of the published literature using PubMed, Web of Science, and Scopus databases (see Table 2.2 for individual search strategies). Additionally, I searched the TB Modelling and Analysis Consortium's (TB MAC) list of mathematical and economic TB modelling studies (55), Global Index Medicus, African Index Medicus, and reference lists of eligible studies. I also consulted four leading global experts in TB modelling to identify additional publications not included in the initial search from their personal databases. The search was conducted up to September 28, 2021. No restriction on the year of publication was applied. I included articles that reported results using population-based, transmission dynamic models of TB in South Africa at country or sub-country level. I was interested in studies that estimated reductions in population-level TB outcomes (incidence, prevalence and/or mortality). The studies were required to model the impact of interventions towards at least one of the WHO's End TB strategy targets (i.e., TB incidence, TB mortality, or catastrophic costs due to TB). I excluded articles that reported statistical models of empirical data or cohort models that were not transmission dynamic. I further excluded reviews of modelling studies and articles describing mathematical models that did not refer to the South African population (or a population in South Africa).

Table 2.2: Search strategies for each of the electronic databases

Database	Search Terms
PubMed	("South Africa*"[Title/Abstract]) AND (Tuberculosis[Title/Abstract] OR TB[Title/Abstract]) AND ((mathem* AND (model or models)) OR (mathem* modell*) OR (mathem* modeling) OR (modelling OR modeling) OR "Population

	Dynamics"[MeSH Terms] OR "Population Dynamics" OR "System Dynamics" OR "Computer Simulation" OR "Computer Simulation"[MeSH Terms] OR "epidemiologic* model" OR "tuberculosis model" or "TB model" OR "transmission model" OR "dynamic model" AND model)
Scopus	(TITLE-ABS-KEY ("South Africa*") AND TITLE-ABS-KEY (Tuberculosis OR TB) AND ALL (((mathem* AND (model OR models)) OR (mathem* AND modell*) OR (mathem* AND modeling) OR (modeling OR modelling) OR "Population Dynamics" OR "System Dynamics" OR "Computer Simulation" OR "epidemiologic* model" OR "tuberculosis model" OR "TB model" OR "transmission model" OR "dynamic model" AND model)))
Web of Science	((AB=tuberculosis OR TI=tuberculosis OR AB=TB OR TI=TB) AND (AB=("South Africa*") OR TI = ("South Africa*")) AND ALL=(((mathem* AND (model OR models)) OR (mathem* modell*) OR (mathem* modeling) OR (modeling OR modelling) OR "Population Dynamics" [MeSH Terms] OR "Population Dynamics" OR "System Dynamics" OR "Computer Simulation" OR "Computer Simulation" [MeSH Terms] OR "epidemiologic* model" OR "tuberculosis model" OR "TB model" OR "transmission model" OR "dynamic model" AND model)))

2.2.2 Data extraction

Titles and/or abstracts of articles identified during the initial search were screened by two reviewers. The full texts of these studies were then retrieved and independently assessed for eligibility. Data extracted from eligible studies included the type of model, study population, intervention details, key study outcomes and model projections. For studies that modelled multiple scenarios of the same intervention, I extracted the scenario that resulted in the greatest impact. I described modelling results by type of intervention and target population with respect to estimated gains towards the End TB strategy targets. In addition, for studies describing country-level TB models, I compared average annual percentage declines (AAPDs) in TB incidence and mortality estimated for different interventions relative to base-case (no intervention). For articles reporting percentage declines over the entire model time horizon, I calculated AAPDs using the following formula

$$AAPD = (1 - \sqrt[t]{1 - PPD/100}) \times 100$$

where t denotes the time horizon of the model, and PPD the period percentage decline attributable to the intervention investigated (i.e., the percentage difference between the baseline scenario and intervention scenario at the end of the time horizon) reported in a study.

I illustrate how AAPDs are calculated in the assumed scenario Figure 2.1 (A) and I include an example of a typical realistic scenario of the reduction in incidence in Figure 2.1 (B) to show a scenario in which the assumption may fail. I assume the difference between baseline and intervention increases linearly over the time horizon as shown in Figure 2.1 (A). If a hypothetical intervention is introduced into a population, TB incidence is estimated to decline by an additional 30% compared to baseline at the end of the time horizon (15 years). The baseline scenario is defined as a continuation of current TB control measures in the country. The period percentage decline (PPD) is thus 30% compared to baseline. Using our AAPD formula for the assumed scenario (Figure 2.1 (A)), we obtain an AAPD of 2.35%.

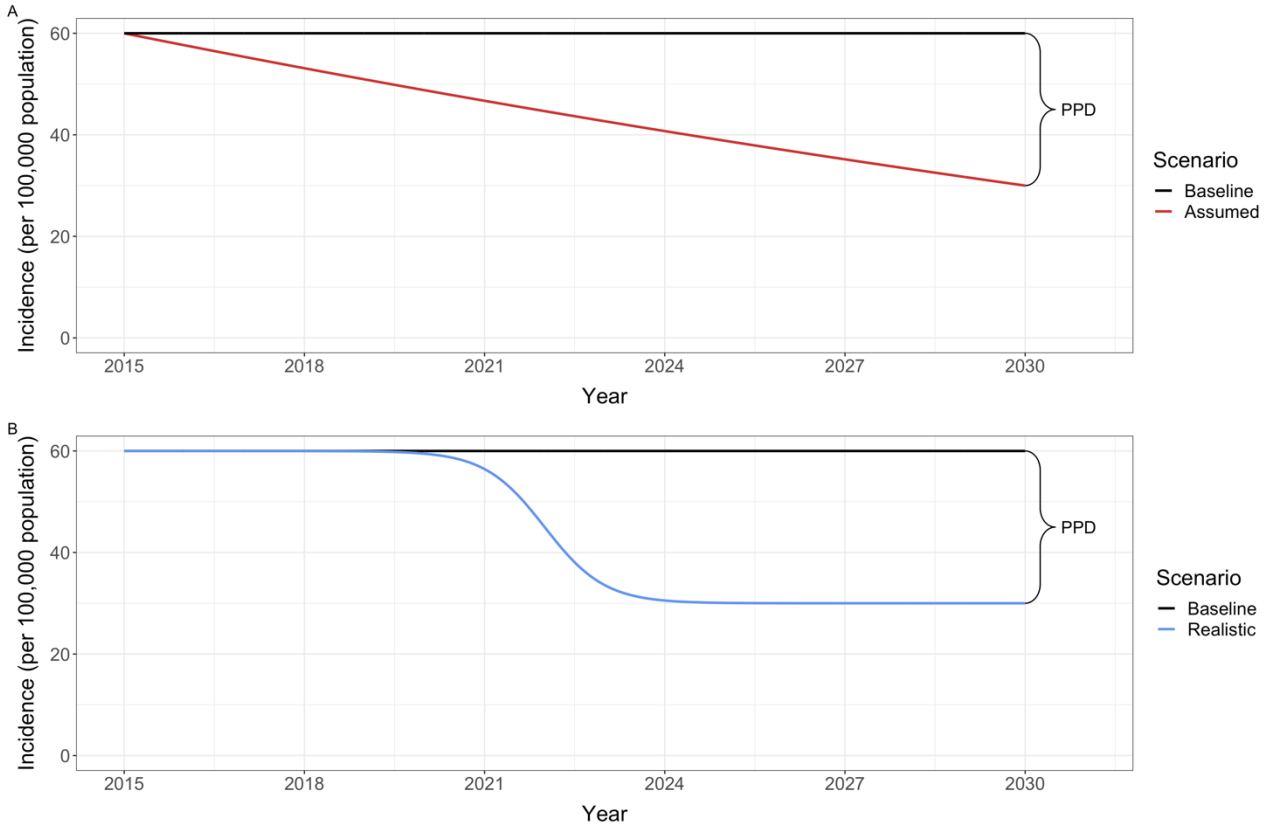

Figure 2.1: (A) Illustrative example of how AAPDs are calculated for different interventions in the review – assumed scenario compared to baseline. (B) Illustrative example of how this assumption may fail.

2.2.3 Risk of bias assessment

An adapted risk of bias tool (41,56,57) was used to assess the methodological quality of eligible modelling studies. Criteria in the tool included aims and objectives, setting and population, intervention(s) and comparator(s), outcome measures and research questions, modelling methods, parameter specifications, assumptions, data quality and uncertainty, fitting methods, validation, results and discussion presentation, funding sources, and conflicts of interest. Table 2.3 gives a full description of each criterion and considerations for the score given, adapted from Harris *et al.* (41). An overall score consideration of 0 was given if no required information was provided, 1 if some aspects of the study were incomplete, and 2 if the necessary information was clear and appropriate for the research question. A risk-of-bias score (0-28) was given to each study by adding itemised scores. In accordance with guidance from previous users of the tool, the quality of eligible studies was deemed very high (> 22), high (19-22), medium (14-18) or low (< 14) according to the risk of bias score.

Table 2.3: Risk of bias tool for the assessment of eligible modelling studies (adapted slightly from Harris *et al.* to fit the research question(41))

	Criterion	Considerations	Score considerations (0, poor to 2, good)	
1	**Are the aims and objectives clear?**	Are the research questions and modelling objectives clearly defined?	0 Not stated 1 Stated but vague 2 Stated and focussed	Definitions: max 8 points
2	**Is the setting and population clearly defined?**	Does the paper clearly state the setting (e.g., geographical location, high/low TB burden)?	0 Not stated 1 Stated but vague or details missing 2 Stated and focussed	
		Does the paper clearly state the modelled population? (e.g., patient or population group characteristics)		
		Have sub-populations necessary for the research question and setting been modelled?		
3	**Are the intervention and comparators adequately defined?**	Does the paper clearly state the population(s) targeted for specific interventions?	0 Not stated or very unclear 1 Stated but details missing 2 Stated and all necessary details stated	
		Does the paper clearly define the intervention characteristics (e.g., specificity/ sensitivity of a test, vaccine efficacy, duration of treatment)?		
		If there is a comparator (current status quo), is it clearly defined?		
4	**Are the outcome measures defined and answer the research question?**	Does the paper clearly define the outcomes of interest?	0 Not stated, very unclear or not suited to research question 1 Stated but details missing or not directly aligned with research question 2 Stated, all necessary details stated, and aligned with research question	
		Do the outcomes correspond to the research question?		
5	**Are the model structure and time horizon clearly described and appropriate for the research question?**	Is the model structure clearly reported and appropriate for the research question?	0 Not appropriate model structure, or poor/no description of model 1 Incomplete description, and/or appropriate in part for research question 2 Complete and reproducible, appropriate structure and time horizon	Model methods: max 4 points
		Does the model reflect current knowledge of disease natural history? Does the model consider subclinical disease in any form?		

		Is the time horizon and time step of the model clearly stated and appropriate to the research question (i.e., is it long enough to capture health effects)?		
6	**Are the modelling methods appropriate for the research question and adequately described?**	Were the modelling methods clearly described, and suited to the research question?	0 Not appropriate model structure, or poor/no description of methods 1 Incomplete description, and/or appropriate in part for research question 2 Complete and reproducible, appropriate method	
7	**Are the parameters, ranges and data sources specified?**	Are all parameters and their ranges reported? Are the data sources for parameters reported?	0 Poorly reported 1 Some information missing 2 Complete reporting of parameters, ranges and data sources	Model inputs: max 6 points
8	**Are any assumptions explicit and justified?**	Are all assumptions explicit and justified?	0 Not reported 1 Explicit 2 Explicit and justified	
9	**Is the quality of data considered and is uncertainty explored through uncertainty and/or sensitivity analyses?**	Are data limitations discussed? Are any of the sources known to the reviewer to be inappropriate (e.g., do not match the parameter, are outdated, or known to be poor quality)? Is uncertainty in model structure, parameters and/or assumptions explored through uncertainty and/or sensitivity analyses?	0 No sources or uncertainty 1 Partially addressed, and/or some data inappropriate 2 Fully addressed	
10	**Is the method of fitting described and suitable?**	Is the method of fitting/calibrating the model clearly described? Is the method of model fitting/calibration suitable?	0 Not done, unsuitable method or poor/no description 1 Incomplete description or method not optimal 2 Complete description and suitable methods	Fitting/ validation: max 4 points
11	**Has the model been validated?**	Has an assessment of validity of the results been made by comparing across one or more different model structures, or against a validation data set?	0 Not considered 1 States criteria for validation 2 Validation undertaken	

12	**Have the results been clearly and completely presented, with a range of uncertainty?**	Have the outcome values and their uncertainty ranges for each intervention/scenario been reported?	0 Not reported, very unclear or not suited to research question 1 Stated, but ranges or planned sensitivity analyses missing and/or not directly aligned with research question 2 Values and ranges and planned sensitivity analyses reported and aligned with research question.	Results: max 4 points
		Do the results match the objectives?		
		Are sensitivity analyses clearly reported?		
13	**Are the results appropriately interpreted and discussed in context?**	Does the discussion reflect a fair and balanced interpretation of the results?	0 No/poor discussion 1 Some discussion but key points, limitations or context missed 2 Full discussion of key points in context, generalisability considered, limitations discussed	
		Are the results of the study discussed in context and is generalisability considered?		
		Are possible biases and limitations discussed?		
14	**Are the funding source and conflicts of interest reported?**	Is the funding and the role of the funder clearly stated?	0 No statement of funding or conflicts 1 Funding or conflicts reported 2 Funding and conflict statement	Conflicts: Max 2 points
		Is there a conflict of interest statement?		

Overall Scoring: Max 28 points	
Very high	>22
High	19-22
Medium	14-18
Low	<14

2.3 Results

2.3.1 Search process and selection of articles

The initial search yielded a total of 2,128 records of which 1,243 were unique records. The majority of articles excluded at title and abstract screening (n=1168) described statistical models, descriptive analyses, or static cost-effectiveness models. Following full-text review of 75 articles, I identified a total of 29 that met the inclusion criteria. A full breakdown of articles identified for this review is shown in Figure 2.2. Detailed reasons for exclusion at full-text review for transmission dynamic modelling studies are provided in addendum A (Table A2).

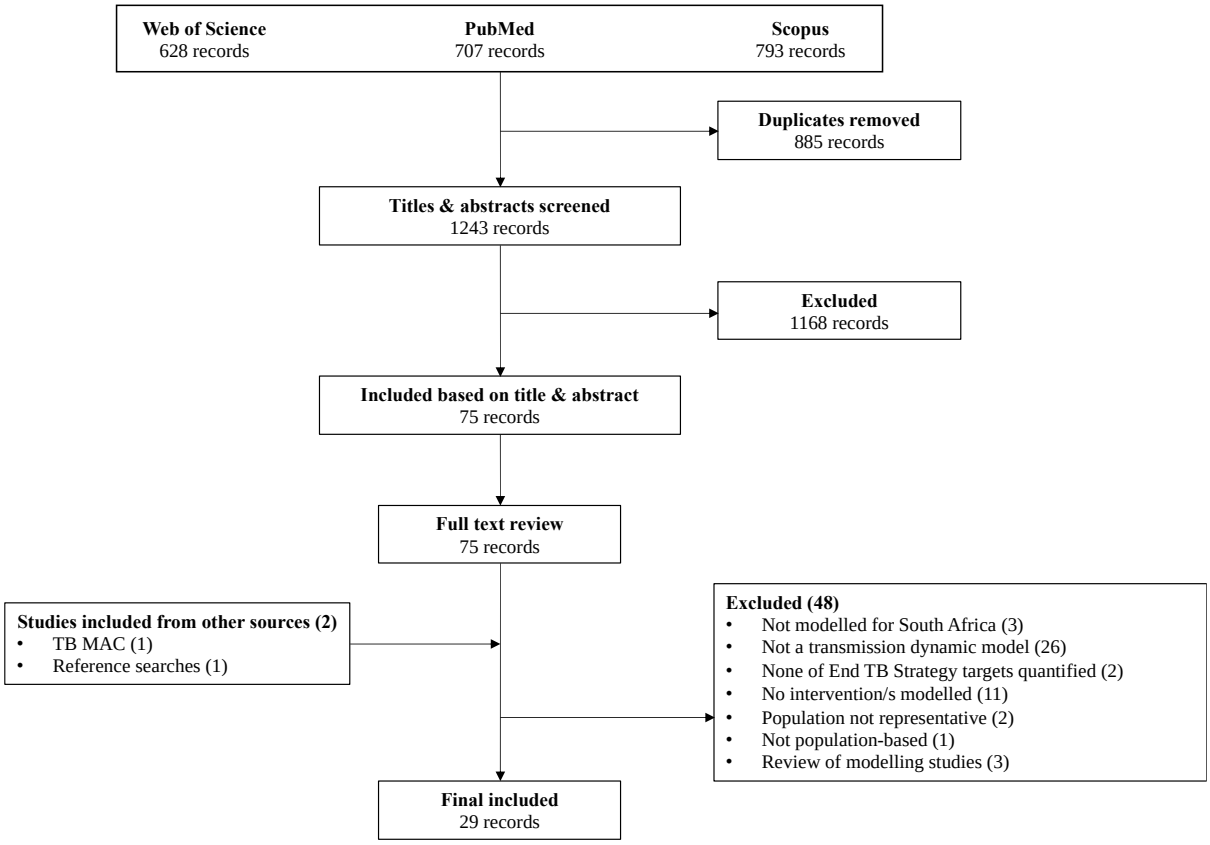

Figure 2.2: Flow diagram of the study selection process.

2.3.2 Risk of bias assessment

From 29 eligible records assessed for quality, 16 received a risk-of-bias score of > 22, and were considered of very high quality, and 13 received a score of 19-22, considered of high quality. A median score of 23 (of 28) was recorded, equivalent to very high quality. Reductions in the score were due to lack of model validation, incomplete parameter descriptions, lack of justification of assumptions made, and several missing limitations and study context in results. Detailed scores of the assessment for the individual studies are provided in Table 2.4.

Table 2.4: Risk of bias assessment of included studies

Study	Risk of Bias item														Final Score	Quality Grading
	Aims & Objectives	Setting & Population	Interventions & Comparators	Outcome measures	Model structure & Time horizon	Modelling methods	Parameters, Ranges & Data sources	Assumptions	Quality of data & Exploration of uncertainty	Methods of fitting	Model validation	Results	Interpretation & Discussion of results	Funding sources & Conflicts of interest		
Azman *et al.* (58)	2	1	1	2	2	2	1	1	2	1	0	2	2	2	21	High
Basu *et al.* (59)	2	1	1	2	2	2	2	2	2	2	2	2	2	2	26	Very High
Basu *et al.* (60)	2	2	2	2	2	1	2	2	2	2	0	2	1	1	23	Very High
Chindelevitch *et al.* (61)	2	2	2	2	2	2	2	1	2	2	1	2	2	2	26	Very High
Dowdy *et al.* (62)	2	2	2	2	2	1	1	2	2	1	0	2	2	1	22	High
Dye *et al.* (63)	2	2	2	1	2	1	1	1	1	2	0	1	1	2	19	High
Dye *et al.* (64)	2	2	2	2	1	2	2	2	1	2	0	2	1	1	22	High
Gilbert *et al.* (65)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28	Very High
Gilbert *et al.* (66)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28	Very High
Harris *et al.* (67)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Hippner *et al.* (45)	2	2	2	2	2	2	2	1	1	1	0	1	1	2	21	High
Houben *et al.* (40)	2	2	2	1	2	2	1	1	1	1	0	1	2	2	20	High
Kendall *et al.* (68)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Kendall *et al.* (69)	2	2	2	2	2	2	2	2	2	2	0	2	2	1	25	Very High
Knight *et al.* (44)	2	2	2	2	2	2	2	1	1	1	0	1	2	2	22	High
Knight *et al.* (70)	2	2	2	2	2	2	1	1	1	2	0	1	2	2	22	High

Marx *et al.* (71)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Marx *et al.* (72)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Menzies *et al.* (38)	2	2	2	2	2	2	2	1	2	2	0	2	2	2	25	Very High
Pretorius *et al.* (73)	2	2	2	2	2	2	1	1	1	2	0	1	1	2	21	High
Rhines *et al.* (74)	2	2	2	2	2	2	1	1	1	1	0	2	1	2	21	High
Ricks *et al.* (75)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Shrestha *et al.* (76)	2	2	2	2	2	1	1	1	1	2	0	1	1	2	20	High
Sumner *et al.* (77)	2	2	2	2	2	2	2	2	2	2	0	1	1	2	24	Very High
Sumner *et al.* (78)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Uys *et al.* (79)	2	2	1	2	2	2	1	1	2	1	0	2	1	0	19	High
Verguet *et al.* (80)	2	2	2	2	2	2	1	2	2	1	0	2	2	2	24	Very High
Vynnycky *et al.* (46)	2	2	2	2	2	2	2	2	2	2	0	1	1	2	24	Very High
Williams *et al.* (81)	2	2	1	2	2	2	1	1	2	1	2	2	1	1	22	High

2.3.3 Characteristics of eligible studies

Studies varied considerably in terms of model design, time horizon over which interventions were modelled, study population, type of intervention and outcomes measured (Figure 2.3). Of the 29 articles included, 20 described deterministic compartmental models, (38,45,46,58,59,61–69,74,75,77–79,81) three stochastic compartmental models, (60,71,72) and three stochastic individual-based models (IBM) (44,70,76). The remaining three studies used a combination of different types of transmission-dynamic models (40,73,80). All but one study included stratifications by HIV status to account for the modifying effect of HIV infection on TB natural history (79). With respect to the End TB strategy targets, all but two studies (60,80) reported outcomes for reductions in TB incidence, 17 reported reductions in TB mortality, (38,44,45,58,60–62,64,65,67–73,75) and only one (80) considered catastrophic costs averted due to TB interventions.

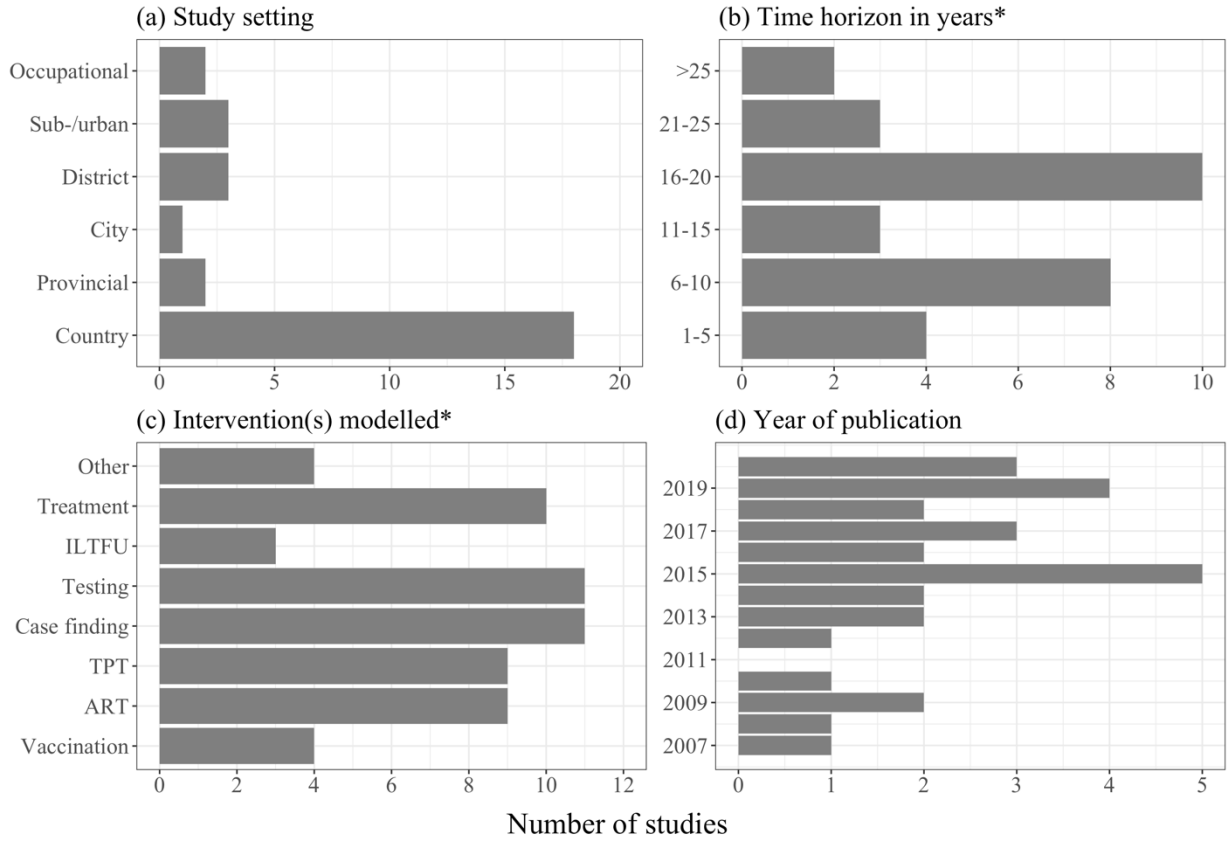

Figure 2.3: The number of included studies grouped by different characteristics.
*Models may use multiple interventions. (ILTFU = initial loss to follow-up, TPT = TB preventive treatment, ART = antiretroviral therapy)

2.3.4 Interventions modelled

Of the 29 studies identified, 22 modelled hypothetical interventions, while seven modelled scenarios for scale up of existing interventions (38,61,63,69,73,77,81). Seven studies modelled preventive interventions, (64,67,69,73,74,76,81) 12 considered interventions along the care cascade for TB, (38,45,58,60,62,68,70,75,77–80) and 10 considered a combination of both (40,44,46,59,61,63,65,66,71,72). Table 2.5 provides an overview of key characteristics and study outcomes by type of intervention and setting for the studies included in this review. Estimates of impact measured in the studies are provided below.

2.3.4.1 Vaccination

Three studies estimated the impact of vaccination against TB, two of which modelled novel vaccines (63,67), and one considered revaccination using the Bacillus Calmette-Guerin (BCG) vaccine (64). Considerable reductions in TB incidence and mortality were projected for a hypothetical novel vaccine with 70% efficacy in preventing *M.tb* infection (63), and a different hypothetical novel vaccine with 100% efficacy, equally effective in PLWH and HIV-negative people, *M.tb* infected and *M.tb* uninfected populations (67). The latter study considered various vaccination strategies including early-adolescent and 10-yearly mass vaccination campaigns (67). Re-vaccinating HIV-negative adolescents in an urban high-transmission setting using the BCG vaccine (efficacy: 10-80%) was estimated to be of limited impact but potentially cost-effective (64).

2.3.4.2 ART for TB prevention

Five studies estimated the impact of ART scale up for TB prevention in South Africa. Two were published in 2015 (44,61) and one in 2014 (73), at a time when ART eligibility in South Africa was limited to people living with HIV (PLWH) with a CD4 count of ≤500 cells per mm^3 (82) and focused on expanding ART towards universal treatment (regardless of CD4 count). Reaching 80% coverage among PLWH was estimated to reduce TB incidence and mortality substantially (61,73), while a coverage of 42% was estimated to be of lower impact (44). Other studies focused on combinations of ART and isoniazid preventive therapy (63), and the introduction of universal HIV testing with immediate ART following a positive test (81).

2.3.4.3 TB preventive treatment

Six studies estimated the impact of TB preventive treatment (TPT) which all considered isoniazid monotherapy. Target groups considered included adolescents, PLWH and people previously treated for TB. Screening adolescents attending secondary schools for latent TB infection followed by TPT for those testing positive was found to be beneficial to both the adolescent and adult populations (74). Scaling up TPT among PLWH on ART after screening for TB disease was estimated to lead to considerable reductions in population-level TB incidence and mortality in one study (63), but was of lower impact in another (40). Limited impact was estimated when extending TPT to HIV-negative individuals (44). Two subsequent studies of TB in a in a suburban high-incidence setting concluded that TPT combined with case finding/follow-up examinations among people who previously completed TB treatment could accelerate declines in TB incidence and mortality at population level and potentially reduce costs (71,72).

2.3.4.4 Case finding/ screening

Seven studies modelled TB screening/ active case finding (ACF) interventions. Target populations considered included the general population, PLWH on ART, people previously treated for TB and public health clinic attendees. Three studies considered case-finding interventions in the general population. Periodic ACF reaching 60% of the general population using a hypothetical, high-sensitivity screening test was estimated to moderately reduce TB incidence with greater impact seen on mortality (44). In a rural setting, symptom-based screening followed by Xpert, culture and/or drug susceptibility testing (DST) was estimated to simultaneously reduce incident multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) TB (66). Increasing the use of a symptom-based screening tool from 40% to 100% among people attending ART was estimated to have limited impact on TB incidence (77). Expanded access to care using outreach clinics and symptom-based screening in primary care was estimated to reduce cases of catastrophic costs due to TB substantially, with larger impact seen after 5-10 years (80). One study in a high-incidence setting focused on ACF among people who previously completed TB treatment. The study showed considerable declines in TB incidence for targeted ACF alone or in combination with TPT (71).

Two studies modelled the impact of TB screening among individuals attending public health care clinics. Verbal TB symptom screening at public health clinic entrances, assuming 100% screening coverage, was estimated to reduce TB incidence countrywide (40). In the Western Cape province, increasing cough-based screening coverage followed by smear microscopy for those positive was estimated to have noticeable impact on TB incidence and mortality (45).

2.3.4.5 Diagnostic interventions

Five modelling studies focused on Xpert-based algorithms as the standard diagnostic test for TB in South Africa, prior to (38,46,61,65) and during (77) its roll-out in 2013. A diagnostic modelling study of TB in five African countries including South Africa suggested that the introduction and scale-up of Xpert could reduce morbidity and mortality, with less impact seen on long-term epidemiological outcomes (38). Replacing all smear-microscopy tests with Xpert (61), increasing the coverage of Xpert-based diagnoses from 80% in 2016 to 100% in 2035 (77) and supplementing DST with Xpert (65) were suggested to have limited impact on TB incidence and mortality. Diagnosing gold miners, an occupational group at high risk for TB in South Africa, with Xpert instead of radiographical screening was estimated to reduce TB incidence in mining settings substantially (46). One study estimated the impact of novel lateral flow urine lipoarabinomannan (LAM) tests for the early detection of TB in South Africa and found that, while future LAM tests could be important for averting TB deaths among PLWH with advanced disease, population-level impact would depend on diagnostic accuracy (75). All three studies that investigated the impact of DST on drug-resistant (DR)-TB concluded that, although transmission could be reduced, additional interventions would be necessary to effectively reduce the burden of drug-resistant TB in the population (60,62,79).

2.3.4.6 Reducing initial loss to follow-up

One study focused on interventions for reducing initial loss to follow-up (ILTFU), defined as the loss of individuals with confirmed TB from care before initiating treatment. It concluded that decreasing ILTFU by 50% through higher efficiency in the diagnostic process, increased education and improved follow-up by healthcare professionals could lead to moderate reductions in TB incidence (44).

2.3.4.7 Treatment

Eight modelling studies focused on TB treatment-related interventions of three types: reducing poor treatment outcomes, introducing novel drugs and treatment regimens, and improving drug-resistant (DR)-TB treatment. Three studies considered reducing poor outcomes of routine TB treatment in South Africa. Identifying treatment failure, improving cure rates (61), and increasing treatment success through improved adherence (44) were estimated to yield limited impact on TB incidence and mortality. However, another study suggested that improving treatment quality by using mobile health care, patient follow-up, adherence counselling and improved staffing for MDR-TB could greatly reduce catastrophic costs in TB-affected households (80). Two studies focused on the introduction of hypothetical novel TB treatment regimens at country level. Focusing on treatment efficacy in clinical trials of novel treatment regimens, in this case a rifampicin-resistant regimen, was estimated to yield significant impact on TB incidence and mortality (68). Rapid scale-up of a four-month TB treatment regimen that was as effective as the standard six-month regimen, but would reduce loss to follow-up during treatment, was estimated to be of low impact (44). Three studies focused on treatment interventions to reduce MDR- and XDR-TB. A study published in 2009, when XDR-TB treatment was only offered in hospitals, estimated that early DST in combination with providing treatment at outpatient health clinics (as opposed to inpatient treatment) could substantially reduce the probability of XDR-TB epidemics (60). Improving first-line and MDR-TB treatment success using patient monitoring and

community outreach programs (40) and MDR-TB treatment decentralization, initialized by shortened hospitalization and home-based treatment for individuals presenting for treatment (65) were estimated to accelerate reductions in TB incidence and mortality.

2.3.4.8 Other interventions

Reducing delay in care seeking among people experiencing TB-characteristic symptoms was found to have substantial impact on TB incidence and mortality (61). Halving the annual risk of infection through a combination of interventions to enhance case management was estimated to reduce TB incidence and mortality four-fold and eight-fold, respectively (63). One modelling study considered the use of a novel mRNA correlate-of-risk (COR) test (83) to target TPT towards high-risk HIV-negative adults. Use of this new test for effective targeting of TPT was estimated to reduce TB incidence considerably (78).

Table 2.5: Outcomes reported for interventions modelled by eligible studies

	Publication Time horizon	**Intervention modelled and target population**	**Study outcome***	**% Reduction compared to baseline at end of time horizon or number averted over time horizon**
Country level	**Vaccination**			
	Dye *et al.* (63) 2025-2050	Hypothetical pre-infection vaccine introduced in 2025 protecting 70% of uninfected, HIV-negative people by 2050	Number of TB cases and deaths would fall from 8,500 to approximately 1,700 and 1,220 to 360 per million, respectively.	Incidence: 80% Deaths: 70.5%
	Harris *et al*. (67) 2025-2050	Hypothetical vaccines with varied efficacy to prevent infection or disease (70/100%), effective in uninfected or infected individuals and duration of protection of 10 years	A pre-/post-infection vaccine (efficacious for PLWH) for protection against infection and disease resulted in an 84% IRR (81-87%) and an 83% reduction in mortality. A vaccine with the same specifications, but with 70% efficacy, resulted in an IRR of 71% (66-89%).	Incidence (100%): 84% Mortality (100%): 83% Incidence (70%): 71%
	ART for TB prevention			
	Chindelevitch *et al.* (61) 2012-2032	Expanding ART eligibility by increasing ART initiation for each CD4 category for PLWH	Universal ART eligibility over 20 years reduced incidence and mortality (000s) by 3,437 (2,387-4,696) and 1,306 (939-1,747), respectively.	Incidence: 50% Mortality: 53.8%
	Dye *et al*. (63) 2010-2050	Increasing ART coverage from 40%-80% (2010-2050) for PLWH on IPT	The efficacy of ART in preventing TB per unit time is 67% which is offset by a 50% reduction in mortality, extending the number of life-years at risk of TB.	Incidence: 2.4% Mortality: 1.6%
	Knight *et al*. (44) 2014-2032	Expanding ART eligibility for PLWH	ART given universally (UTT) reduced incidence and mortality by 21% and 30%, respectively.	Incidence: 23% Mortality: 33%

	Pretorius *et al.* (73) 2014-2033	Improving pre-ART and ART services, and expanding ART eligibility for PLWH	Expanding ART access to all PLWH (universally), with 80% coverage, would reduce incidence and mortality by 10-23% and 13-36%, respectively.	Incidence: 10-23% Mortality: 13-36%
	Williams *et al.* (81) 2010-2050	Regular HIV testing and immediate ART for PLWH	HIV test-and-treat could avert 0.6 of 2.17 million cases of TB between 2010 and 2015 and 4.58 of 9.82 million cases between 2015 and 2050.	Cases (2010-2015): 28% Cases (2015-2050): 47%
	TB preventive treatment			
	Dye *et al.* (63) 2025-2050	Increasing coverage of ART-linked IPT (from 0% -75%) for PLWH between 2025 and 2035	IPT scale-up could reduce the number of cases and deaths from 8,500 to approximately 1,400 and 1,220 to 200 per million, respectively, by 2050.	Incidence (IPT): 83.5% Mortality (IPT): 83.6%
	Houben *et al.* (40) 2015-2025	Providing continuous ART-linked IPT to PLWH	In addition to the 2-5% annual decline in incidence, continuous IPT reduced incidence by a further 16% (range 8-51%).	Incidence: 16%
	Knight *et al.* (44) 2014-2032	Providing IPT to HIV-negative people	By 2032, incidence and mortality were reduced by 17% and 25%, respectively, for the same intervention.	Incidence: 17% Mortality: 25%
	Rhines *et al.* (74) 2012-2032	Scale-up of IPT to adolescents in secondary schools (from 5% to 90%)	90% IPT coverage in adolescents testing positive for infection reduces incidence in adolescents and adults by 55% and 36%, respectively.	Incidence (adolescents): 55% Incidence (adults): 36%
	Case finding/ screening			
	Azman *et al.* (58) 2012-2022	Sustained ACF programs in the general population	Sustaining an increase of 25% of cases diagnosed and treated in their first year could reduce incidence and mortality by 22-27% and 40-44%, respectively.	Incidence: 22-27% Mortality: 40-44%
	Basu *et al.* (60) Over 5 years	Early XDR-TB screening in hospitals and the community	In combination with improved treatment, early screening prevented approximately 50 deaths per 100,000 over 5 years.	Deaths: 50 per 100,000 over 5 years

	Houben *et al.* (40) 2015-2025	Screening of all attendees at primary-health clinics	In addition to the 2-5% annual decline in incidence, screening reduced incidence by a further 20% (7-35%).	Incidence: 20%
	Knight *et al.* (44) 2014-2032	ACF in the general population measured in 2032	Periodic ACF with high sensitivity and high coverage reduced incidence and mortality by 48% and 58%, respectively, by 2032.	Incidence: 48% Mortality: 58%
	Sumner *et al.* (77) 2016-2035	Intensified case finding (symptom-based screening) for PLWH	Symptom-based screening for PLWH reduced incidence by 14.5% (12.2-16.3%).	Incidence: 14.5%
	Verguet *et al.* (80) 2016-2035	Expanding access to care in outreach clinics and symptom screening in primary care facilities for households facing catastrophic costs due to TB	Decreasing population without access to care from 5% to 0% would avert 60,000-240,000 (5-20%) cases of catastrophic costs. Households in the lowest two income quintiles benefitted the most with 65-90% of cases of catastrophic costs averted.	% Cases of catastrophic costs: 5-20% Cases of catastrophic costs (lowest two income quintiles): 65-90%
	Diagnostic interventions			
	Basu *et al.* (60) Over 5 years	Rapid DST in hospitals and the community	To obtain XDR DST results in 1 week instead of the current 6-week delay, mortality was reduced from 230 to 215 deaths per 100,000 over 5 years.	Deaths: 15 per 100,000 over 5 years
	Chindelevitch *et al.* (61) 2012-2032	Using more sensitive diagnostics (replacing a proportion of smear microscopy with Xpert) in the general population	Improved diagnostics over 20 years reduced incidence and mortality (000s) by 6,428 (4,797-8,735) and 2,284 (1,644-3,308), respectively.	Incidence: 6.6% Mortality: 19.9%
	Dowdy *et al.* (62) 2007-2017	Improving diagnosis for adults with access to expanded culture and DST	Performing culture and DST in 37% of new suspects and 85% of previously treated patients averted 17.2% of deaths (95% S.I.: 8.9-24.4%), 3% (1.1-5.9%) of incident cases, 14.1% (5.3-23.8%) of incident MDR-TB cases and 46.6% (32.6-56%) of MDR-TB deaths.	Mortality: 17.2% MDR-TB cases: 14.1% MDR-TB deaths: 46.6%
	Menzies *et al.* (38) 2012-2022	Improving diagnosis (scale-up of Xpert for initial diagnosis up to full	Xpert initiation reduced prevalence, incidence, and mortality by 28% (14-40%), 6% (2-13%), 21% (10-32%), respectively. The number of	Incidence: 6% Mortality: 21% Incidence (MDR-TB): 25%

		coverage over 2012-2015) for individuals suspected to have TB	MDR-TB cases would be lowered by 25% (6-44%).	
	Ricks *et al.* (75) 2020-2035	Improving testing (future LAM tests compared current LAM tests) for people receiving HIV care and HIV-negative patients.	Future LAM tests deployed to inpatients, outpatients and routine TB care reduced incidence and mortality by 17.7% (8.62-29%) and 29.6% (17.8-43.6%), respectively.	Incidence: 17.7% Mortality: 29.6%
	Sumner *et al.* (77) 2016-2035	Increased usage of Xpert as a first-line test in the general population (80% to 100% coverage)	Using Xpert testing alone reduced incidence by 1.6% (2.5^{th}-97.5^{th} PR, 0.9-2.4%).	Incidence: 1.6%
	Reducing ILTFU			
	Knight *et al.* (44) 2014-203	Decreasing pre-treatment LTFU in the general population measured in 2032	A 50% decrease in pre-treatment LTFU reduced incidence and mortality by 30% and 52%, respectively, by 2032.	Incidence: 30% Mortality: 52%
	Treatment			
	Basu *et al.* (60) Over 5 years	Improving treatment for XDR-TB at community- and hospital-based levels	In combination with early XDR-TB screening, improving XDR treatment prevented approximately 50 deaths per 100,000.	Deaths: 50 per 100,000
	Chindelevitch *et al.* (61) 2012-2032	Improving treatment (identifying treatment failure and improving cure rates) in the general population	Improved treatment over 20 years reduced incidence and mortality (000s) by 5,904 (4,418-8,109) and 2,276 (1,610-3,322), respectively.	Incidence: 14.2% Mortality: 19.4%
	Houben *et al.* (40) 2015-2025	Improving first-line/ MDR-TB treatment success by monitoring patients and outreach programs in communities	In addition to the 2-5% annual decline in incidence, improving treatment reduced incidence by a further 8% (0-25%).	Incidence: 8%
	Kendall *et al.* (68) Over 25 years	Improving RR-TB treatment with novel regimens in the general population	Optimal RR-TB regimen reduced incidence and mortality by 30.1% (15.4-47.7%) and 30.3% (17.1-45.4%), respectively.	Incidence (RR-TB): 30.1% Mortality (RR-TB): 30.3%
	Knight *et al.* (44) 2014-2032	Increasing treatment success in the general population	A 50% increase in treatment success reduced incidence and mortality by 17% and 31%, respectively.	Incidence: 17% Mortality: 31%

	Knight *et al.* (70) 2015-2035	Shortening TB treatment length with novel 4-month regimen in the general population	Novel 4-month treatment regimen reduced incidence and mortality by 1% compared to the standard 6-month regimen.	Incidence: 1% Mortality: 1%
	Verguet *et al.* (80) 2016-2035	Improving treatment quality (mobile health care, patient follow-up, adherence counselling, improved staffing for MDR-TB) for households facing catastrophic costs due to TB	Improving treatment for DS-TB and MDR-TB would avert 90,000-220,000 and 70,000-220,000 cases of catastrophic costs, respectively. Households in the lowest two income quintiles would avert 90% of cases of catastrophic costs in both scenarios.	Cases of catastrophic costs (DS-TB): 90,000-220,000 Cases of catastrophic costs (MDR-TB): 70,000-220,000 Cases of catastrophic costs (lowest two income quintiles): 90%
	Other interventions			
	Chindelevitch *et al.* (61) 2012-2032	Improving healthcare coverage (reducing delay of disease development to clinic attendance) in the general population	Improved coverage over 20 years reduced incidence and mortality (000s) by 4,236 (3,223-5,609) and 1,347 (927-2,054), respectively.	Incidence: 38.4% Mortality: 52.3%
	Dye *et al.* (63) 2025-2050	Enhancing case management (early case detection, accurate diagnosis and high cure rate)	Halving the ARI over 20 years reduced the number of cases and deaths from 8,500 to approximately 3,700 and 1,220 to 530 per million, respectively.	Incidence: 56.5% Mortality: 56.6%
	Sumner *et al.* (78) 2020-2035	Improving testing (use of mRNA expression signature COR test to target PT) for HIV-uninfected adults	COR reaches a reduction in incidence of 20.4% (15.2-26.9%) and IGRA a reduction of 38.8% (31.2-48%) after 15 years.	Incidence (COR): 20.4% Incidence (IGRA): 38.8%
Provincial level	**Case finding/ screening**			
	Hippner *et al.* (45) 2017-2035	Increasing screening coverage in the general population	Screening reduced incidence and mortality in KZN, LP and WC by 11.5% and 18.8%, 3.4% and 8.8%, and 25% and 41.4%, respectively.	Incidence (KZN, LP, WC): 11.5%, 3.4%, 25% Mortality (KZN, LP, WC): 18.8%, 8.8%, 41.4%
	Uys *et al.* (79) Over 20 years	Screening in the community	Screening in combination with rapid diagnosis of DR-TB reduced incidence from 11.2 cases per month (per 100,000) to 1.6 cases.	Cases: 85.7%
	Diagnostic interventions			

	Uys *et al.* (79) Over 20 years	Improving diagnosis (earlier diagnosis of DR-TB) in the community	Rapid diagnosis of resistance with 97% sensitivity reduced incidence from 11.2 cases per month (per 100,000) to 2.4 cases.	MDR-TB cases: 78.6%
	Reducing initial loss to follow-up			
	Hippner *et al.* (45) 2017-2035	Improving linkage to care (ILTFU reduced by 80% by 2021) in the general population	Improving linkage to care reduced incidence and mortality in KZN, LP and WC by 4.9% and 10.2%, 5.2% and 13.2%, and 13.8% and 22.8%, respectively.	Incidence (KZN, LP, WC): 4.9%, 5.2%, 13.8% Mortality (KZN, LP, WC): 10.2%, 13.2%, 22.8%
	Treatment			
	Hippner *et al.* (45) 2017-2035	Improving DS-/DR-TB treatment (DS-TB to 85% and DR-TB to 67%) in the general population	Improving treatment reduced incidence and mortality in KZN, LP and WC by 5.6% and 14.8%, 11.5% and 26.2%, and 4.6% and 11.6%, respectively.	Incidence (KZN, LP, WC): 5.6%, 11.5%, 4.6% Mortality (KZN, LP, WC): 14.8%, 26.2%, 11.6%
City level	**Vaccination**			
	Dye *et al.* (64) 2009	BCG revaccination of HIV-negative adolescents and teenagers (efficacy of 80% with protection of 10 years)	With a revaccination efficacy of 80%, the percentage of cases averted reaches 17% (1,554 of 9,290 cases) and the annual risk of infection is reduced from 5.7% to 4.8% per year.	Cases: 17%
Rural community/ district level	**TB preventive treatment**			
	Gilbert *et al.* (65) 2001-2011	ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive)	IPT averted 7% (95% CI 4-9%) of total TB and 8% (5-10%) of DS-TB cases. Minimally impacted MDR-/XDR-TB and TB/HIV mortality.	Cases (TB, DS): 7%, 8%
	Gilbert *et al.* (66) 2015-2025	ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive and lifetime for PWH)	Expanding IPT from 36/12 months to lifetime (without screening) reduced incidence from 298 to 254 cases per 100,000. Negligible impact on MDR-/XDR-TB.	Incidence: 14.8%
	Case finding/ screening			

	Gilbert *et al.* (65) 2001-2011	TB/ HIV CICF and improving case detection for individuals interested in voluntary TB or HIV testing	Cases averted for total TB, DS-TB, MDR-TB, and XDR-TB were 23% (95% CI 13-27%), 24% (15-31%), 10% (6-20%), and 9% (18-23%), respectively. TB/HIV mortality was reduced by 13% (9-18%).	Cases (TB, DS, MDR, XDR): 23%, 24%, 10%, 9% Deaths (TB/HIV): 13%
	Gilbert *et al.* (66) 2015-2025	Community-based TB/ HIV screening for individuals interested in voluntary TB or HIV screening	Introducing community-based screening reduced total TB, MDR-TB, and XDR-TB incidence from 298 to 274-233, from 54 to 15-14, and from 12 to 5-4 cases per 100,000, respectively.	Incidence (TB, MDR, XDR): 8-22%, 72%-74%, 58-67%
	Diagnostic interventions			
	Basu *et al.* (59) 2007-2012	Drug susceptibility testing using different assays (e.g., phage-based and line probe assays) in hospital wards and the catchment community population	Rapid DST prevented between 2 and 4% of XDR-TB cases (26-52 cases).	Cases: 2-4%
	Gilbert *et al.* (65) 2001-2011	Improving diagnosis (Xpert) in the general population	Xpert averted 31% (95% CI 11-65%) and 41% (10-72%) of MDR-TB and XDR-TB cases, respectively. Minimally impacted TB and DS-TB incidence, and TB/HIV mortality.	Cases (MDR, XDR): 31%, 41%
	Treatment			
	Gilbert *et al.* (65) 2001-2011	Improving TB/MDR-TB treatment and first-line treatment cure rates for patients presenting for diagnosis at hospitals or clinics	Increasing cure rates to 80% reduced DS-TB and MDR-TB cases by 6% (95% CI 2-11%) and 9% (3-20%), respectively, and TB/HIV mortality was reduced by 3% (1-4%). Improving MDR-TB treatment reduced MDR-TB and XDR-TB cases by 43% (18-71%) and 72% (35-92%).	Cases (CR: DS, MDR): 6%, 9% Deaths (CR): 3% Cases (Treatment: MDR, XDR): 43%, 72%
	ART for TB prevention			
	Gilbert *et al.* (65) 2001-2011	ART-linked IPT for PWH (expanding ART coverage)	Expanding coverage averted 10% (95% CI 2-14%) of total TB cases.	Cases: 10%

	Basu *et al.* (59) 2007-2012	Offering ART with voluntary counselling and testing at community-level for PLWH	ART averted 312 (221-391) XDR-TB cases	Cases: 24%
	Other			
	Basu *et al.* (59) 2007-2012	Reducing length of stay, detention of confirmed XDR-TB cases, mechanical ventilation, natural ventilation, air purifiers, using individual isolation facilities, reducing clusters of patients (5/10), and ensuring staff/ patients wear N95 masks for diagnosed XDR-TB patients or hospital staff	In order of intervention specification, XDR-TB cases prevented: 78 (39-117), -39 (-26- -52), 430 (104-456), 156 (130-326)/ 286 (260-456), 417 (391-586), 742 (664-820), 482 (417-586)/ 391 (352-456), and 26 (13-39)/ 65 (26-130).	Cases: 6%, -3%, 33%, 12%, 22%/ 32%, 57%, 37%/ 30%, 2%/ 5%
Township or sub/urban level	**TB preventive treatment**			
	Kendall *et al.* (69) 2008-2013	Continuous ART-linked IPT for PWH	Continuous IPT regimen reduced incidence and mortality by 10.5% (6.9-14.8) and 6.7% (3.8-10.7%), respectively.	Incidence: 10.5% Mortality: 6.7%
	Marx *et al.* (71) 2016-2025	Secondary IPT for previously treated TB patients	Secondary IPT in addition to ACF would avert 40% (21-56%) of all incident cases and 41% (16-55%) of deaths.	Incidence: 40% Mortality: 41%
	Marx *et al.* (72) 2019-2028	Secondary IPT for previously treated TB patients	Continuous follow up in combination with secondary IPT would avert 20.4% (5.9-35.9%) of cases and 18.2% (0.7-34.2%) of deaths.	Incidence: 20.4% Mortality: 18.2%
	Case finding/ screening			
	Marx *et al.* (71) 2016-2025	Active case finding for previously treated TB patients	ACF alone would avert 14% (0.4-28%) of all incident cases and 21% (2.5-39%) of deaths.	Incidence: 14% Mortality: 21%
	ART for TB prevention			
	Kendall *et al.* (69) 2008-2013	ART-linked IPT for PWH (expanding levels of ART)	Increasing ART coverage in the presence of IPT reduced incidence by 7.2% (4.3-12.6%). In the presence of IPT, ART reduced mortality by 5.4% (2.8-9.6%).	Incidence: 7.2% Mortality: 5.4%

	Other			
	Marx *et al.* (72) 2019-2028	Post-treatment follow-up examinations for previously treated TB patients	Continuous follow up in combination with IPT would avert 20.4% (5.9-35.9%) of cases and 18.2% (0.7-34.2%) of deaths.	Incidence: 20.4% Mortality: 18.2%
Occupational level	**Vaccination**			
	Shrestha *et al*. (76) Over 20 years	Hypothetical post-infection vaccine with 60% efficacy over 10 years for miners or people in associated labour-sending communities	Vaccines targeted to labor-sending community averted a median of 5,510 (95% range 2,360-10,000) cases. Vaccines targeted to miners averted a median of 8,090 (3,750-13,300) cases.	Cases (labor): 5,510 Cases (mine): 8,090
	TB preventive treatment			
	Vynnycky *et al*. (46) 2003-2017	IPT scenario with 100% cure and 100% protection for gold miners	Incidence was reduced by 24.5% (95% CI: 24.2-25%) using an IPT regimen with 100% cure and 100% protection against infection.	Incidence: 24.5%
	Diagnostic interventions			
	Vynnycky *et al*. (46) 2003-2017	Improving diagnosis (using Xpert) for gold miners	An approximate 30% reduction in predicted true incidence.	Incidence: 30%
	Reducing initial loss to follow-up			
	Vynnycky *et al.* (46) 2003-2017	Reducing ILTFU for gold miners	Decrease in ILTFU and treatment delay reduced incidence by approximately 40%.	Incidence: 40%
	Treatment			
	Vynnycky *et al*. (46) 2003-2017	Decreasing treatment delay for gold miners	Decrease in LTFU and treatment delay reduced incidence by approximately 40%.	Incidence: 40%
	ART for TB prevention			
	Vynnycky *et al.* (46) 2003-2017	Scale up of ART to 80% for gold miners with HIV	An approximate 50% reduction in predicted true incidence.	Incidence: 50%

* Uncertainty intervals are reported where provided in the article.

ACF: active case finding
ART: antiretroviral therapy
ARI: annual risk of infection
BCG: Bacille Calmette Guérin
CI: confidence interval
CICF: community-based intensified case finding
COR: correlate of risk
CR: cure rates
DS-TB: drug susceptible TB
DST: drug susceptibility testing
HAART: highly active ART
HIV: human immunodeficiency virus
IGRA: interferon gamma release assay
IPT: isoniazid preventive therapy
KZN: KwaZulu-Natal
LAM: lipoarabinomannan
LP: Limpopo province
(I)LTFU: (initial) loss to follow-up
MDR-TB: multidrug resistant TB
PHC: primary health care facility
PR: percentile range
PT: TB preventive treatment
PLWH: people living with HIV
RR-TB: rifampicin resistant TB
RS-TB: rifampicin susceptible TB
TLTI: treatment of latent TB infection
TST: tuberculin skin test
UR: uncertainty range
UTT: universal test and treat program
WC: Western Cape
XDR-TB: extensively drug resistant TB

Key	**Setting**
	Country level
	Provincial level
	City level
	Rural community/ district level
	Township/ suburban/ urban level
	Occupational level

2.3.5 Estimated impact by type of intervention

Figure 2.4 shows AAPDs in TB incidence and mortality for different interventions, calculated from reported model outcomes and time horizons. AAPDs varied between 0.05% and 7.1% for TB incidence, and between 0.02% and 7.1% for TB mortality. Larger impacts were estimated for preventive interventions (TB vaccination, TPT among PLWH on ART, and ART with high coverage), than for improved diagnosis and treatment. Interventions along the care cascade (e.g., case finding, diagnosis, treatment) were estimated to have greater AAPDs in TB-associated mortality than in TB incidence.

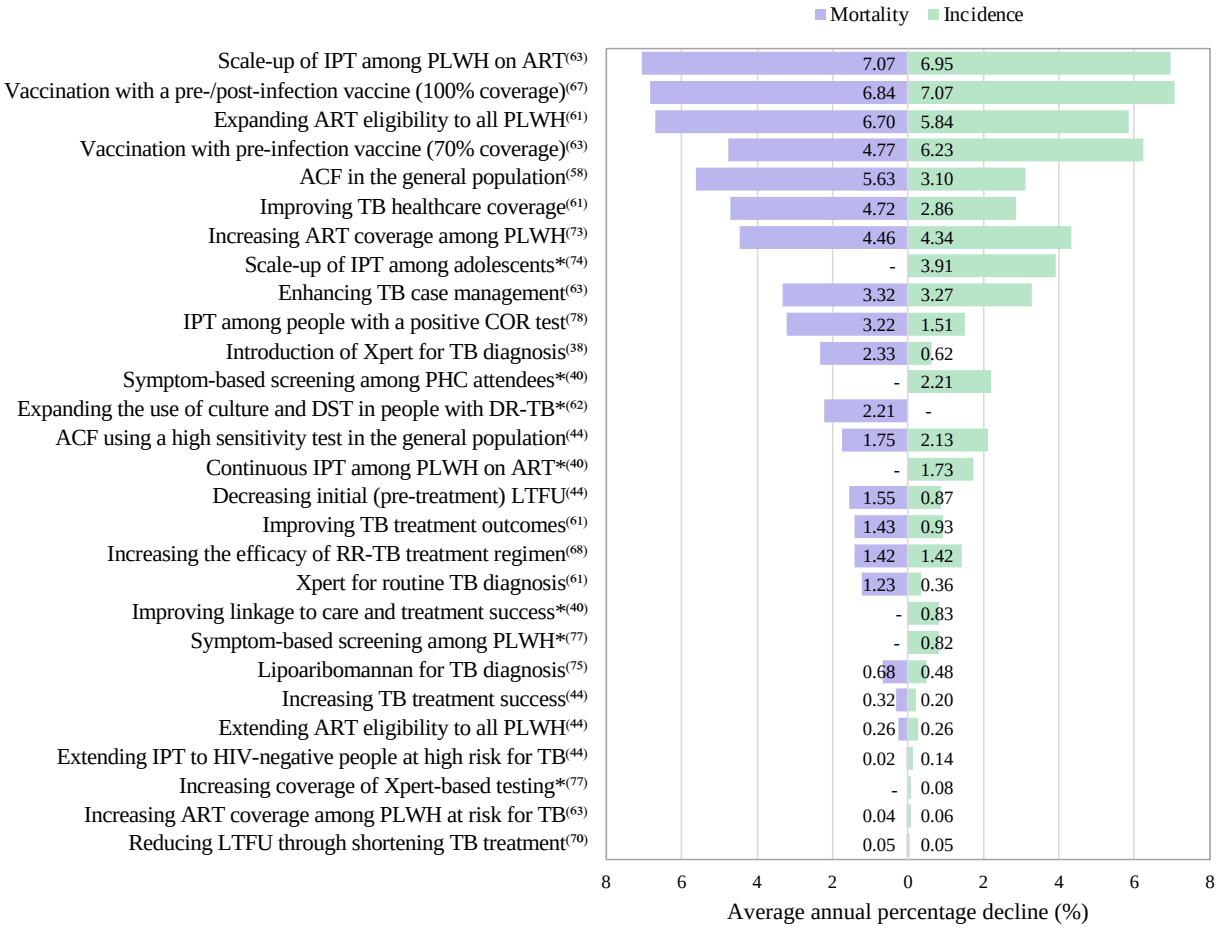

Figure 2.4: Average annual percentage declines (AAPDs) for different interventions modelled at country level.
AAPDs were calculated from reported percentage declines in incidence and mortality relative to the baseline scenario at the end of model time horizons. (-) denotes missing result as impact was not estimated for the indicator. (IPT = isoniazid preventive therapy, PLWH = people living with HIV, ART = antiretroviral therapy, ACF = active case finding, TB = tuberculosis, COR = correlate of risk, PHC = primary health care facility, DST = drug susceptibility testing, DR-TB = drug-resistant TB, LTFU = loss to follow-up, RR-TB = rifampicin-resistant TB, HIV = human immunodeficiency virus).

Another way to visualize a comparison of the impact of different interventions is to stratify AAPDs for TB incidence and mortality according to intervention categories. Figure 2.5 shows AAPDs for incidence (A) and mortality (B), calculated from reported model outcomes and time horizons. Interventions that were estimated to have the largest impact on TB incidence were of the vaccination (light blue), preventive treatment categories (light green), and ART for TB prevention

(dark blue), with AAPDs estimated above 4% for incidence. Interventions of improved diagnosis, and improved treatment were estimated to be of lower impact (AAPDs for incidence estimated below 3%).

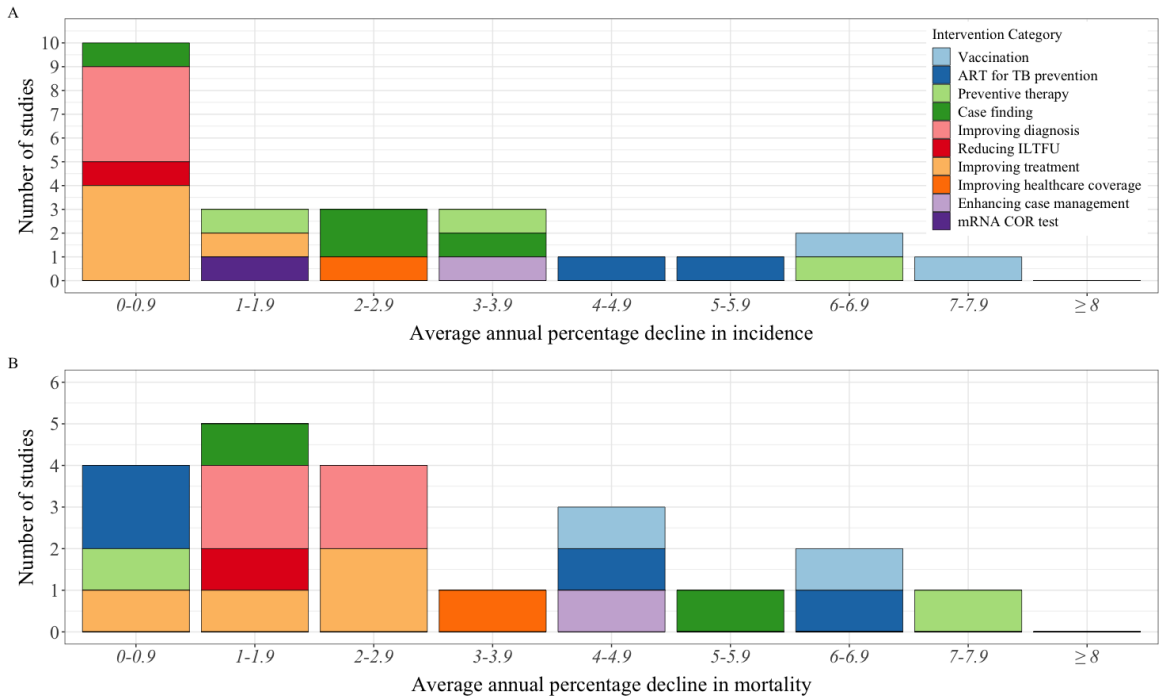

Figure 2.5: The number of studies corresponding to average annual percentage declines which were ascertained using reported percentage declines in incidence (A) and mortality (B) from eligible studies in addition to the baseline scenario, and time horizons over which interventions were modelled at country level.

2.4 Discussion

I conducted this systematic review to synthesise the evidence for TB prevention and care in South Africa from studies using transmission-dynamic mathematical models.

I identified 29 eligible modelling studies, the majority of which were published in the past 6-7 years. Studies focused on a variety of interventions for preventing TB and strengthening the care cascade for TB. Most studies (22 of 29) investigated the impact of hypothetical novel interventions, with the remainder focusing on the scale up of existing interventions. All but one study projected the impact of interventions on the End TB strategy target indicators of TB incidence, TB mortality, or both. The remaining study (80) extended earlier modelling studies (38,52,72,84) to estimate the impact of interventions on the number of households experiencing TB-related catastrophic costs.

I calculated crude estimates of AAPDs in TB incidence and mortality from study outcomes of impact over different time horizons. I found that preventive interventions including TB vaccination, TPT among PLWH, and scaling up ART were most promising to reduce TB incidence and mortality in South Africa. The use of novel vaccines to prevent *Mycobacterium tuberculosis* infection and/or TB disease was estimated to lead to substantial reductions, above 5% per annum, in TB incidence at country level, highlighting the importance of vaccine research and development in the fight against TB in South Africa. These findings are consistent with a recent systematic review that emphasized the important role of novel vaccines towards achieving TB elimination

globally (41). Prior to, and with the arrival of novel vaccines, specific and data-driven strategies for delivering vaccines to key populations in South Africa will be important (85). Varying levels of impact were projected for TPT implementation and scale up. This variation is explained by different target populations for TPT considered and different model assumptions, including about intervention coverage and time horizons. All studies of TPT focused on isoniazid monotherapy, and none considered the impact of novel shorter regimens for TB prevention such as 3RH (a 3-month rifampicin-isoniazid course) (86). Prior to the roll-out of universal ART to PLWH in 2016, extending ART eligibility for TB prevention with high coverage was predicted to have substantial impact on TB incidence and mortality. This is also consistent with a retrospective study conducted in 2019 which showed that recent declines in TB incidence and mortality in South Africa were associated with expanding access to and coverage of ART among PLWH (87).

The majority of studies focused on interventions along the care cascade for TB. Interventions considered include screening/active case finding, scale up of current and introduction of novel TB diagnostic tests, reducing initial loss to follow-up, and improving TB treatment. While interventions of case finding and strengthening the care cascade for TB are essential to reduce suffering from TB and improve individual-level health outcomes, their impact on reducing transmission and TB incidence may be lower compared with preventive interventions. Consistently, we found that most care-cascade interventions were estimated to have a greater effect on TB mortality than on TB incidence (Figure 2.4). One exception might be interventions to reduce initial loss to follow-up, i.e., the loss of people who have been diagnosed but are lost before initiating TB treatment, a serious challenge in South Africa (27). Furthermore, a large fraction of people with subclinical TB have recently been reported in South Africa's first national TB prevalence survey (88), raising concerns about onward transmission from this group (89). As people with subclinical TB are less likely to self-present for TB diagnosis, interventions to detect subclinical TB may be important in South Africa. Several studies estimated that Xpert-based algorithms had no significant impact on TB incidence and mortality. These findings align with results reported in recent studies (90,91).

This review identified gaps for TB modelling research in South Africa that, if addressed, could provide valuable additional information for decision making. More vulnerable groups should be considered for future case finding initiatives, as was highlighted in a recent systematic review (92). New developments in TB diagnosis and treatment are currently underway (93). Modelling the effect of these novel diagnostic tests and treatment regimens for active TB could assist in understanding how they should be optimally implemented in the population. Shortening the length of preventive treatment regimens is associated with higher rates of treatment success and lower loss to follow-up (94). Modelling the impact of TPT in different target populations will be important. Additional modelling of interventions to reduce ILTFU in South Africa could help understand how these interventions could help reduce transmission and TB deaths in South Africa (95). Beyond impact, future modelling research should also address the affordability and cost-effectiveness of interventions to inform decision making. Only 9 of the 29 modelling studies identified addressed cost-effectiveness (38,58,64,66,70,72,77,79,80). Reducing the number of TB-affected households facing catastrophic costs due to TB to zero represents one of the three targets of the WHO's End TB strategy. We found that only one modelling study estimated the effect of interventions on reducing households facing catastrophic costs in South Africa (80). More modelling research is needed to estimate the financial impact of TB on families in South Africa, and to estimate the impact of TB interventions on reducing catastrophic costs. This gap is of particular relevance for South Africa where over one quarter of people face barriers such as unemployment, limited access to transport for clinic attendance and household overcrowding (96), and where these challenges amplify TB.

This review has limitations. I restricted the analysis to modelling studies of TB in the South African population. Findings from other TB modelling studies focusing on populations outside of South Africa may still be relevant to the South African context and should be taken into consideration for policy making. While I report findings from modelling studies at different population levels, findings from studies at sub-country level might not be readily generalizable to the national level. Likewise, generalizability of country-level analyses to different local areas in South Africa may be limited given the considerable heterogeneity in TB burden and epidemiology in the country (97). This study focused on impact with respect to the End TB strategy target indicators. I did not focus on resource availability and cost-effectiveness of interventions, which are also relevant for decision-making. Heterogeneity in model structure, study design and reported outcomes, limited the ability to compare interventions with respect to their potential to generate progress towards the End TB strategy targets. I also note that the estimated impact of the interventions depends on the baseline to which they are compared, and these baselines are not always consistent between the modelling studies. While I report impact with crude measures of annual reductions in TB incidence and mortality for single interventions, many studies considered combinations of interventions. I estimated that a 12% and 19% decline in incidence and mortality, respectively, is required between 2022 and 2035 to meet the End TB strategy targets for South Africa (Addendum A, Table A3). Of note, none of the single interventions were estimated to yield sufficient reductions over time, consistent with the idea that a combination rather than single interventions will be necessary to achieve the End TB targets (40).

In conclusion, I highlight an extensive body of modelling research with relevance for TB decision making in South Africa. I present these findings at a time where additional guidance is urgently needed to confront recent setbacks in the fight against TB caused by health service disruptions during the COVID-19 pandemic, and to ensure progress towards the 2035 End TB strategy targets in South Africa. I found that interventions focusing on prevention, including vaccination, TPT among PLWH and scaling-up ART, would have the greatest potential to reduce TB incidence and mortality. However, relating estimates of impact to the progress that would be needed in South Africa to achieve the End TB strategy targets revealed that single interventions will be unlikely to generate sufficient progress. Combinations of interventions rather than single interventions are therefore needed to effectively reduce TB incidence and mortality in South Africa. This review discusses important knowledge gaps in modelling research, including studies of novel diagnostic tests for TB, interventions in vulnerable and high-risk populations, and interventions towards reducing TB-related catastrophic costs. Closing these gaps through additional modelling research could help prioritize novel interventions and accompany already implemented interventions to better understand how they will aid progress towards TB elimination in South Africa.

3 Modelling the population-level impact of reducing initial loss to follow-up among individuals diagnosed with tuberculosis

This chapter aims to address an important modelling gap, also identified in Chapter 2, to determine the impact of reducing ILTFU in South Africa. I adapted an existing TB transmission-dynamic mathematical model to determine the number of cases and deaths averted when reducing ILTFU in South Africa. This project made use of data and expert opinion provided by researchers of the LINKEDIn study, which implemented an intervention to reduce ILTFU in three South African provinces: KwaZulu-Natal, Gauteng and the Western Cape.

3.1 Introduction

TB continues to be a major threat to public health in South Africa; the country is currently among five globally with a TB incidence rate of over 500 per 100,000 population (2). At the current rate of decline, South Africa is unlikely to reach the 2035 targets of the End TB strategy, defined by the World Health Organization (WHO) and partners, to reduce TB incidence by 90% and the number of TB deaths by 95% compared to 2015 (14). In 2020 and 2021, response measures to contain the spread of COVID-19 have led to disruptions in TB services; a setback in efforts to reduce TB is expected (10). Substantial efforts will thus be needed in the forthcoming years to accelerate the decline in TB incidence and mortality and get back on track towards the proposed End TB targets (11).

A key obstacle to reducing TB burden in South Africa is losses along the care cascade for TB. Individuals with presumptive TB may be lost along the care cascade anywhere between accessing health care services, receiving test results, initiating TB treatment, and successfully completing their treatment. Identifying and quantifying these losses is useful for highlighting gaps in health systems, and planning strategies to improve the quality of care (18). Care cascades have been widely used in HIV research in South Africa (19–21), and are being increasingly used to evaluate TB control (16,22). It is estimated that only 53% of individuals who accessed care in South Africa were successfully treated, highlighting the need for increased efforts to improve existing measures and close the gaps along the cascade (13).

Initial loss to follow-up (ILTFU), defined by the WHO as a “TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more” (23), is an important gap in the South African TB care cascade (24–26). Individuals who are ILTFU are a concern for TB programmes as they are associated with poor patient outcomes (24,27) and are expected to contribute to onward transmission. An estimated 21% of diagnosed TB patients in South Africa are initially lost to follow-up (13). Several studies have reported underlying reasons and risk factors for ILTFU in South Africa (24,26,28). Healthcare-related factors identified include poor communication and lack of counselling by health care workers, misinterpretation of diagnostic results, under-resourced facilities, and negative staff attitudes. Patient-level factors include poor knowledge on TB treatment, stigma surrounding TB (especially its linkage to HIV), and other socioeconomic factors (such as poverty and lack of transport to primary health care facilities). Among TB patients with ILTFU in the Western Cape, South Africa, approximately 20% of diagnosed patients did not link to treatment within 30 days of diagnosis (30). Of these patients, 17% died within 60 days of diagnosis. This highlights the need for improvement in health care service quality to reduce ILTFU in South Africa. Various interventions to avert ILTFU have been proposed. These include more attention to keep track of, register, and report TB patients who did not timely initiate treatment (29), ensuring that correct contact information is recorded upon registration of a patient, in case follow-up is necessary, clear communication of diagnostic results to patients (26), interventions to support treatment initiation such as registration of TB patients in

hospitals (30), and early interaction with TB patients to facilitate timely registration and treatment initiation (31).

The LINKEDIn study was a large quasi-experimental, implementation study conducted between July 2018 and December 2020 in three provinces of South Africa: Western Cape, KwaZulu-Natal, and Gauteng. Its main goal was to implement and investigate an intervention to support patient registration, linkage to TB treatment and prevent ILTFU among individuals diagnosed with TB. The intervention consisted of two components. First, a patient management system was established, to support linkage to care among individuals diagnosed in hospitals and primary health care. The patient management system included efforts to strengthen data and information about newly diagnosed TB patients and an alert-and-response system for health care workers to support treatment initiation among patients at risk of ILTFU. Second, to ensure that reports of TB patients who were diagnosed in hospitals were complete, hospitals were turned into reporting units. Results from sub-district locations in the Western Cape demonstrated that the intervention was feasible and effective in facilitating early TB treatment initiation (31), and scaling-up this intervention could support linkage to care (98).

The LINKEDin intervention and other efforts to ILTFU will likely produce individual-level benefits as TB patients timely initiate TB treatment, and therefore will experience less morbidity and mortality. The benefits of these interventions could extend to the population level if onward transmission of TB from individuals with ILTFU will be reduced. The extent to which implementing and scaling up these interventions would reduce transmission and therefore accelerate declines in TB incidence and mortality in South Africa is currently not known.

The aim of this study was to use an existing transmission-dynamic mathematical model of TB in South Africa to investigate the impact of reducing ILTFU on TB incidence and mortality in South Africa, assuming scale up of the LINKEDin interventions country-wide between 2023 and 2028. The study further aimed to interpret the expected impact with respect to the 2035 targets of the End TB strategy.

3.2 Methods

3.2.1 Underlying study

This modelling study was centred around findings from the LINKEDIn study, a quasi-experimental study conducted in three South African Provinces, KwaZulu Natal, Western Cape, and Gauteng. The aim of the LINKEDIn study was to reduce ILTFU among diagnosed patients attending primary health care facilities (PHCs) by systematically following up those detected as ILTFU to supporting linkage to care (31,98). The study used a patient management intervention that was targeted to individuals diagnosed in PHCs and non-PHCs (including hospitals). The intervention is made up of two parts. The first, a community intervention, or an “alert-and-response” system, assumed a TB patient management system was put in place that tracks patients who do not link to a TB treatment facility. In summary: if a TB patient did not link to a treatment facility within 3 days of receiving their diagnosis, a short message service (SMS) was sent. If they did not link to treatment after an additional 3 days, they received a telephone call. Finally, if after a further 3 days there was no linkage to treatment, a referral to a community health care worker was sent for a home visit. The second was a hospital-based intervention that used the TB care cascade to identify TB patients diagnosed in TB hospitals and ensured the infection and prevention control team were notified for appropriate clinical management. Using preliminary results and consultation with researchers from the study, I estimated what a national scale-up of the intervention within an existing mathematical TB model could look like.

3.2.2 Details of the transmission-dynamic model used in the analysis

The model I was provided with and used was jointly developed by researchers at the Desmond Tutu TB Centre (DTTC) and the South African Centre for Epidemiolocal Modelling and Analysis (SACEMA) TB modelling group. Prior to this analysis, the model was initialized, the parameters were estimated, and calibration to specific TB targets was conducted. Here, I provide relevant details of the transmission-dynamic model. Additional detailed information is available in Addendum B which was provided by the developers of the model and includes the original model structure and overview, model parameters, model initialization, and the calibration approach.

3.2.2.1 Modelling approach and overview

The structure of the transmission-dynamic mathematical model of TB in South Africa follows conventions of previously published models (38,63,71). It is implemented as a series of ordinary differential equations describing the movement of individuals between disease compartments over time. The TB model includes stratifications by HIV status to account for the modifying effect of HIV infection on TB natural history. The model considers HIV infection, progression of HIV disease with decreasing CD4+ T-cell counts of cells/mm^3 (CD4), and antiretroviral therapy (ART) for the different HIV states. The model uses external estimates of HIV incidence obtained from UNAIDS (8) and the Thembisa model (99) to simulate population-level HIV infection; HIV transmission-dynamics are not modelled. The model structure is provided in Figure 3.1.

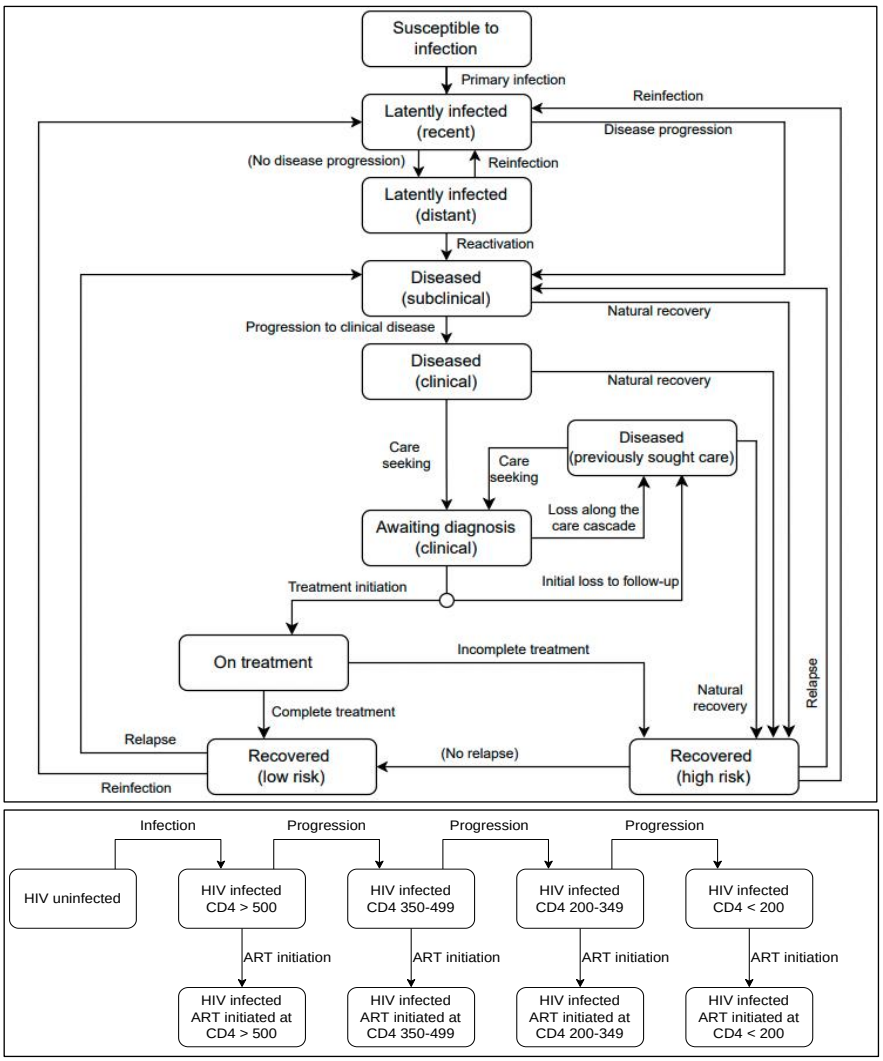

Figure 3.1: Model structure (provided by the developers of the model)

Upon primary infection with *M.tb*, susceptible individuals transition to the recent latently infected state. From there, individuals either progress to the subclinical infectious disease state or they move to the distant latently infected state. Research has shown that the distinction between recent and distant latent infection is important, since the risk of progression to active disease is lowered the longer an individual is latently infected (100,101). Reinfection to recent latently infected or reactivation to the subclinical infectious state can occur from this stage. Once infectious (in a subclinical state where an individual has asymptomatic disease), progression to symptomatic clinical disease occurs. An individual may seek care upon symptom onset, at which point they move to the symptomatic awaiting diagnosis state. Once in the awaiting diagnosis state, individuals enter the TB care cascade, depicted in Figure 3.2.

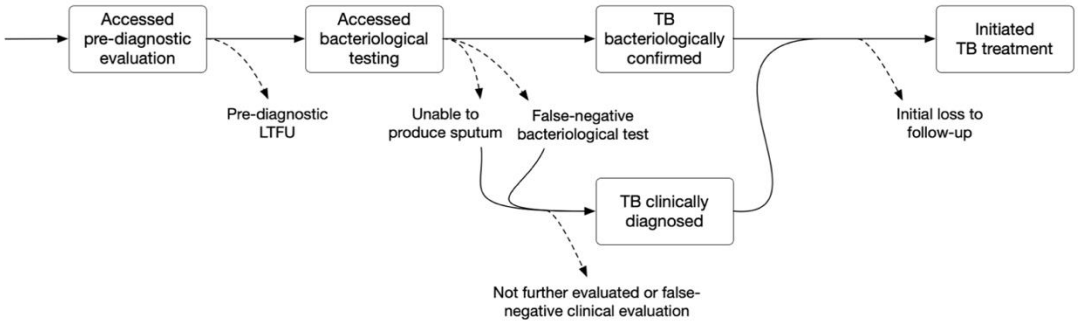

Figure 3.2: The TB care cascade and losses at each step (provided by developers of the model)

The model takes different losses along the TB care cascade into account. These losses include pre-diagnostic loss to follow-up, patients being unable to produce sputum for a bacteriological test, false-negative bacteriological tests due to imperfect sensitivity of diagnostic tests, and ILTFU, when a patient is diagnosed with TB and referred for treatment, but never initiates treatment. The model distinguishes between ILTFU individuals in PHCs versus non-PHCs (not explicitly depicted), which is important considering TB patients are only able to register at community PHCs and selected specialized TB hospitals in South Africa (30). If a patient is lost before initiating treatment, they move to the compartment for individuals who previously sought care and are still infectious. From there, these individuals can re-seek care at a rate faster than initial care seeking, and transition back to the awaiting diagnosis state. If a patient is linked to TB treatment, they move onto the on-treatment state. From treatment, individuals can recover and be at high-risk (if they have not successfully completed treatment) or low-risk (if they have successfully completed treatment). From clinical diseased states, individuals can recover naturally to the high-risk state and may subsequently transition to the low-risk state. Not explicitly depicted in the model diagram are births into the susceptible class and deaths that can occur due to TB infection or other causes.

For people living with HIV (PLWH), TB risk was accounted for based on categories of CD4 cell counts (Figure 3.1) as well as ART initiation in the population. HIV has an impact on several of the TB model parameters as shown by the prior parameters, available in Addendum B. The effect of HIV on these parameters includes increasing the proportion of progression from latent to active TB disease (and subclinical to clinical disease), increasing the relative risk of reinfection from either latent infection or recovery, increasing the rate of relapse from recovered, decreasing the rate of natural recovery, and increasing the rate of excess mortality due to TB for treated and untreated TB, among others, as CD4 cell count decreases. These parameters are all negatively affected by HIV, consistent with an observational cohort study conducted in South Africa describing the risk of TB associated with CD4 cell recovery during ART (102). If individuals are on ART, however, the effect of HIV on the parameters is reduced (103).

3.2.2.2 Model initialization and parameter estimation

The transmission-dynamic model used for this analysis was previously calibrated to data from 2016 to 2020. The model simulations were initiated in 1995 to allow for a 20-year burn in period. The time horizon for model projections of TB incidence and mortality is between 2020 and 2035. Calibration dates were chosen according to the availability of data, including estimates from the first South African TB prevalence survey conducted in 2018 (97). Feasible ranges were used to exclude simulated trajectories that could be considered unrealistic through the calibration process.

A Bayesian calibration approach, similar to previous studies (71,72), was used to identify parameter values that fit the calibration targets. Prior distributions for parameters used in the model are found in Addendum B. A sampling-importance-resampling algorithm was used to implement the approach (104). Parameter values were sampled independently from defined uniform prior distributions of all model parameters to create 100,000 parameter sets ("sampling"). Parameter sets that result in infeasible model outcomes are removed at this step using predefined feasible ranges for calibration targets. The total likelihood of the data given a parameter combination was calculated to determine the goodness-of-fit of an individual parameter combination's model outcomes to the calibration targets ("importance"). The parameter sets were then resampled with replacement by assigning weights to each parameter combination proportional to the likelihood of observing the calibration data ("resampling"). The set of resampled parameter combinations approximates the posterior distributions of the model parameters. Figure 3.3 shows the simulated trajectories of the model outcomes using the 1,000 resampled parameter sets against the calibration targets and feasible ranges.

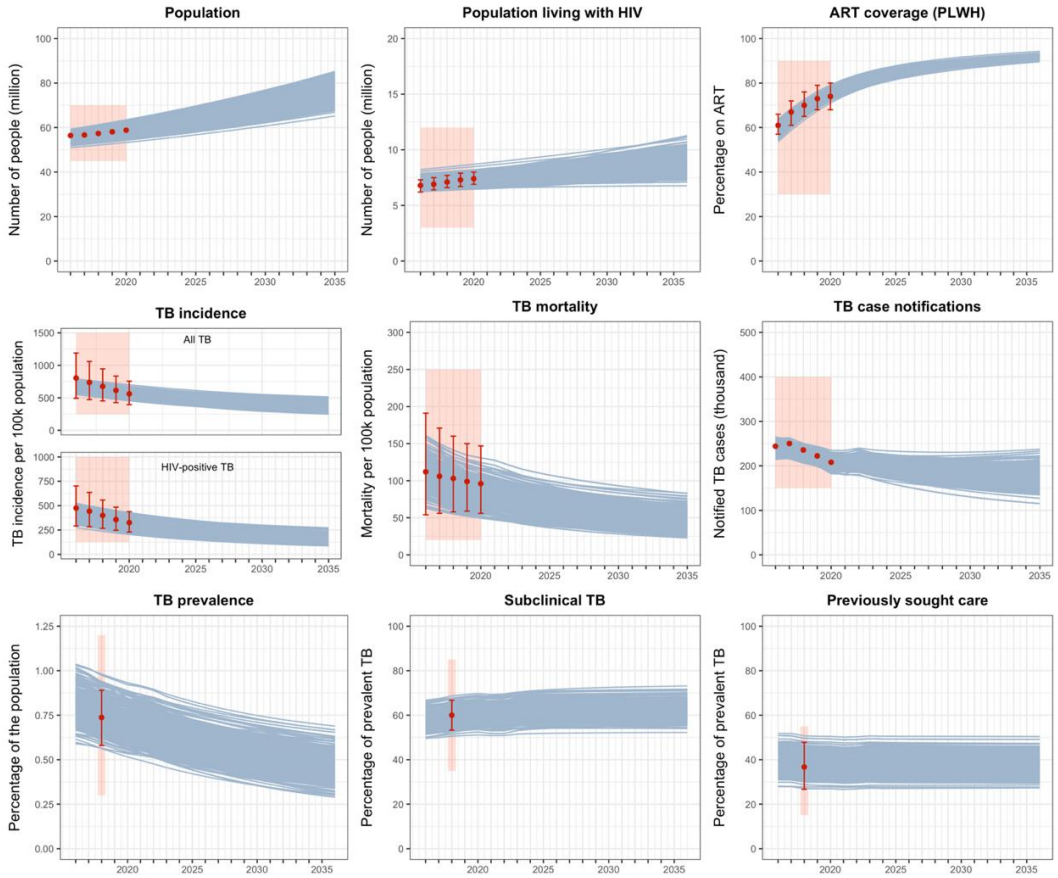

Figure 3.3: Calibration targets and fitted trajectories of the model.
Red dots represent the calibration targets with 95% uncertainty intervals where applicable. Grey lines represent the 1,000 model trajectories obtained by calibration. Shaded regions represent feasible ranges for trajectories. Data used to build this graph was provided by the developers of the TB model.

3.2.3 Adaptations to the provided transmission-dynamic model for this analysis

In this section I describe adaptations to the model that was developed and provided for prior to this analysis, including calculations of baseline estimates for ILTFU in PHCs and non-PHCs, scenario analyses and a sensitivity analysis for parameters used in the model.

3.2.3.1 Development of a LINKEDIn scale-up scenario for South Africa

I made several assumptions surrounding ILTFU in South Africa base on the LINKEDIn study. Beginning with baseline ILTFU in South Africa, I assumed the proportion of people who are lost before initiating treatment in PHCs and non-PHCs remains constant over the model time horizon. Under the baseline scenario, suspected TB cases are diagnosed in either primary health care facilities (PHCs) or non-PHCs, including hospitals. Data from the Electronic TB Register (ETR) shows that 70% of people are diagnosed in PHCs and 30% are diagnosed in non-PHCs. A study assessing the care cascade in South Africa was recently updated and estimated that 21% of diagnosed TB patients are lost prior to starting treatment (13). Given consultation with researchers from the LINKEDIn experimental study who have received preliminary results, I assumed TB patients diagnosed in non-PHCs (such as hospitals) are twice as likely to be ILTFU than TB patients diagnosed in PHCs. In accordance with these data, I was able to estimate prior ranges for the proportion of TB patients who are ILTFU in PHCs and non-PHCs.

Overall ILTFU:

$$\left(0.7 * \left(ILTFU_{PHC}\right)\right) + \left(0.3 * \left(ILTFU_{non-PHC}\right)\right) = 0.21$$

ILTFU in non-PHCs as a function of PHCs:

$$ILTFU_{non-PHC} = 2 * ILTFU_{PHC}$$

Solving both these equations simultaneously leads to prior estimates of ILTFU of ~15% in PHCs and ~30% in non-PHCs. Wide ranges of uncertainty in the uniform prior distributions were used: 10-20% for ILTFU in PHCs and 20-40% in non-PHCs.

In the intervention scenario, I assumed that the intervention would be implemented countrywide between 2023 and 2028 and would prevent losses prior to treatment initiation in the population. Through consultation with LINKEDIn researchers, I assumed the maximum effect of the intervention would reach 50% after five years (i.e., the intervention would reduce ILTFU in South Africa by half) and would remain constant thereafter. I assumed it would take two years to reach half the maximum effect in the population (i.e., after two years the intervention reduces ILTFU by 25%). Individuals prevented from being lost are assumed to successfully begin TB treatment and have the same probability of completing treatment as patients who initiated treatment without the intervention.

3.2.3.2 Scenario analyses

The baseline scenario, used for the comparator for reducing ILTFU in South Africa, is defined as the continuation of current TB prevention and care strategies. Under this scenario, the model includes a linear decline in the rate at which people access diagnosis by between 1-10% between 2020 and 2023 due to COVID-19 disruptions to TB health services. Levels of accessing diagnosis recover back to normal, or what was observed prior to the introduction of COVID-19, after 2023.

Unlike the baseline scenario, analyses regarding the intervention scenarios represent accelerated progress in TB control strategies. I modelled the effect of the patient management intervention by

reducing the proportion of ILTFU using a negative logistic function, as seen below, with accompanying parameters defined in Table 3.1.

$$ILTFU = \alpha + \frac{\beta - \alpha}{1 + e^{\delta(x - x_m)}}$$

Table 3.1: Table of parameters for the logistic function that represents the implementation of the intervention in the South African population

Parameter	Definition
$ILTFU$	Proportion population ILTFU
α	Minimum proportion of ILTFU (after intervention implementation)
β	Maximum proportion of ILTFU (baseline proportion of ILTFU)
δ	Logistic curve parameter: steepness of the curve
x	Model time point
x_m	Logistic curve parameter: inflection point (represents the timepoint to reach half of maximum effect)

I was thus able to specify the minimum (α) and maximum (β) effect of the interventions as well as simulate the delay of implementing the interventions in PHCs and non-PHCs (x_m). For the primary analysis, I assumed the maximum effect of the intervention was a 50% reduction in ILTFU and implementation is such that it takes 2 years to reach half the maximum effect in the population. Alternatively, in a secondary analysis I varied the maximum effect of the intervention (25% and 75%) as well as the time to mid-implementation (2 years and 3 years). Figure 3.4 illustrates the scale-up scenarios for the reduction in ILTFU in PHCs compared to baseline levels. Scenarios for non-PHCs are similar.

I conducted a further scenario analysis on the duration at which people who are ILTFU re-seek care. This is a necessary addition to the study as it can be argued that the time to re-seek care can either increase or decrease if people are lost prior to initiating treatment. For example, if an individual begins to experience more severe symptoms than when they were initially diagnosed, they are more likely to seek care faster. Alternatively, if a patient is afraid of stigma surrounding TB or is affected by their socioeconomic status (e.g., they cannot afford transport to a nearby PHC), they will take longer to re-seek care if at all. This allows increased transmission in the population which results in an increased number of individuals that require diagnosis and treatment. I implement this scenario in the model in a similar way to the LINKEDIn intervention, using a logistic function. I increase and decrease the duration by 10% and 20% while running the primary analysis (i.e., implementing the intervention) and determine the effect on population-level outcomes. This analysis has a direct implication on the effectiveness of the intervention. If patients take longer to seek care, they may contribute to ongoing transmission within their communities leading to increased incidence and, potentially, increased mortality.

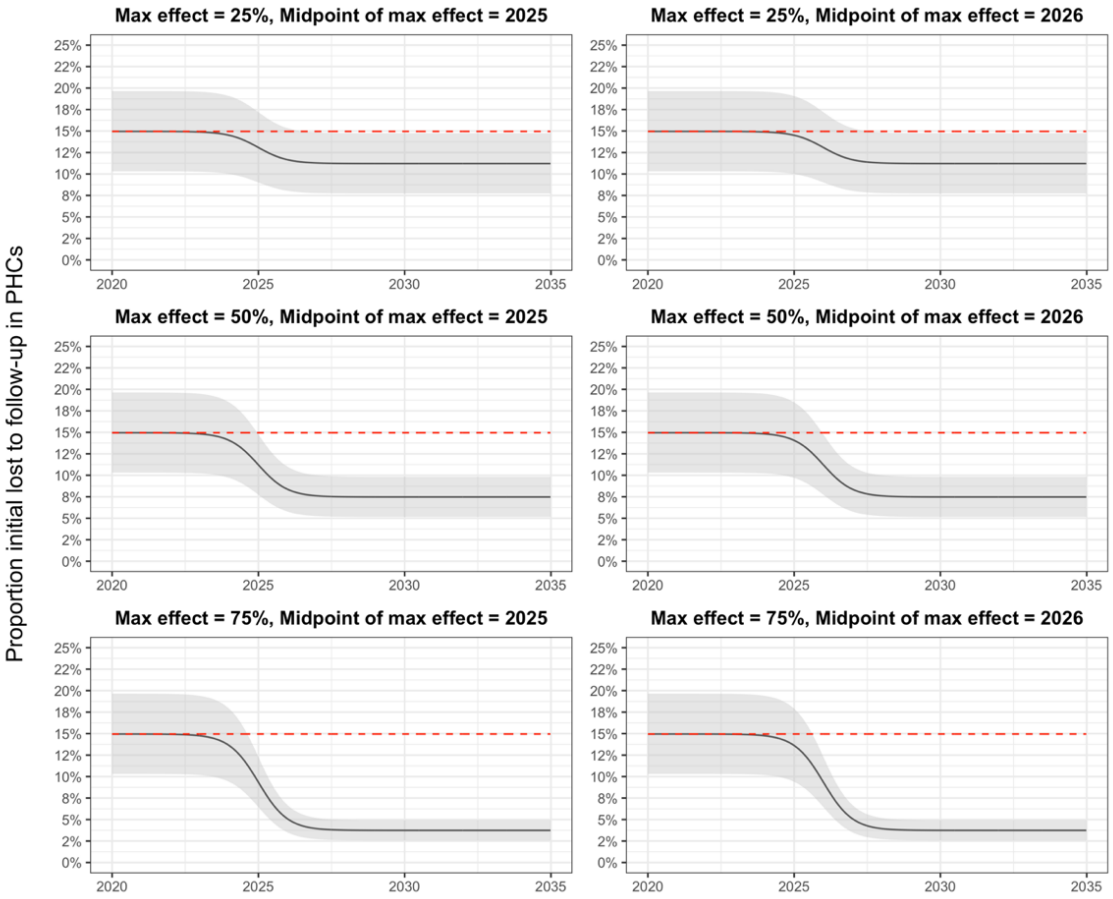

Figure 3.4: Illustration of how the intervention scenarios were implemented under different conditions.
The black solid line represents the effect of the intervention on the ILTFU parameter while the red dashed line represents the baseline parameter value. Shaded regions represent 95% uncertainty intervals.

3.2.4 Model outcomes

I simulated trajectories for TB incidence and mortality over a 13-year time horizon (2023-2035). I considered a baseline scenario and different intervention scenarios for ILTFU in PHCs and non-PHCs. The impact of these interventions was defined as the number and percentage of incident TB cases and deaths averted during the 13-year period relative to the baseline scenario. Additionally, percentage reductions in TB incidence and mortality rates were calculated. I estimated the proportion of overall losses along the care cascade (Figure 3.2) attributed to ILTFU as well as the increased proportion of people who initiated TB treatment due to the LINKEDIn intervention. The results are presented as the mean and 95% uncertainty intervals of the outcome values from 1,000 simulated model trajectories.

3.2.5 Sensitivity analysis

I performed a sensitivity analysis to determine how sensitive the outcome measure of the model was due to each of the input parameters using partial rank correlation coefficients (PRCCs). The analysis was conducted using the *prcc* function in the *epiR* (version 2.0.52) package for *R* (version 4.1.2). This analysis is applicable when the relationship between the model output and the input parameters is monotonic and nonlinear (105). PRCCs were calculated using resampled parameter sets produced by the calibration process. One parameter is varied at a time, while the rest remain constant, and the correlation between the highlighted parameter and outcome was measured. The model outcome (percentage of incident TB cases averted) is based on results from the primary

analysis, assuming the maximum achievable effect of the intervention is 50% and the time to mid-implementation in the population is 2 years.

3.3 Results

3.3.1 Baseline scenario

Under the baseline scenario, the model projected a total number of 3.7 million incident TB cases (95% uncertainty interval [UI]: 3.0 – 4.7 million) and 503,524 TB deaths (UI: 309,232 – 754,141), to occur between 2023 and 2035. Modelled baseline projections for TB incidence, mortality, and case notifications between 2016 and 2035 are shown in Figure 3.5.Among people seeking health care for clinical TB under the baseline scenario, the model estimates that 43.6% (UI: 35.9 – 53.7%) of HIV-negative people and 39.1% (UI: 32.5 – 46.6%) of PLWH are diagnosed for TB and initiate treatment as a direct consequence of this health care visit. ILTFU among HIV-negative individuals and PLWH accounted for 17.5% (UI: 11.7 – 23.1%) and 14.5% (UI: 10.2 – 19.9%) of overall losses along the care cascade, respectively.

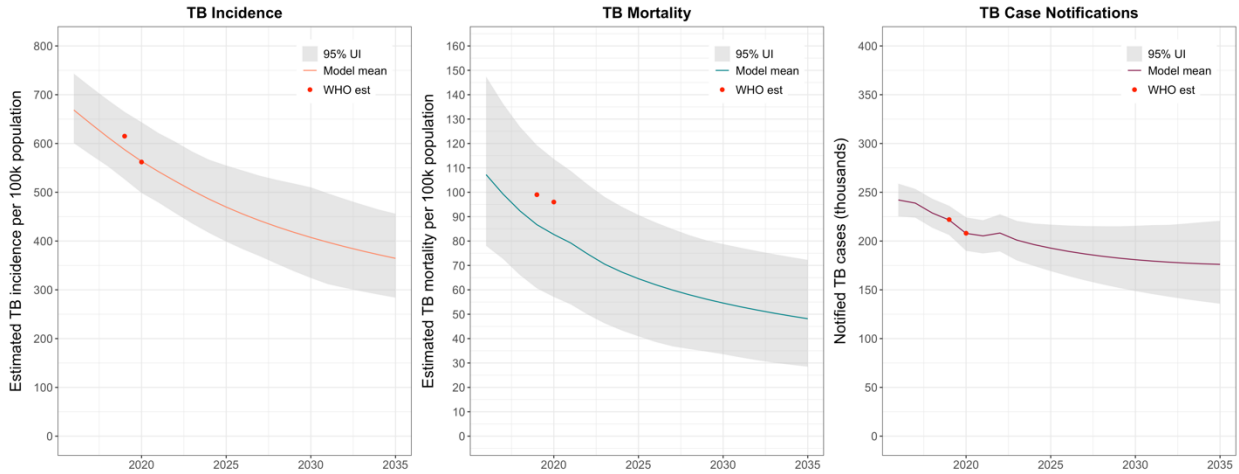

Figure 3.5: Model projections (mean represented by solid lines, 95% UIs represented by shaded areas) compared to WHO 2019 and 2020 estimates (red points; source: (2)) for TB incidence, mortality, and case notifications.

3.3.2 Intervention scenarios

Implementation of the LINKEDIn intervention between 2023 and 2028 would avert 49,812 (UI: 21,258 – 84,644) incident TB cases and 21,479 (UI: 9,500 – 32,661) TB deaths, equivalent to percentage reductions of 0.8% (UI: 0.4 – 1.4%) and 2.5% (UI: 1.3 – 3.5%) for cases and deaths, respectively. The proportion of individuals who would initiate TB treatment under the LINKEDIn intervention would increase by 4.4% (UI: 3.2 – 5.5%) among HIV-negative individuals and 4.9% (UI: 3.6 – 6.3%) among PLWH compared to the number initiating treatment under the baseline scenario. Figure 3.6 shows the mean TB incidence and mortality rates for the baseline and intervention scenarios. Baseline TB incidence and mortality rates were estimated at 364 (UI: 283 – 456) and 48 (UI: 28 – 72) per 100,000 population, respectively, at the end of the time horizon.

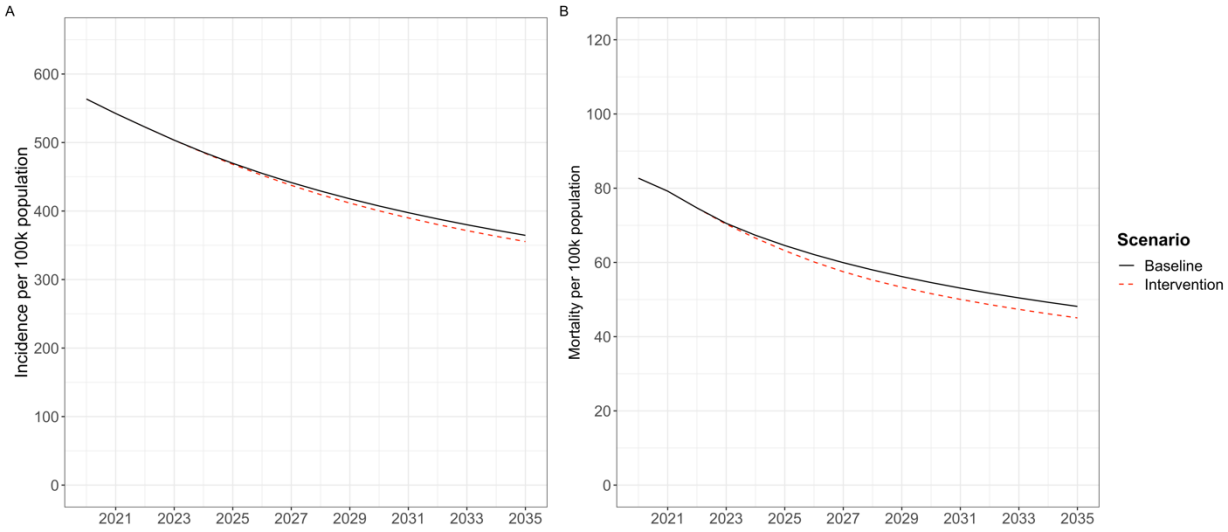

Figure 3.6: TB incidence (A) and mortality (B) rates for baseline and intervention scenarios. Lines represent the means of 1,000 model trajectories.

Under the intervention scenario, corresponding incidence and mortality rates were 355 (UI: 274 – 449) and 45 (UI: 27 – 68) per 100,000 population. Hence, the resulting percentage reduction in TB incidence and mortality rates due to the LINKEDIn intervention at the end of the time horizon were 2.5% and 6.3%, respectively. Using methods described in section 2.2.2 of this thesis, the projected average annual percentage declines (AAPDs) were calculated as 0.2% for TB incidence and 0.5% for mortality. Scenario analysis showed that the impact of interventions varied with the maximum effect and the duration of implementing the LINKEDIn intervention (Table 3.2).

Table 3.2: Results for different intervention scenarios reported as the number and percentage of cases and deaths averted over a 13-year time horizon.
"Scenario" is split into the year at which the effect of the intervention is half the maximum and the percentage of maximum effect of the intervention. *Indicates scenarios for the primary analysis. (UI: Uncertainty interval).

Cases			
Scenario		**Number cases averted (95% UI)**	**Percentage cases averted (95% UI)**
2025	25%	25,831 (10,938 – 43,979)	0.4% (0.2 – 0.7%)
	50%*	49,812 (21,258 – 84,644)	0.8% (0.4 – 1.4%)
	75%	72,144 (31,012 – 122,498)	1.2% (0.6 – 2.0%)
2026	25%	22,455 (9,575 – 38,107)	0.4% (0.2 – 0.6%)
	50%	43,369 (18,629 – 73,555)	0.7% (0.3 – 1.2%)
	75%	62,904 (27,206 – 106,618)	1.0% (0.5 – 1.8%)
Deaths			
Scenario		**Number deaths averted (95% UI)**	**Percentage deaths averted (95% UI)**
2025	25%	11,145 (4,887 – 17,074)	1.3% (0.7 – 1.8%)
	50%*	21,479 (9,500 – 32,661)	2.5% (1.3 – 3.5%)
	75%	31,092 (13,861 – 46,972)	3.6% (1.9 – 5.0%)
2026	25%	9,934 (4,355 – 15,141)	1.2% (0.8 – 1.6%)
	50%	19,169 (8,472 – 29,014)	2.2% (1.5 – 3.1%)
	75%	27,781 (12,372 – 41,796)	3.2% (2.2 – 4.5%)

Reductions in the number and percentage of incident TB cases and TB deaths averted are shown in Figure 3.7 and Figure 3.8, respectively. As the maximum effect of the intervention increases (from 25% to 75%), the model outcomes (number and percentage of cases and deaths averted) increase. Conversely, when the time to reach half the maximum effect of the intervention in the population increases from 2 years to 3 years, the model outcomes decrease. The resulting effect of the intervention is larger for TB mortality than for incidence as shown by the overall percentage of outcomes averted in Figure 3.7(B).

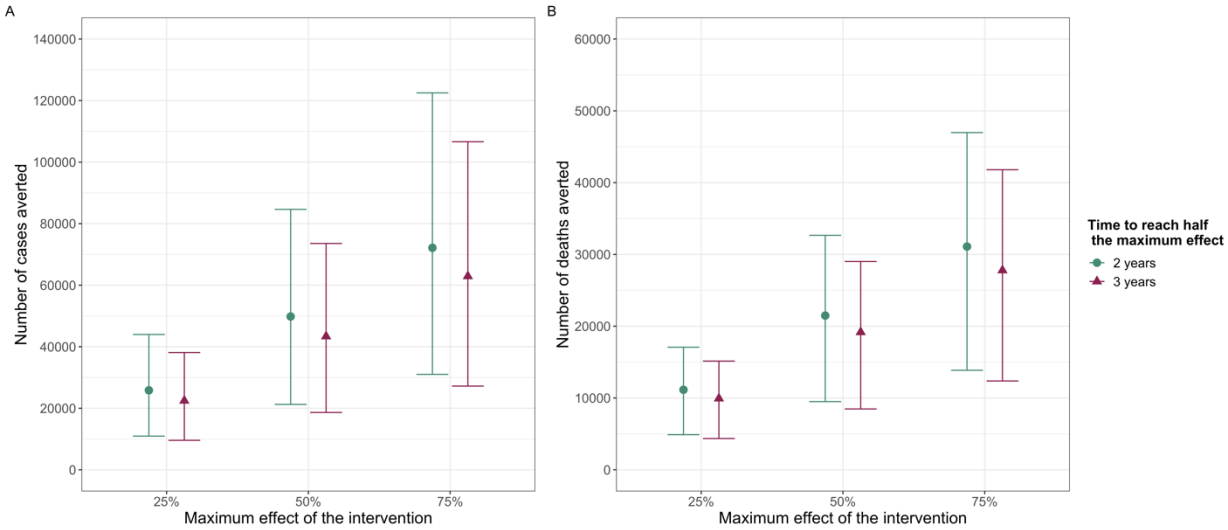

Figure 3.7: Resulting number of cases (A) and deaths (B) averted when the maximum effect of the intervention is varied, as well as the time of implementation of the intervention.
Points represent the mean of 1,000 model trajectories with 95% uncertainty intervals.

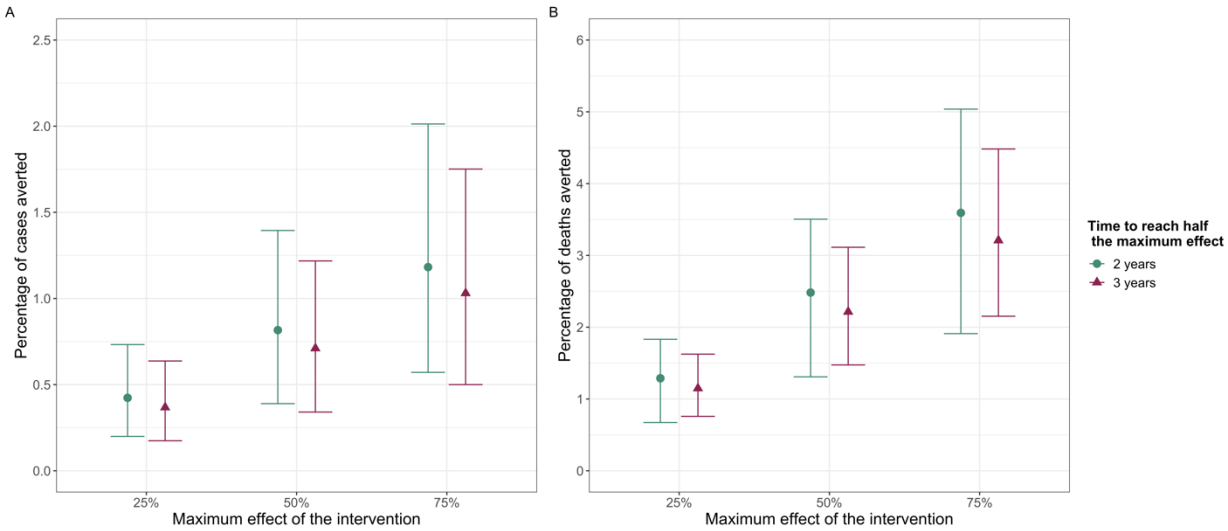

Figure 3.8: Resulting percentage of cases (A) and deaths (B) averted when the maximum effect of the intervention is varied, as well as the time of implementation of the intervention.
Points represent the mean of 1,000 model trajectories with 95% uncertainty intervals

Figure 3.9 shows the results of the scenario analysis after varying the relative rate of seeking care among people who had previously sought care but were lost (using the rate of care seeking among those who never sought care before as a reference). By increasing the rate of accessing diagnosis after being lost before starting treatment, I decreased the duration that an individual resides in the particular compartment ("Diseased (previously sought care)", see Figure 3.1). As the parameter is increased, the number of cases and deaths averted increases. Conversely, if the parameter is decreased, the outcomes are reduced. When reducing the rate of re-seeking care by 20%, the effect of the intervention is almost nullified. As with the primary analysis, the resulting effect of the intervention on mortality is larger than TB incidence as represented by the percentage of cases and deaths averted in Figure 3.9 (B).

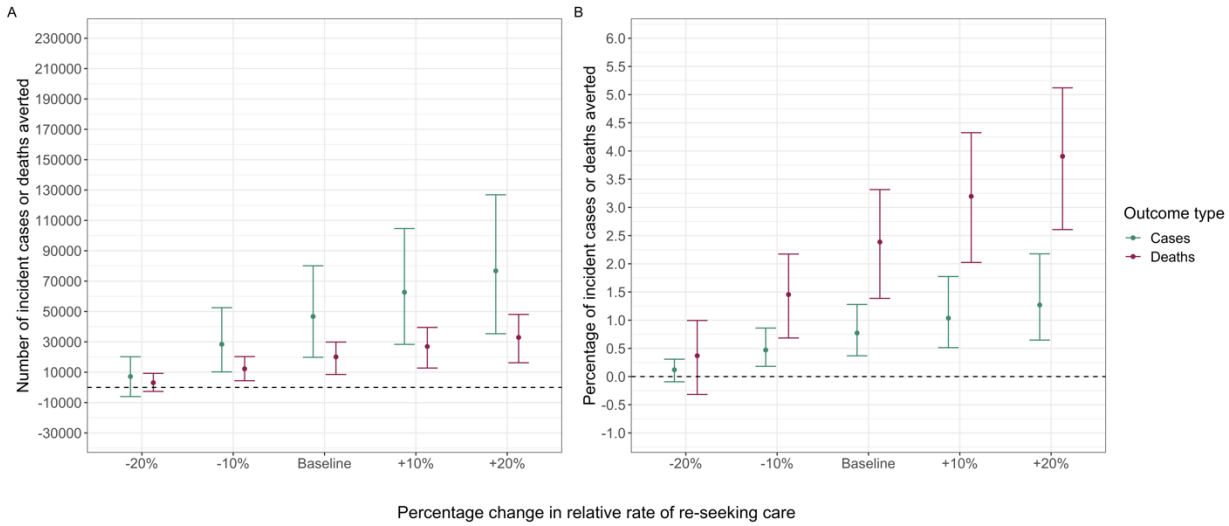

Figure 3.9: The number of cases deaths averted (A) and the percentage of cases and deaths averted (B) due to the intervention while varying the relative rate that individuals lost along the care cascade re-seek care.
Points represent the mean of 1,000 model trajectories with 95% uncertainty intervals.

3.3.3 Sensitivity analysis

I conducted a PRCC analysis of the model parameters and outcomes to determine how sensitive outcomes were to model parameters. The outcome used for the PRCC was the percentage of cases averted due to the LINKEDIn intervention. The twenty most sensitive parameters resulting from the PRCC analysis are shown in Figure 3.10.

The most sensitive parameters include the percentage ILTFU in PHCs and non-PHCs (including hospitals), the rate at which individuals lost along the care cascade re-seek care, the proportion of the population in the susceptible class, and the rate of initial care seeking, among others. The most influential parameter, namely ILTFU in PHCs, has a positive correlation with the outcome of the model, suggesting that an increase in the parameter results in an increase in the outcome. Alternatively, a negative correlation, such as the relative transmissibility of TB in people with subclinical disease, suggests that a decrease in the parameter value results in an increase in the outcome, or vice versa.

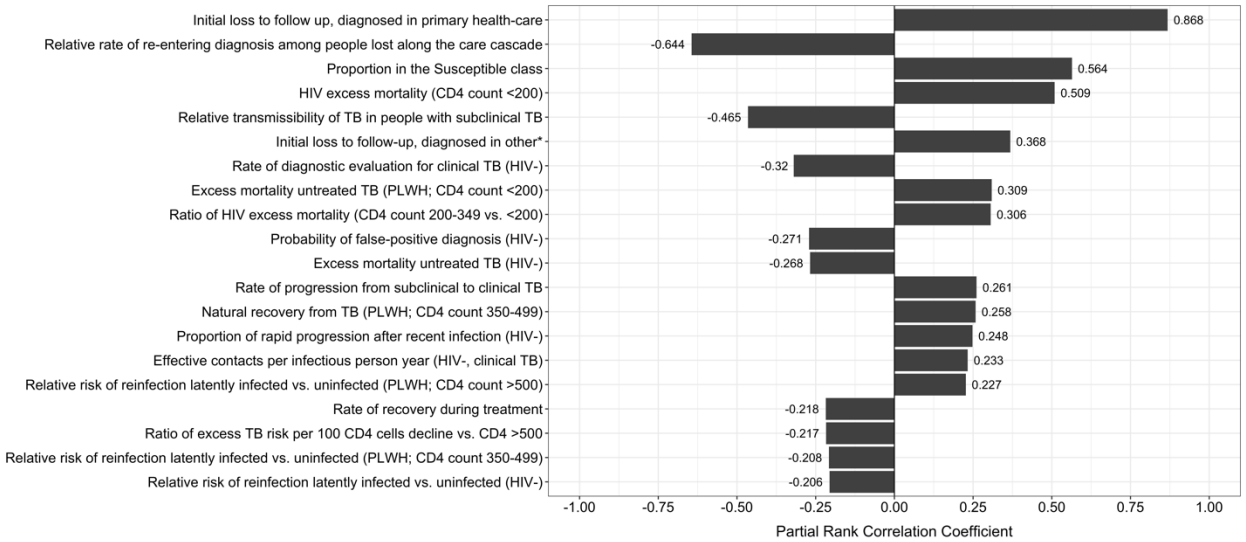

Figure 3.10: Results from the PRCC analysis.
The outcome corresponds to the percentage of cases averted due to the intervention with a 50% maximum effect and 2-year period to reach half the maximum effect. Model parameters are listed on the y-axis, PRCC values on the x-axis. *ILTFU in other facilities includes hospitals. (HIV = Human immunodeficiency virus, HIV- = HIV-negative individuals, PLWH = people living with HIV).

3.4 Discussion

This study made use of an existing transmission-dynamic mathematical model to determine the impact of reducing ILTFU on TB incidence and mortality in South Africa based on findings from LINKEDIn study, a large implementation study in three South African Provinces that aimed to reduce ILTFU among people diagnosed with TB. I estimated the impact of country wide scale-up of the LINKEDIn intervention. The findings suggest that implementing the LINKEDIn intervention to reduce ILTFU by 50% could lead to notable reductions in TB incidence and mortality. It was estimated that the intervention would prevent approximately 50,000 incident TB cases and 21,500 TB deaths between 2023 and 2035. Without additional interventions, however, the impact was not sufficient to reach the End TB strategy targets.

The population-level impact estimated in this study differs from that estimated in other modelling studies at national (44) and sub-national level (45,46). Knight *et al.* compared a variety of interventions for reducing TB in the South African population, including decreasing ILTFU (44). The study suggested that substantial reductions in TB incidence and mortality (30% and 52%, respectively) could be achieved over a 17-year time period if ILTFU was reduced. The study made similar assumptions about the effect of the intervention (50% reduction in ILTFU). However, it assumed a shorter time to full scale up of the intervention (1 year vs. ~5 years in my study) and a longer time horizon for impact after full implementation (16 years vs. ~8 years in my study). More importantly, the study assumed lower overall losses along the care cascade and a higher increase in the proportion of individuals with TB who would initiate treatment as a result of the intervention (11.6% vs. 4.5%/4.9% HIV negative/positive).

Two other studies modelled a reduction in ILTFU at sub-national level in South Africa, namely provincial-level (45) and occupational setting in South African mines (46). Scaling up an intervention that improved linkage to care for diagnosed individuals in three provinces of South Africa (KwaZulu-Natal, Limpopo, and Western Cape) was assumed to reduce ILTFU by 80% between 2015 and 2021 (45). A reduction in TB incidence of 4.9 – 13.8% and mortality of 11.6 –

26.2% was estimated in the different provinces. Targeting South African miners with a hypothetical intervention to reduce ILTFU by 86%, on average, for smear-positive and smear-negative individuals was estimated to reduce TB incidence by 40% over 10 years (46). These settings estimated a larger impact on population-level outcomes; however, they may not be generalizable to the whole of South Africa and, therefore, the outcomes may not be directly comparable. Different estimates of the impact of ILTFU observed across these different studies (44–46) suggests that impact will be context specific. More research is required to understand the role of differential losses along the care cascade for TB.

At secondary analysis, I considered additional scenarios describing the maximum effect and implementation duration of the LINKEDin intervention. The first scenario consisted of varying levels for the maximum effect of the intervention (25%, 50% - primary analysis, and 75%) and delays of implementing the intervention in the population (2 years – primary analysis, and 3 years to reach half the maximum effect of the intervention). These analyses showed that the impact of reducing ILTFU is greatest when intervention strategies can be implemented more rapidly, and when the maximum effect of the intervention is increased. These findings are plausible, since a larger intervention effect and a shorter delay would ensure less individuals are lost prior to treatment, leading to better survival and less infectious individuals transmitting the disease in the population. The second scenario consisted of varying the time at which individuals re-seek care after they are lost within different stages of the care cascade. This has direct implication on the effectiveness of the intervention, since the longer individuals with TB take to link to treatment, the greater their potential of transmitting the disease to others in the population and the higher the likelihood of death (106).

The variation in impact observed under the latter analysis is consistent with the findings from the sensitivity analysis, which showed that epidemiological impact is sensitive to the rate at which people lost along the care cascade (e.g., due to ILTFU) are re-seeking care. The sensitivity analysis also showed that the number of cases averted is dependent on the proportion of people initially lost to follow-up in PHC and non-PHC facilities. This is expected because higher ILTFU at baseline leads to greater absolute effect of the intervention.

I note the following important limitations of this study. The model aggregates all losses along the care cascade into a compartment called “Diseased (previously sought care)” and are allowed to re-seek care at the same rate after some time, see Figure 3.1. This is a limitation, since individuals lost at different stages in the care cascade are likely to have different care-seeking behaviour (17). I do, however, consider this rate in the secondary analysis to account for variability. This analysis focused on South Africa, a country with high rates of ILTFU. The impact of this intervention may not be generalizable to other settings, since factors such as the prevalence of ILTFU in other settings may result in a lower, or higher, return on the intervention. There is considerable uncertainty in parameters of natural history and parameters of ILTFU in PHCs and non-PHCs, partly because prior estimates are based on different data sources. Additionally, the uncertainty around the different losses along the care cascade is significant. To reduce bias, the model was calibrated prior to this analysis with prior ranges that represent the substantial uncertainty in parameters. There was also much uncertainty in the maximum achievable level of the intervention and the delay of implementation in the population, however, these factors were considered at secondary analysis to determine what outcomes could look like with different scenarios. In this study, individuals who were prevented from being ILTFU and initiated on treatment through the LINKEDIn intervention were assumed to complete treatment at the same rate as people who did not need support to link to TB care. It is, however, possible that these individuals will have a higher risk of being LTFU during treatment. Ideally, individuals who are detected as ILTFU and started on treatment would receive support throughout the process to ensure they successfully complete their treatment. I did not vary initial loss to follow-up based on HIV and/or ART status due to data

limitations and this may have affected model outcomes. Final results of the impact of the LINKEDIn intervention at sub-national level were not readily available at the time of this modelling study, and so preliminary data were used. An update of the model, once this data can be utilized, will be beneficial for a more realistic representation of what the scale-up of this intervention could look like at country level.

Since a cost-effectiveness analysis was out of the scope of this study, the cost and resource implications of scaling up this intervention in the South African population should be considered. Analysis of the cost-effectiveness of implementing this intervention will provide further evidence in determining whether a scale-up will be beneficial in the planning of TB control activities. Costs and resources to implement the LINKEDIn intervention, such as SMS's, telephonic calls, and visits by HCWs to those who do not start treatment following diagnosis could be prohibitive. As such, more information on which populations are at high risk of being initially lost to follow-up should be considered so interventions can be optimally targeted. A combination of interventions, including those to reduce ILTFU, is likely to have a larger population-level effect and should be modelled to determine an optimal effect strategy for South Africa. Data is required from empirical studies to determine the risk of previously ILTFU individuals successfully completing treatment following an intervention such as this. This may highlight the need for continuous support for linkage to TB treatment and successful completion. Further modelling should be conducted on the impact of reducing a combination of losses along the TB care cascade to strengthen the process of individuals with active TB seeking care and completing their treatment.

In conclusion, I used an existing transmission-dynamic model to determine the population-level impact of reducing ILTFU in South Africa based on early results from a large quasi-experimental study. I found that the LINKEDIn intervention would have a notable effect on TB mortality with a more moderate effect on TB incidence. The observed indirect effects from reducing transmission extend individual-level benefits among individuals at risk of ILTFU who are more likely to initiate TB treatment through the LINKEDIn intervention. Since ILTFU is a growing concern in South Africa, this study highlights the need for prioritisation of a combination of interventions to reduce ILTFU when planning for TB control efforts. Furthermore, integrated interventions to reduce different types of losses along the care cascade are needed.

4 Discussion and conclusions

4.1 Overview

TB continues to be a major public health threat in South Africa. This thesis aimed to synthesize the impact of different interventions on TB incidence and mortality as estimated in studies using transmission-dynamic mathematical models, in order to explore which interventions should be prioritised to maximise impact. It further aimed at addressing an important research gap by estimating the population-level impact of reducing ILTFU in South Africa. Original research conducted towards this thesis is presented in Chapters 2 and 3.

In Chapter 2, I conducted a systematic review of mathematical modelling studies that focused on South Africa and estimated the impact of various interventions of TB prevention and care on outcomes linked to the End TB strategy. Through this study, I explored which types of interventions would be most promising in reducing TB burden in South Africa and identified several gaps for further mathematical modelling research. The study presented in Chapter 3 addresses one of the gaps identified in the systematic review. I used an existing TB transmission-dynamic model to estimate the impact of reducing ILTFU in South Africa by scaling-up the LINKEDIn intervention that has been implemented in 3 South African provinces.

This chapter discusses the key findings of the two studies in the context of existing literature. I then highlight strengths and limitations of this thesis as a whole and end with a summary of recommendations for future research and important conclusions

4.2 Discussion of key findings

4.2.1 A systematic review of mathematical modelling studies

To meet the first objective, I performed a systematic review of transmission-dynamic TB models to synthesize evidence for TB prevention and control interventions in South Africa. This review was designed to support decision making by highlighting interventions with the greatest potential to accelerate progress towards reaching the End TB strategy targets. The 2035 targets include a 90% reduction in the TB incidence rate, a 95% reduction in the number of TB deaths and the number of families facing TB-related catastrophic costs to zero, compared to 2015 levels (49).

The systematic review showed that all 29 eligible studies, except one, projected the impact of interventions towards reducing the End TB strategy target indicators of TB incidence, mortality, or both. The remaining study estimated the impact of interventions on the number of households experiencing TB-related catastrophic costs (80). This is an outcome that is particularly relevant for South Africa since TB is amplified by the high proportion of the population facing unemployment, household crowding, and other resource limitations such as transport for clinic attendance (96). Crude measures of average annual percentage declines in TB incidence and mortality were calculated to compare the impact of different interventions. Preventive interventions including vaccination, TPT among PLWH, and scaling up ART, were most promising in terms of estimated impact. This finding is supported by studies that have emphasized the need to develop novel, more effective vaccines targeted to key populations (41,85), and to expand the usage of other preventive strategies in high-burden settings (107). Although the majority of studies considered interventions along the TB care cascade, including active case finding or screening, the scale-up of existing and development of novel diagnostic tests, reducing ILTFU, and improving treatment, their impact on TB transmission and incidence was found to be lower. An example was the scale-up of Xpert-based algorithms in South Africa prior to and during its roll-out in 2013. Summarized findings from this review showed that introducing Xpert as a

diagnostic test had a moderate effect on TB mortality and diagnostic yield, consistent with findings from a recent meta-analysis (90) and implementation study (13).

Several gaps in TB modelling research were identified through this review, including a lack of modelling studies that focused on targeting interventions towards vulnerable groups (for example, PLWH and exposed household contacts), and modelling the effect of newly developed diagnostic tests and regimens for active TB (93). More modelling studies should consider the potential for South Africa to reach the End TB target of reducing catastrophic costs faced by TB-affected households to zero. Another important gap that should be considered is the impact of reducing ILTFU in South Africa. Only one study measured this impact at country-level (44). People who are lost prior to initiating TB treatment present a challenge for TB programmes since they are associated with poor treatment outcomes and are expected to contribute to onward transmission (24,27).

4.2.2 Mathematical modelling to reduce ILTFU in South Africa

The second objective was chosen to complement the LINKEDIn study, a quasi-experimental study that aimed to support prompt registration and linkage to treatment through a patient management intervention (31,98). I used an existing transmission-dynamic mathematical model of TB to estimate the number of cases and deaths that could be averted if the LINKEDIn intervention was brought to scale in South Africa. Furthermore, I related the anticipated impact estimated in this modelling study to the 2035 End TB strategy targets.

The analysis suggested that implementing the intervention to reduce ILTFU by 50% could avert approximately 50,000 cases and 21,500 deaths between 2023 and 2035. Due to the delay of ~5 years to implement the LINKEDIn intervention fully in the population, there was less time to measure impact (~8 years). The year 2035 was chosen as the end time point, as I aimed to link the estimated reduction in TB incidence and mortality to the 2035 End TB strategy targets. A reduction in the incidence and mortality rates of 2.5% and 6.3% were estimated at the end of the 13-year time horizon. These results differ from those in an earlier study which estimated that a 50% reduction in ILTFU could reduce TB incidence and mortality rates by 30% and 52% over 17 years (44). Knight *et al.* assumed a shorter time to fully implement the intervention in the population, and a longer time horizon following full implementation (44). More importantly, the study assumed lower overall losses along the care cascade and a higher increase in the proportion of individuals with TB who would initiate treatment as a result of the intervention (11.6% vs. 4.5%/4.9% HIV negative/positive).

Given that detailed losses along the TB care cascade were considered, I was able to model ILTFU in relation to other losses along the care cascade. The model suggested that ILTFU represented a small proportion of the overall losses along the care cascade and, thus, would explain the smaller impact I estimated compared to Knight *et al.* (44).The relatively modest reductions in TB incidence and mortality rates indicate that the addition of the LINKEDIn intervention alone is not likely to assist South Africa in meeting the End TB strategy targets. This finding is consistent with the idea that a combination of interventions to reduce TB burden in South Africa is necessary to reach a 90% reduction in the TB incidence rate and a 95% reduction in the number of TB deaths (39,40), which was also an important finding in the systematic review presented in Chapter 2.

This modelling study addresses an important gap also identified in the systematic review presented in Chapter 2. Among diagnosed individuals, people who are lost before initiating treatment are an increasing concern in South Africa (30); only one study in the systematic review focused on reducing ILTFU at country-level (44). The scale up of the LINKEDIn intervention to reduce 50% of ILTFU resulted in a larger effect on mortality than incidence. This is consistent with findings from other modelling studies highlighted in Chapter 2 and is plausible since people who are ILTFU

have already developed TB and initiating them on treatment yields direct effects in terms of reducing mortality. Additionally, reducing ILTFU has an indirect effect on incidence and mortality through the reduction of onward transmission. Comparing AAPDs due to different interventions calculated for other modelling studies in the aforementioned systematic review, AAPDs calculated in my study (0.2% for incidence and 0.5% for mortality; section 2.2.2) were moderate compared to other interventions (61,63,67). Figure 4.1 shows the comparison between the impact of other interventions modelled at country-level, calculated in Chapter 2, and the impact of the LINKEDIn intervention, highlighted in red. The relatively modest impact estimated for an intervention to reduce ILTFU suggests that integrated interventions are required to comprehensively address the different losses along the TB care cascade rather than focusing on ILTFU alone.

At secondary analysis, I varied several parameters related to the effectiveness of the LINKEDIn

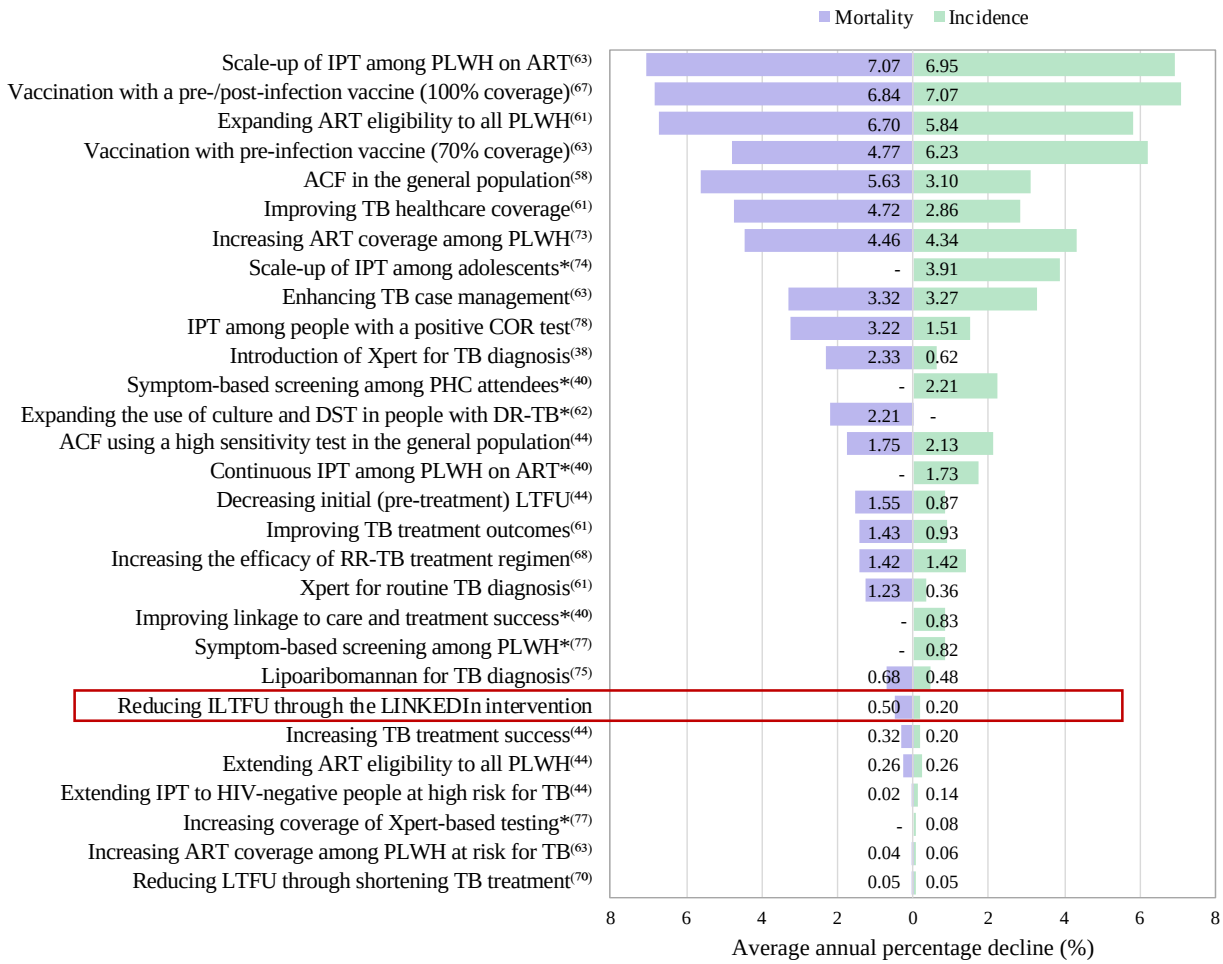

Figure 4.1: Comparison of AAPDs for modelling studies included in the systematic review in Chapter 2 and reducing ILTFU through the LINKEDIn study presented in Chapter 3

intervention, since there is uncertainty in what the scale-up could look like at country level. This analysis showed that the impact of reducing ILTFU in South Africa is greatest when the interventions can be implemented more rapidly and when the maximum effect is increased. Similarly, removing people, who would otherwise be ILTFU, through the LINKEDIn intervention from the "awaiting diagnosis" group reduces the average time to re-seek care and, thus, has an indirect effect and the resulting impact of the intervention is higher. These findings are supported by the idea that linking more people to treatment, and faster, will reduce the potential for transmission and increase the probability of a positive treatment outcome (106).

4.3 Strengths and limitations

This thesis consists of two studies, a systematic review, and a mathematical modelling study, which, in their own way and in conjunction, add to the existing body of research investigating the impact of interventions towards TB prevention and control in South Africa. I highlight several important limitations in this research.

The generalizability of findings from this thesis may be limited, since the primary setting was South Africa at the national level. The systematic review in Chapter 2 also considered populations at sub-national level, however findings may not be generalizable to whole of South Africa due to the vast heterogeneity of TB burden and epidemiology between sub-populations in the country (97). For example, miners in South Africa have been estimated to contribute substantially to TB infections on a per-capita basis, but only a small fraction of overall infections in the country (108). This could be attributed to the relatively small mining population and the heterogeneity in TB epidemiology between the different settings. Furthermore, in the modelling study in Chapter 3, I focused on estimating population-level TB incidence and mortality at the country level. Data and expert opinion used to infer estimates of ILTFU and the potential effect the LINKEDIn intervention could have on the population are based on provincial-level results in KwaZulu-Natal, Western Cape, and Gauteng. Again, these estimates may not be a fair representation of the population. I did, however, consider different scenarios to allow for variation in the maximum effect of the intervention as well as the time it would take to implement the intervention in the population. The modelling study focused on South Africa, a country with high rates of ILTFU. The impact of this intervention may not be generalizable to other settings, since factors such as the prevalence of ILTFU in other settings may result in a lower, or higher, return on the intervention.

Consideration of the cost and resource requirements of interventions is important for policymakers when targeting interventions for TB prevention and control. In this thesis, I did not consider the cost-effectiveness of interventions when determining which types were most promising in reducing TB burden in South Africa or when estimating the effect of reducing ILTFU on population-level incidence and mortality in the country. Only nine out of 29 eligible studies in the systematic review included cost-effectiveness analyses of their interventions, which limited the ability to make a fair comparison based on both impact and cost. Additionally, I did not include a cost-effectiveness analysis of the LINKEDIn intervention in reducing ILTFU in South Africa as it was out of the scope of this thesis.

Uncertainty in mathematical models of infectious diseases is necessary to support the plausibility of their outcomes (109). The lack of uncertainty reported in several of the articles included in the systematic review in Chapter 2 limited the ability to calculate upper and lower bounds of average annual percentage declines in TB incidence and mortality. We could not assume that the mean and confidence intervals for model outcomes would directly translate to confidence intervals for AAPDs and so, they should be interpreted with caution. Parameters for the TB model presented in Chapter 3 are subject to substantial uncertainty. Additionally, there is uncertainty around assumptions made for the LINKEDIn intervention, including the feasibility of reaching a reduction in ILTFU by 50% and the extent to which the specifics of the intervention are applicable to the whole country. To represent this uncertainty, wide prior ranges for model parameters were used in calibration by the researchers who developed the model. Additionally, results are presented as the mean and 95% uncertainty intervals from 1,000 model runs of re-sampled parameter sets to account for uncertainty in outcomes.

Several important limitations were specific to the two studies. Comparing different interventions between studies in the systematic review presented in Chapter 2 was limited by the heterogeneity in model structure, study design and reported outcomes (for example, some studies estimated the number of cases and deaths averted, some measured the percentage decline in incidence and mortality rates, or both). In my modelling study, presented in Chapter 3, it's assumed that

individuals lost at different stages along the care cascade re-seek care at the same rate. This is a limitation since these people are likely to have different care seeking behaviour depending on which type of loss they were recorded as (17). I do, however, vary this rate at secondary analysis to account for these potential differences. Additionally, individuals who were prevented from being ILTFU and initiated on treatment through the LINKEDIn intervention were assumed to not be at additional risk of being lost to follow-up during treatment. This may not be the case, since they may require additional support to complete their treatment compared to individuals who did not need support to link to care.

4.4 Overall conclusions and relevance of this research

In conclusion, this thesis provides a summary of the impact of TB prevention and care interventions on population-level outcomes as estimated by previous transmission-dynamic modelling studies to explore which interventions should be prioritised to maximise impact within South Africa. Furthermore, it addresses an important research gap, namely estimating the impact of reducing ILTFU on TB incidence and mortality in South Africa.

Summarizing results from existing modelling studies showed that interventions focusing on prevention, including vaccination, TPT among PLWH, and scaling-up ART, would have the greatest potential to reduce TB incidence and mortality rather than interventions along the care cascade such as ACF, and improving testing and treatment strategies. There is a lack of studies estimating the impact of interventions to reduce ILTFU in South Africa, hence this thesis included a modelling study to address this gap. Using data and expert opinion from the LINKEDIn study, scaling-up their intervention to reduce ILTFU country-wide was found to have notable impact on the population-level TB incidence and mortality. An important finding in this thesis was that single interventions would be unlikely to generate sufficient progress towards the End TB strategy targets, as such, combinations of interventions are needed to effectively reduce TB incidence and mortality in South Africa. This thesis offers insights at a time where additional guidance is needed following TB health service disruptions caused by the COVID-19 pandemic. Due to these disruptions, progress towards the 2035 End TB strategy targets have slowed and thus, evidence is required for policymakers to better understand how different interventions will aid progress towards TB elimination in South Africa. These results are also useful as part of the consultation process towards the 2023-2028 NTP strategic plan for South Africa.

4.5 Recommendations for further research

Several recommendations for further research in TB modelling have been highlighted in this thesis. Through the systematic review in Chapter 2, gaps that should be considered for future TB mathematical modelling research include the need for studies to model the effect of novel diagnostic tests for TB, interventions offered specifically to vulnerable and high-risk populations such as people living in poverty, exposed household contacts, and PLWH, and importantly, interventions aimed at reducing catastrophic costs for TB-affected households, the third target of the End TB strategy. Although it was shown that combinations of interventions would be necessary to reach the targets of the 2035 End TB strategy, a simplification of the review was to only consider the impact of single interventions. Future work should consider which combinations would have the greatest potential in reducing TB burden in South Africa. The study presented in Chapter 3, which addressed a modelling gap identified in Chapter 2, did not consider the cost or resource implications of reducing ILTFU through the LINKEDIn intervention country wide. Future work should be done to determine the cost-effectiveness and resources required to scale-up this intervention, and whether it would be worthwhile in the South African context. Given that this study estimated a modest reduction in a single loss along the care cascade, ILTFU, understanding how interventions could be integrated to comprehensively address losses along the TB care

cascade will be important. Estimates for losses along the care cascade in South Africa, including from this modelling study, highlight substantial gaps in the care cascade and closing these gaps will be important to successfully reduce TB morbidity and mortality. Further analyses should be conducted to determine the effect of the intervention in combination with other complementary strategies, such as early case detection, accurate diagnosis, and high treatment completion rates.

References

1. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg. 2017;58(1):E9–12.
2. World Health Organization. Global tuberculosis report 2022 [Internet]. 2022 [cited 2022 Nov 11]. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
3. World Health Organization. WHO guidelines on tuberculosis infection prevention and control, 2019 update [internet]. 2019 [cited 2022 Nov 11]. Available from: https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf
4. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2(1):16076. https://doi.org/10.1038/nrdp.2016.76
5. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. European Respiratory Journal. 2009;33(5):1085–94. https://doi.org/10.1183/09031936.00155708
6. Narasimhan P, Wood J, MacIntyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013;2013: 828939. https://doi.org/10.1155/2013/828939
7. Karim SSA, Churchyard GJ, Karim QA, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. The Lancet. 2009;374(9693):921–933. https://doi.org/10.1016/S0140-6736(09)60916-8
8. Joint United Nations Programme on HIV/AIDS (UNAIDS). South Africa 2021 HIV and AIDS estimates [Internet]. 2021 [cited 2022 Oct 18]. Available from: https://aidsinfo.unaids.org/
9. 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 modeling analysis. International Journal of Infectious Diseases. 2022 Sep;122:811–819. https://doi.org/10.1016/j.ijid.2022.07.047
10. McQuaid CF, McCreesh N, Read JM, Sumner T, Houben RMGJ, White RG, et al. The potential impact of COVID-19-related disruption on tuberculosis burden. European Respiratory Journal. 2020;56(2): 2001718. https://doi.org/10.1183/13993003.01718-2020
11. Abdool Karim Q, Baxter C. COVID-19: impact on the HIV and tuberculosis response, service delivery, and research in South Africa. Curr HIV/AIDS Rep. 2022;19(1):46–53. https://doi.org/10.1007/s11904-021-00588-5
12. World Health Organization. Draft global strategy and targets for tuberculosis prevention, care and control after 2015 [Internet]. 2014 [cited 2022 Oct 18]. Available from: https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_11-en.pdf
13. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. Journal of Infectious Diseases. 2017;216(suppl_7):S702-S713. https://doi.org/10.1093/infdis/jix335
14. Sloot R, Maarman GJ, Osman M, Marx FM. Variation in HIV prevalence and the population-level effects of antiretroviral therapy in reducing tuberculosis incidence in South Africa. S Afri Med J. 2018;108(8):12370. https://doi.org/10.7196/SAMJ.2018.v108i8.13394
15. Churchyard GJ, Mametja LD, Mvusi L, Ndjeka N, Hesseling AC, Reid A, et al. Tuberculosis control in South Africa: Successes, challenges and recommendations. S Afri Med J. 2014;104(3):244-248. https://doi.org/10.7196/SAMJ.7689
16. Shapiro AE, van Heerden A, Schaafsma TT, Hughes JP, Baeten JM, van Rooyen H, et al. Completion of the tuberculosis care cascade in a community-based HIV linkage-to-care study in South Africa and Uganda. J Int AIDS Soc. 2018;21(1):e25065. https://doi.org/10.1002/jia2.25065
17. Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. J Clin Tuberc Other Mycobact Dis. 2020;19:100144. https://doi.org/10.1016/j.jctube.2020.100144
18. Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N, et al. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754. https://doi.org/10.1371/journal.pmed.1002754
19. Lippman SA, el Ayadi AM, Grignon JS, Puren A, Liegler T, Venter WDF, et al. Improvements in the South African HIV care cascade: findings on 90-90-90 targets from successive population-representative surveys in North West Province. J Int AIDS Soc. 2019;22(6): e25295. https://doi.org/10.1002/jia2.25295

20. Lurie MN, Kirwa K, Callaway J, Cornell M, Boulle A, Bengtson AM, et al. Quantifying the HIV treatment cascade in a South African health sub-district by gender: retrospective cohort study. Tropical Medicine & International Health. 2020;25(2):186–92. https://doi.org/10.1111/tmi.13334
21. Haghighat R, Toska E, Bungane N, Cluver L. The HIV care cascade for adolescents initiated on antiretroviral therapy in a health district of South Africa: a retrospective cohort study. BMC Infect Dis. 2021;21(1):60. https://doi.org/10.1186/s12879-020-05742-9
22. de Vos E, Scott L, Voss De Lima Y, Warren RM, Stevens W, Hayes C, et al. Management of rifampicin-resistant TB: programme indicators and care cascade analysis in South Africa. Int J Tuberc Lung Dis. 2021;25(2):134–141. https://doi.org/10.5588/ijtld.20.0598
23. World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision [Internet]. 2013 [cited 2022 Oct 25]. Available from: https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf
24. Skinner D, Claassens M. It's complicated: why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. BMC Infect Dis. 2016;16(1):712. https://doi.org/10.1186/s12879-016-2054-5
25. du Preez K, Schaaf HS, Dunbar R, Swartz A, Naidoo P, Hesseling AC. Closing the reporting gap for childhood tuberculosis in South Africa: improving hospital referrals and linkages. Public Health Action. 2020;10(1):38–46. https://doi.org/10.5588/pha.19.0053
26. Botha E, den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis. 2008;12(7):820–823.
27. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis. 2013;17(5):603–607. https://doi.org/10.5588/ijtld.12.0505
28. Mwansa-Kambafwile JRM, Jewett S, Chasela C, Ismail N, Menezes C. Initial loss to follow up of tuberculosis patients in South Africa: perspectives of program managers. BMC Public Health. 2020;20(1):622. https://doi.org/10.1186/s12889-020-08739-w
29. Harries AD, Schwoebel V, Monedero-Recuero I, Aung TK, Chadha S, Chiang CY, et al. Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries. Int J Tuberc Lung Dis. 2019;23(2):241–251. https://doi.org/10.5588/ijtld.18.0207
30. Osman M, Meehan SA, von Delft A, du Preez K, Dunbar R, Marx FM, et al. Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa. PLoS One. 2021;16(6):e0252084. https://doi.org/10.1371/journal.pone.0252084
31. Viljoen L, Hendricks P, Hoddinott G, Vanqa N, Osman M, Hesseling AC, et al. Early interactions with newly diagnosed TB patients in hospital can support linkage to care. Public Health Action. 2022;12(3):121–127. https://doi.org/10.5588/pha.22.0012
32. Siettos CI, Russo L. Mathematical modeling of infectious disease dynamics. Virulence. 2013;4(4):295–306. https://doi.org/10.4161/viru.24041
33. Grassly NC, Fraser C. Mathematical models of infectious disease transmission. Nat Rev Microbiol. 2008 Jun 13;6(6):477–487. https://doi.org/10.1038/nrmicro1845
34. Lugnér AK, Mylius SD, Wallinga J. Dynamic versus static models in cost-effectiveness analyses of anti-viral drug therapy to mitigate an influenza pandemic. Health Econ. 2009;19(5):518-531. https://doi.org/10.1002/hec.1485
35. Cohen T, White P. Transmission-dynamic models of infectious diseases. In: Ibrahim Abubakar and others, editors. Infectious Disease Epidemiology. Oxford: Oxford University Press; 2016. p. 223–242.
36. Welta A, van Schalkwyk C. Mathematical models of transmission and control of infectious agents. In: Detels R, Karim QA, Baum F, Li L, Leyland AH, editors. Oxford Textbook of Global Public Health. 7th ed. Oxford: Oxford Academic; 2021. p. 241-258.
37. Renard P, Alcolea A, Ginsbourger D. Stochastic versus Deterministic Approaches. In: Wainwright J, Mulligan M, editors. Environmental Modelling. Chichester: John Wiley & Sons, Ltd; 2013. p. 133–49.
38. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population Health Impact and Cost-Effectiveness of Tuberculosis Diagnosis with Xpert MTB/RIF: A Dynamic Simulation and Economic Evaluation. PLoS Med. 2012;9(11): e1001347. https://doi.org/10.1371/journal.pmed.1001347
39. Menzies NA, Gomez GB, Bozzani F, Chatterjee S, Foster N, Baena IG, et al. Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models. Lancet Glob Health. 2016;4(11):e816–826. https://doi.org/10.1016/S2214-109X(16)30265-0

40. Houben RMGJ, Menzies NA, Sumner T, Huynh GH, Arinaminpathy N, Goldhaber-Fiebert JD, et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. Lancet Glob Health. 2016;4(11):e806–815. https://doi.org/10.1016/S2214-109X(16)30199-1
41. Harris RC, Sumner T, Knight GM, White RG. Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines. Human Vaccines & Immunotherapeutics. 2016;12(11):2813-2832. https://doi.org/10.1080/21645515.2016.1205769
42. Melsew YA, Adekunle AI, Cheng AC, McBryde ES, Ragonnet R, Trauer JM. Heterogeneous infectiousness in mathematical models of tuberculosis: A systematic review. Epidemics. 2020;30:100374. https://doi.org/10.1016/j.epidem.2019.100374
43. Menzies NA, Wolf E, Connors D, Bellerose M, Sbarra AN, Cohen T, et al. Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. Lancet Infect Dis. 2018;18(8):e228–238. https://doi.org/10.1016/S1473-3099(18)30134-8
44. Knight GM, Dodd PJ, Grant AD, Fielding KL, Churchyard GJ, White RG. Tuberculosis prevention in South Africa. PLoS One. 2015;10(4): e0122514. https://doi.org/10.1371/journal.pone.0122514
45. Hippner P, Sumner T, Houben RMGJ, Cardenas V, Vassall A, Bozzani F, et al. Application of provincial data in mathematical modelling to inform sub-national tuberculosis program decision-making in South Africa. PLoS One. 2019;14(1): e0209320. https://doi.org/10.1371/journal.pone.0209320
46. Vynnycky E, Sumner T, Fielding KL, Lewis JJ, Cox AP, Hayes RJ, et al. Tuberculosis control in South African gold mines: Mathematical modeling of a trial of community-wide isoniazid preventive therapy. Am J Epidemiol. 2015;181(8):619–632. https://doi.org/10.1093/aje/kwu320
47. Statistics South Africa. Mortality and causes of death in South Africa: Findings from death notification [Internet]. 2017 [cited 2022 Mar 21]. Available from: http://www.statssa.gov.za/publications/P03093/P030932017.pdf
48. Ismail N, Moultrie H. Impact of COVID-19 Intervention on TB Testing in South Africa. [Internet]. 2020 [cited 2022 May 2]. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/05/Impact-of-Covid-19-interventions-on-TB-testing-in-South- Africa-10-May-2020.pdf
49. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. The Lancet. 2015;385(9979):1799-1801. https://doi.org/10.1016/S0140-6736(15)60570-0
50. Starks MA, Sanders GD, Coeytaux RR, Riley IL, Jackson LR, Brooks AM, et al. Assessing heterogeneity of treatment effect analyses in health-related cluster randomized trials: A systematic review. PLoS One. 2019;14(8):e0219894. https://doi.org/10.1371/journal.pone.0219894
51. Garnett G, Cousens S, Hallett TB, Walker N, Rey G, et al. Mathematical models in the evaluation of health programmes. The Lancet. 2011;378:515–25. https://doi.org/10.1016/S0140-6736(10)61505-X
52. Houben RMGJ, Lalli M, Sumner T, Hamilton M, Pedrazzoli D, Bonsu F, et al. TIME Impact - a new user-friendly tuberculosis (TB) model to inform TB policy decisions. BMC Medicine. 2016;14(1):56. https://doi.org/10.1186/s12916-016-0608-4
53. Saaiq M, Ashraf B. Modifying 'Pico' Question into 'Picos' Model for More Robust and Reproducible Presentation of the Methodology Employed in A Scientific Study. World J Plast Surg. 2017;6(3):390–392.
54. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. https://doi.org/10.1186/s13643-021-01626-4
55. TB Modelling and Analysis Consortium. TB modelling literature reviews [Internet]. 2018 [cited 2021 Oct 6]. Available from: https://tb-mac.org/tb-mac-resource/systematic-literature-review-of-existing-academic-papers-describing-mathematical-and-economic-modelling-of-tb/
56. Fone D, Hollinghurst S, Temple M, Round A, Lester N, Weightman A, et al. Systematic review of the use and value of computer simulation modelling in population health and health care delivery. Journal of Public Health Medicine. 2003;25(4):325-335. https://doi.org/10.1093/pubmed/fdg075
57. Jaime Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: An ISPOR-AMCP-NPC good practice task force report. Value in Health. 2014;17(2):174–182. https://doi.org/10.1016/j.jval.2014.01.003
58. Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. BMC Med. 2014 Oct 30;12(1):216. https://doi.org/10.1186/s12916-014-0216-0

59. Basu S, Andrews JR, Poolman EM, Gandhi NR, Shah S, Moll A, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. The Lancet. 2007;370(9597):1500-1507. https://doi.org/10.1016/S0140-6736(07)61636-5
60. Basu S, Friedland GH, Medlock J, Andrews JR, Shah NS, Gandhi NR, et al. Averting epidemics of extensively drug-resistant tuberculosis. PNAS. 2009;106(18):7672–7677. https://doi.org/10.1073/pnas.0812472106
61. Chindelevitch L, Menzies NA, Pretorius C, Stover J, Salomon JA, Cohen T. Evaluating the potential impact of enhancing HIV treatment and tuberculosis control programmes on the burden of tuberculosis. J R Soc Interface. 2015;12(106):20150146. https://doi.org/10.1098/rsif.2015.0146
62. Dowdy DW, Chaisson RE, Maartens G, Corbett EL, Dorman SE. Impact of enhanced tuberculosis diagnosis in South Africa: A mathematical model of expanded culture and drug susceptibility testing. PNAS 2008;105(32):11293-11298. https://doi.org/10.1073/pnas.0800965105
63. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health. 2013;34:271–286. https://doi.org/10.1146/annurev-publhealth-031912-114431
64. Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette–Guérin revaccination reconsidered. J R Soc Interface. 2013;10(87):20130365. https://doi.org/10.1098/rsif.2013.0365
65. Gilbert JA, Long EF, Brooks RP, Friedland GH, Moll AP, Townsend JP, et al. Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa. PLoS One. 2015;10(5): e0126267. https://doi.org/10.1371/journal.pone.0126267
66. Gilbert JA, Shenoi S v., Moll AP, Friedland GH, Paltiel AD, Galvani AP. Cost-effectiveness of community-based TB/HIV screening and linkage to care in rural South Africa. PLoS One. 2016;11(12): e0165614. https://doi.org/10.1371/journal.pone.0165614
67. Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. Sci Transl Med. 2020;12(564):4607. https://doi.org/10.1126/scitranslmed.aax4607
68. Kendall EA, Shrestha S, Cohen T, Nuermberger E, Dooley KE, Gonzalez-Angulo L, et al. Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model. PLoS Med. 2017;14(1): e1002202. https://doi.org/10.1371/journal.pmed.1002202
69. Kendall EA, Azman AS, Maartens G, Boulle A, Wilkinson RJ, Dowdy DW, et al. Projected population-wide impact of antiretroviral therapy-linked isoniazid preventive therapy in a high-burden setting. AIDS. 2019;33(3):525–536. https://doi.org/10.1097/QAD.0000000000002053
70. Knight GM, Gomez GB, Dodd PJ, Dowdy D, Zwerling A, Wells WA, et al. The impact and cost-effectiveness of a four-month regimen for first-line treatment of active tuberculosis in South Africa. PLoS One. 2015;10(12): e0145796. https://doi.org/10.1371/journal.pone.0145796
71. Marx FM, Yaesoubi R, Menzies NA, Salomon JA, Bilinski A, Beyers N, et al. Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. Lancet Glob Health. 2018;6(4):e426–435. https://doi.org/10.1016/S2214-109X(18)30022-6
72. Marx FM, Cohen T, Menzies NA, Salomon JA, Theron G, Yaesoubi R. Cost-effectiveness of post-treatment follow-up examinations and secondary prevention of tuberculosis in a high-incidence setting: a model-based analysis. Lancet Glob Health. 2020;8(9):e1223–1233. https://doi.org/10.1016/S2214-109X(20)30227-8
73. Pretorius C, Menzies NA, Chindelevitch L, Cohen T, Cori A, Eaton JW, et al. The potential effects of changing HIV treatment policy on tuberculosis outcomes in South Africa: Results from three tuberculosis-HIV transmission models. AIDS. 2014;28(Supplement 1):S25-S34. https://doi.org/10.1097/QAD.0000000000000085
74. Rhines AS, Feldman MW, Bendavid E. Modeling the implementation of population-level isoniazid preventive therapy for tuberculosis control in a high HIV-prevalence setting. AIDS. 2018;32(15):2129-2140. https://doi.org/10.1097/QAD.0000000000001959
75. Ricks S, Denkinger CM, Schumacher SG, Hallett TB, Arinaminpathy N. The potential impact of urine-LAM diagnostics on tuberculosis incidence and mortality: A modelling analysis. PLoS Med. 2020;17(12): e1003466. https://doi.org/10.1371/journal.pmed.1003466
76. Shrestha S, Chihota V, White RG, Grant AD, Churchyard GJ, Dowdy DW. Impact of targeted tuberculosis vaccination among Amining population in South Africa: A model-based study. Am J Epidemiol. 2017;186(12):1362–1369. https://doi.org/10.1093/aje/kwx192
77. Sumner T, Bozzani F, Mudzengi D, Hippner P, Houben RM, Cardenas V, et al. Estimating the impact of tuberculosis case detection in constrained health systems: An example of case-finding in South Africa. Am J Epidemiol. 2019;188(6):1155–1164. https://doi.org/10.1093/aje/kwz038

78. Sumner T, Scriba TJ, Penn-Nicholson A, Hatherill M, White RG. Potential population level impact on tuberculosis incidence of using an mRNA expression signature correlate-of-risk test to target tuberculosis preventive therapy. Sci Rep. 2019;9(1):11126. https://doi.org/10.1038/s41598-019-47645-z
79. Uys PW, Warren R, van Helden PD, Murray M, Victor TC. Potential of rapid diagnosis for controlling drug-susceptible and drug-resistant tuberculosis in communities where Mycobacterium tuberculosis infections are highly prevalent. J Clin Microbiol. 2009;47(5):1484–1490. https://doi.org/10.1128/JCM.02289-08
80. Verguet S, Riumallo-Herl C, Gomez GB, Menzies NA, Houben RMGJ, Sumner T, et al. Catastrophic costs potentially averted by tuberculosis control in India and South Africa: a modelling study. Lancet Glob Health. 2017;5(11):e1123–1132. https://doi.org/10.1016/S2214-109X(17)30341-8
81. Williams BG, Granich R, de Cock KM, Glaziou P, Sharma A, Dyeb C. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Natl Acad Sci USA. 2010;107(45):19485–19489. https://doi.org/10.1073/pnas.1005660107
82. Meyer-Rath G, Johnson LF, Pillay Y, Blecher M, Brennan AT, Long L, et al. Changing the South African national antiretroviral therapy guidelines: The role of cost modelling. PLoS One. 2017;12(10):e0186557. https://doi.org/10.1371/journal.pone.0186557
83. Scriba TJ, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Kimbung Mbandi S, Borate B, et al. Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. Lancet Infect Dis 2021;21(3):354–65. https://doi.org/10.1016/S1473-3099(20)30914-2
84. Zwerling A, Shrestha S, Dowdy DW. Mathematical modelling and tuberculosis: Advances in diagnostics and novel therapies. Adv Med. 2015;2015:1–10. https://doi.org/10.1155/2015/907267
85. White RG, Hanekom WA, Vekemans J, Harris RC. The way forward for tuberculosis vaccines. Lancet Respir Med. 2019;7(3):204–206. https://doi.org/10.1016/S2213-2600(19)30040-2
86. Schwoebel V, Koura KG, Adjobimey M, Gnanou S, Wandji AG, Gody JC, et al. Tuberculosis contact investigation and short-course preventive therapy among young children in Africa. Int J Tuberc Lung Dis. 2020;24(4):452–60. https://doi.org/10.5588/ijtld.19.0712
87. Dye C, Williams BG. Tuberculosis decline in populations affected by HIV: a retrospective study of 12 countries in the WHO African Region. Bull World Health Organ. 2019;97(6):405–414. https://doi.org/10.2471/BLT.18.228577
88. Moyo S, Ismail F, van der Walt M, Ismail N, Mkhondo N, Dlamini S, et al. Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: a multistage, cluster-based, cross-sectional survey. Lancet Infect Dis. 2022;22(8):1172–1180. https://doi.org/10.1016/S1473-3099(22)00149-9
89. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical tuberculosis disease—A review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. Clinical Infectious Diseases. 2021;73(3):e830–841. https://doi.org/10.1093/cid/ciaa1402
90. di Tanna GL, Khaki AR, Theron G, McCarthy K, Cox H, Mupfumi L, et al. Effect of Xpert MTB/RIF on clinical outcomes in routine care settings: individual patient data meta-analysis. Lancet Glob Health. 2019;7(2):e191–199. https://doi.org/10.1016/S2214-109X(18)30458-3
91. Naidoo P, Dunbar R, Lombard C, du Toit E, Caldwell J, Detjen A, et al. Comparing tuberculosis diagnostic yield in smear/culture and Xpert® MTB/RIF-based algorithms using a non-randomised stepped-wedge design. PLoS One. 2016;11(3):e0150487. https://doi.org/10.1371/journal.pone.0150487
92. Bohlbro AS, Hvingelby VS, Rudolf F, Wejse C, Patsche CB. Active case-finding of tuberculosis in general populations and at-risk groups: a systematic review and meta-analysis. European Respiratory Journal. 2021;58(4):2100090. https://doi.org/10.1183/13993003.00090-2021
93. Gill CM, Dolan L, Piggott LM, McLaughlin AM. New developments in tuberculosis diagnosis and treatment. Breathe. 2022;18(1):210149. https://doi.org/10.1183/20734735.0149-2021
94. Ndjeka N, Campbell JR, Meintjes G, Maartens G, Schaaf HS, Hughes J, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. Lancet Infect Dis. 2022;22(7):1042–1051. https://doi.org/10.1016/S1473-3099(21)00811-2
95. Osman M, Meehan SA, von Delft A, du Preez K, Dunbar R, Marx FM, et al. Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa. PLoS One. 2021;16(6):e0252084. https://doi.org/10.1371/journal.pone.0252084

96. Stracker N, Hanrahan C, Mmolawa L, Nonyane B, Tampi R, Tucker A, et al. Risk factors for catastrophic costs associated with tuberculosis in rural South Africa. Int J Tuberc Lung Dis. 2019;23(6):756–763. https://doi.org/10.5588/ijtld.18.0519
97. van der Walt M, Moyo S. The First National TB Prevalence Survey, South Africa 2018: Short report [Internet]. 2018 [cited 2022 Jun 15]. Available from: https://www.nicd.ac.za/wp-content/uploads/2021/02/TB-Prevalence-survey-report_A4_SA_TPS-Short_Feb-2021.pdf
98. Osman M, Meehan SA, von Delft A, Boulle A, Dunbar R, Smith M, et al. Reducing initial loss to follow-up among people with TB in Cape Town, South Africa. Int J Tuberc Lung Dis. 2020;25(10Suppl 2):S350.
99. Johnson LF, Meyer-Rath G, Dorrington RE, Puren A, Seathlodi T, Zuma K, et al. The effect of HIV programs in South Africa on national HIV incidence trends, 2000–2019. JAIDS. 2022;90(2):115–23. https://doi.org/10.1097/QAI.0000000000002927
100. Horsburgh CR. Priorities for the treatment of latent tuberculosis infection in the United States. New England Journal of Medicine. 2004;350(20):2060–2067. https://doi.org/10.1056/NEJMsa031667
101. Vynnycky E, Fine PEM. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect. 1997;119(2):183–201. https://doi.org/10.1017/S0950268897007917
102. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS. 2009;23(13):1717–1725. https://doi.org/10.1097/QAD.0b013e32832d3b6d
103. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, de Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? [Unresolved issues]. Int J Tuberc Lung Dis. 2011;15(5):571–581. https://doi.org/10.5588/ijtld.10.0483
104. Menzies NA, Soeteman DI, Pandya A, Kim JJ. Bayesian methods for calibrating health policy models: A tutorial. Pharmacoeconomics. 2017;35(6):613–624. https://doi.org/10.1007/s40273-017-0494-4
105. Marino S, Hogue IB, Ray CJ, Kirschner DE. A methodology for performing global uncertainty and sensitivity analysis in systems biology. J Theor Biol. 2008;254(1):178–196. https://doi.org/10.1016/j.jtbi.2008.04.011
106. Vanqa N, Hoddinott G, Mbenyana B, Osman M, Meehan SA. Linkage to TB care: A qualitative study to understand linkage from the patients' perspective in the Western Cape Province, South Africa. PLoS One. 2021;16(11):e0260200. https://doi.org/10.1371/journal.pone.0260200
107. Fox GJ, Nguyen TA, Coleman M, Trajman A, Velen K, Marais BJ. Implementing tuberculosis preventive treatment in high-prevalence settings. Int J Tuberc Lung Dis. 2021;113:S13–15. https://doi.org/10.1016/j.ijid.2021.02.094
108. Chang ST, Chihota VN, Fielding KL, Grant AD, Houben RM, White RG, et al. Small contribution of gold mines to the ongoing tuberculosis epidemic in South Africa: a modeling-based study. BMC Med. 2018;16(1):52. https://doi.org/10.1186/s12916-018-1037-3
109. Christley RM, Mort M, Wynne B, Wastling JM, Heathwaite AL, Pickup R, et al. "Wrong, but Useful": Negotiating uncertainty in infectious disease modelling. PLoS One. 2013;8(10):e76277. https://doi.org/10.1371/journal.pone.0076277

Addendum A

Table A1: PRISMA 2020 Checklist (54)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page i
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 7, Table 2.1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table 2.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8, Page 9, Table 2.5
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8, Page 9, Page10, Table 2.5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10, Table 2.3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7,8,9

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8,9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Table A3
Study characteristics	17	Cite each included study and present its characteristics.	Table 2.5, Page 18-21
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 15, Table 2.4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Table 2.5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 18-21
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 33, Page 34, Table A3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 34, Page 35
	23b	Discuss any limitations of the evidence included in the review.	Page 36
	23c	Discuss any limitations of the review processes used.	Page 36
	23d	Discuss implications of the results for practice, policy, and future research.	Page 35-36
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 8
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding section
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data from addendum referred to throughout, Page 8

Table A2: Table of studies excluded at full text in the systematic review in Chapter 2

Publication (year)	Reason for exclusion
Bacaer (2008)	None of the End TB targets quantified
Basu (2008)	Review of modelling studies
Blaser (2016)	No intervention modelled
Cohen (2009)	Review of modelling studies
Chang (2018)	No intervention modelled
Currie (2003)	Not modelled for South Africa: modelled for Kenya
Du Toit (2007)	Not a population-based study: The number of cells over time (T_4, infected cells, CTLs, APC's, viral load, and bacterial load) represent the state variables that are modelled dynamically.
Enagi (2017)	Not modelled for South Africa: modelled for Nigeria
Houben (2014)	Not representative of the population: model reflects a closed cohort of individuals during and after TB preventive therapy
Houben (2016)	No intervention modelled
McCreesh (2018)	No intervention modelled
McCreesh (2020)	No intervention modelled
Menzies (2016)	None of the End TB targets quantified
Pretorius (2011)	No intervention modelled
Reid (2015)	Secondary report of modelling studies
Salvatore (2019)	No intervention modelled
Sharma (2017)	No intervention modelled
Sumner (2016)	Not representative of the population: model reflects a closed cohort of individuals during and after TB preventive therapy & none of population-level outcomes measured
Viljoen (2012)	Not modelled for South Africa: not calibrated to South African data
Witbooi (2017)	No intervention modelled
Wood (2011)	Intervention not modelled (explicitly – do show a model and discuss ART intervention, but focus on evidence gained from literature)

Table A3: Estimated AAPDs required to meet the WHO's End TB strategy targets for incidence and mortality

Incidence (90% reduction compared to 2015 levels)			
Year	**Incidence (per 100k)**	**PPD (time horizon)**	**AAPD**
2015	988	44% (5 years)	11%
2020	554		
2022	554 (Assumed)	82% (13 years)	12%
2035	98.8 (Target)		
Mortality (90% reduction compared to 2015 levels)			
Year	**Mortality (per 100k)**	**PPD (time horizon)**	**AAPD**
2015	116	11% (5 years)	2.3%
2020	103		
2022	103 (Assumed)	94% (13 years)	19%
2035	5.8 (Target)		

Addendum B

SUPPLEMENT

Brief description of the transmission-dynamic mathematical model used for the modelling study presented in Chapter 3

(Modelling the population-level impact of reducing initial loss to follow-up among individuals diagnosed with tuberculosis)

Important information: This supplementary information contains preliminary and unpublished information about the transmission-dynamic mathematical model developed by the DTTC-SACEMA TB modelling partnership**. Any questions arising from this document shall be directed to Dr. Florian Marx** (fmarx@sun.ac.za).

TABLE OF CONTENTS

S1. Overview

A deterministic, compartmental transmission-dynamic mathematical model of tuberculosis (TB) and HIV in the South African population was developed. The model was implemented as ordinary differential equations in R (statistical application). It consists of 11 TB-specific compartments describing the natural history of TB, TB diagnosis and treatment, and includes 9 subdivisions for HIV infection, progression, and antiretroviral treatment (ART). The model is transmission-dynamic for TB and uses external information on the incidence of HIV infection in the population to allow for modifications of the TB natural history and transmission dynamics by HIV status and ART. The model is initialized in 1995, and a burn-in period of 20 years is applied. The model is calibrated to a total of 10 calibration targets for selected epidemiological and programmatic indicators using a Bayesian posterior estimation (sampling-importance-resampling) approach. The calibration period is 2016-2020. The complete model time horizon is 1995 to 2035.

S2. Model structure

Figure S1 shows the model structure.

Main component: Individuals are born into the susceptible state. Upon primary infection, susceptible individuals transition from the susceptible to the latently infected 'recent' state. Individuals in the latently infected 'recent' state are assumed to either contain their infection and transition to a latently infected 'distant' state, or they rapidly progress to a diseased state. Individuals with distant latent infection may reactivate their infection and progress to disease, and they may become reinfected. The model distinguishes two disease states, a pre-clinical (pre-symptomatic) and a clinical (symptomatic) state. It assumes that all individuals who develop TB disease following either primary infection, reinfection or reactivation (relapse) enter the preclinical disease state and subsequently progress to a symptomatic disease state. Individuals in the symptomatic disease state, upon seeking care, transition into an 'awaiting diagnosis' state in which they enter the TB care cascade (see below). Individuals lost along the care cascade for any reason enter a 'previously sought care' diseased state and may seek care again at a rate that differs from that among individuals who never sought care before. Individuals diagnosed with TB may be initially lost to follow-up before initiating TB treatment. Those who are treated for TB enter the 'On treatment' state. Individuals who successfully complete treatment enter a recovered 'low risk' state. Those who do not complete their treatment and those with untreated TB disease who recover naturally enter a recovered 'high risk state'. Individuals in the recovered 'high-risk' state transition may relapse or transition into the recovered 'high-risk' state. Recovered individuals may relapse upon which they re-enter the pre-clinical disease state, or they may become reinfected upon which they enter the latently infected 'recent' state. Individuals may die from natural causes or from TB. The rate of death from TB distinguishes between untreated individuals and those on TB treatment.

Model subdivisions for HIV infection and ART: The model includes 9 subdivisions for HIV infection, progression and antiretroviral treatment (Figure S1). Upon HIV infection, HIV-negative individuals transition to an HIV-infected state and transition through 4 immunocompromised states (CD4 count levels). People in the HIV infected states may initiate ART (at any state) upon which they transition to ART treatment states. ART initiation is independent of the prevailing TB state. An additional process for ART initiation is implemented for people who initiate TB treatment. Individuals in the two lowest CD4 count level states may die from diseases associated with HIV infection including TB.

TB care cascade component: The TB care cascade component simulates different types of losses on the way to TB diagnosis and treatment (Figure S2). It is implemented as a simple decision function and distinguishes between individuals seeking care in primary health care facilities vs. other facilities. Individuals who seek care access a pre-diagnostic evaluation at which they may be referred for TB testing. Conditional on their ability to produce sputum and the sensitivity of the diagnostic test, individuals may be confirmed with TB, and initiate TB treatment. The model allows for clinical diagnosis in the absence of bacteriological confirmation. It also allows for the diagnosis among individuals with sputum-negative TB, and for false-positive TB diagnosis and treatment among TB-free individuals (not shown in Figure S2).

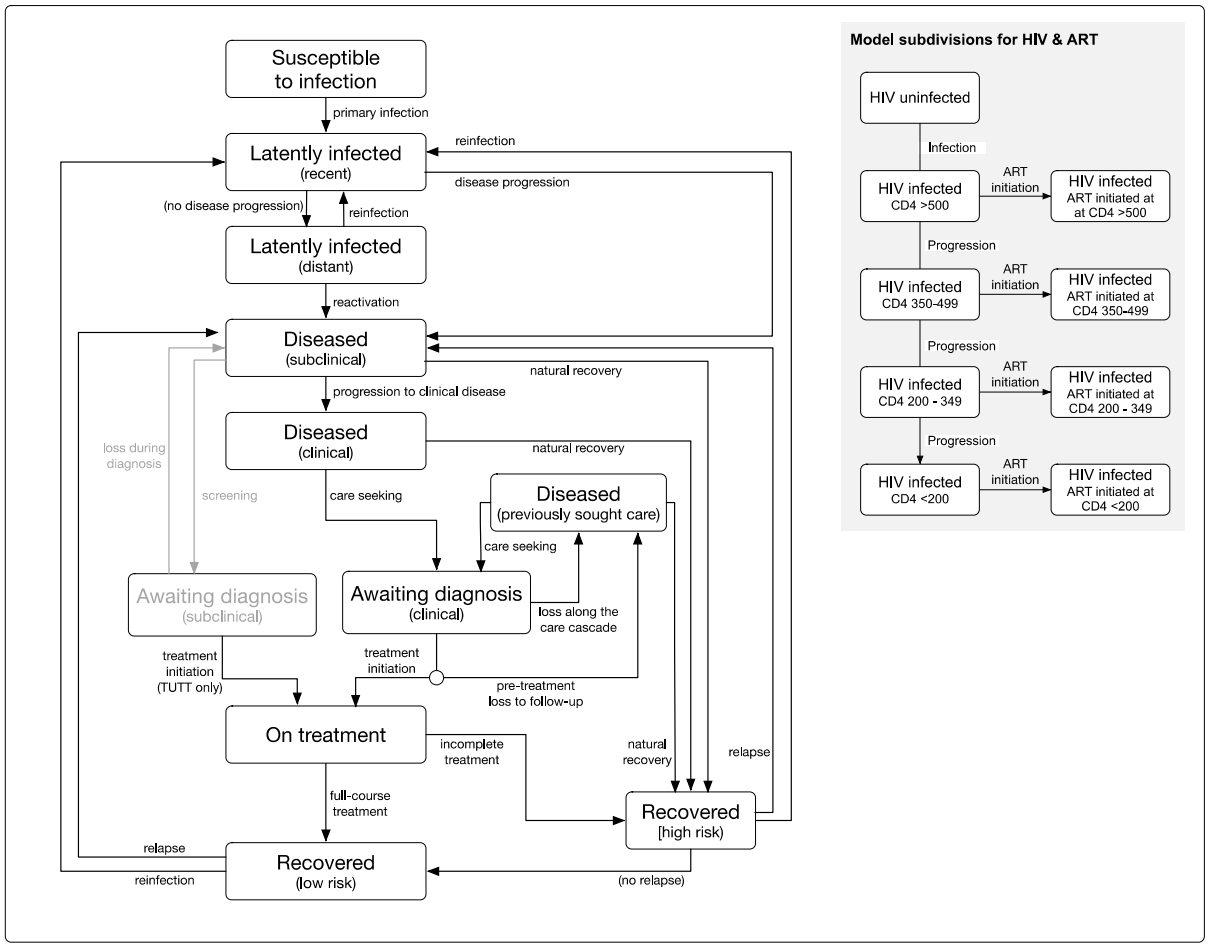

Figure S1. Structure of the compartmental transmission-dynamic model (Compartment and transitions in grey were not used in the study.

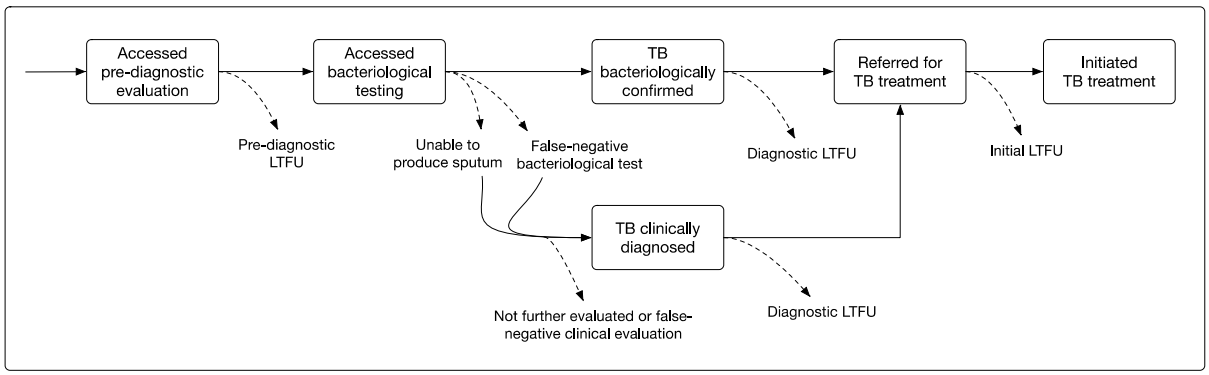

Figure S2. TB care cascade component

S3. Model parameterization

Prior parameter values and ranges used in the model along with their sources are provided in the subsequent sections and tables. Rates stated are per year unless otherwise specified.

S3.1. Demographic parameters

Table S1.

Measure	Mean value	Uncertainty range	Source
Annual birth rate	0.023	0.020 - 0.026	[1]
Natural death rate	0.0060	0.0046–0.0077	[1]

S3.2. TB transmission

Table S2.

Measure	Mean value	Uncertainty range	Source
Number of effective contacts per infectious person-year (symptomatic, HIV negative)	11	2 - 18	[2, 3]
Relative infectiousness of sub-clinical vs. clinical TB disease	0.635	0.270 - 1.000	[4, 5]
Relative infectiousness of TB among HIV-positive individuals (compared to HIV negative)			
CD4 > 500 cells/µl	0.95	-	[6, 7]
CD4 350-499 cells/µl	0.85	-	
CD4 200-349 cells/µl	0.65	-	
CD4 <200 cells/µl	0.45	-	
Relative risk of reinfection (distant latently infected vs. uninfected)	0.500	0.200 - 0.800	[8-10]
Relative risk of reinfection (recovered vs. uninfected)	0.750	0.500 - 1.000	[8-10]

S3.3. Natural TB history (HIV-negative)

Table S3.

Measure	Mean value	Uncertainty range	Source
Duration of the 'recently infected' period with elevated risk of TB progression (years)	2.0	-	[11]
Probability of rapid progression to pre-clinical TB during the recent latently infected period	0.060	0.040 - 0.120	[12-16]
Rate of delayed reactivation to pre-clinical TB after distant latently infected period	0.001	0.0005 - 0.0025	[9, 10, 17]
Rate of progression from pre-clinical to clinical TB disease	1.100	0.500 - 1.200	[18]
Rate of natural recovery from TB (regression from symptomatic to pre-symptomatic to latent infection)			[9, 10]
HIV negative	0.275	0.200 - 0.350	
CD4 >500 cells/µl	0.175	0.100 – 0.250	
CD4 350-499 cells/µl	0.175	0.100 – 0.250	
CD4 200-349 cells/µl	0	-	
CD4 <200 cells/µl	0	-	
Rate of transition from high-risk to low-risk of relapse recovery from TB (two year duration in high-risk of relapse recovery state)	0.5	-	assumption
Relative risk of relapse from high-risk recovery from TB	0.125	0.100 - 0.150	[9, 10, 17]
Rate of relapse after recovering from TB	0.001	0.0005 - 0.0025	[9, 10, 17]

S3.4. Care cascade: care seeking, TB diagnosis and treatment initiation

Table S4.

Parameter	Mean value	Uncertainty range	Source
Time between onset of clinical disease and care-seeking (years)	6.000	0.2500 - 1.500	[18]
Time between care-seeking and TB treatment initiation (weeks)	1.500	1.000 - 2.000	[19, 20]
Probability of pre-diagnostic loss to follow-up (before being referred to TB diagnostic assessment)	0.200	0.100 - 0.300	[21-24]
Probability of sputum-scarcity among individuals with sputum-positive TB			
Clinical TB, HIV negative	0.150	0.100 - 0.200	
Clinical TB, HIV positive	0.250	0.200 - 0.300	[25, 26]
Sub-clinical TB	0.450	0.300 - 0.600	
Sensitivity of the diagnostic test			
Xpert Ultra, HIV-negative	0.900	0.860 - 0.940	[27, 28]
Xpert Ultra, HIV-positive	0.880	0.850 - 0.910	
Probability of clinical or empirical diagnosis among people with TB who are sputum scarce or sputum test-negative			
HIV negative	0.150	0.100 - 0.200	[29, 30]
HIV positive	0.300	0.200 - 0.400	
Diagnostic loss to follow-up			
Xpert Ultra, HIV-negative	0.080	0.060 - 0.100	Assumption
Xpert Ultra, HIV-positive	0.060	0.040 - 0.080	
Pre-treatment (initial) loss to follow-up			
PHC	0.150	0.100 - 0.200	[31]
Non-PHC	0.250	0.200 - 0.300	

S3.5. Natural history of HIV infection and antiretroviral treatment

Table S5.

Measure	Baseline value	Uncertainty range	Source
Probability of perinatal HIV infection	Time-varying		[32]
Rate of HIV infection	Time-varying		[33]
Rate of HIV progression in the absence of ART:			[34]
From CD4 >500 to 350–500 cells/µl	0.340	0.280 - 0.390	
From CD4 350–500 to 200–349 cells/µl	0.480	0.400 - 0.580	
From CD4 200–349 to <200 cells/µl	0.320	0.250 - 0.390	
HIV-associated excess mortality rate, CD4 <200 cells/µl	0.210	0.160 - 0.270	[34]
Ratio: HIV-associated excess mortality rate, CD4 < 200–349 cells/µl vs. 200 cells/µl	0.145	0.050 – 0.240	[34]
Relative risk of dying from HIV whilst on ART vs. not on ART			[10]
CD4 200-349 cells/µl	0.100	-	
CD4 <200 cells/µl	0.770	-	

S3.6. TB mortality

Table S6.

Excess mortality due to **untreated** TB not on ART			
HIV negative	0.12	0.1 – 0.2	[9, 10, 17]
CD4 500-200 cells/µl	0.12	0.1 – 0.2	[9, 10, 17]
CD4 <200 cells/µl	0.25	0.30 – 1.0	assumption
Excess mortality due to **treated** TB not on ART			SA TB programme data (ETR)
HIV negative	0.080	0.070 – 0.090	
CD4 >500 cells/µl	0.080	0.070 – 0.090	
CD4 350-499 cells/µl	0.100	0.080 – 0.120	
CD4 200-349 cells/µl	0.150	0.120 – 0.180	

S4. Model initialization and parameter estimation (calibration) approach

Model simulations were initiated in 1995 followed by a 20-year burn in period; the model was calibrated to data between 2016 and 2020. We specified an initial population size of 41,436,000, based on United Nations population estimates [1]. The model was calibrated to data on TB incidence, mortality, and case notifications published by the WHO [39], data from South Africa's first national TB prevalence survey 2017-19 [40, 41] United National population estimates [1], and data on HIV prevalence and ART coverage published by UNAIDS [33]. We adopted a Bayesian parameter estimation approach [42] to identify model parameters that resulted in simulated trajectories with good fit to the calibration data. To implement this approach, we used a sampling-importance resampling algorithm. Prior parameter ranges were obtained from the published literature, and uniform prior distributions were specified for each parameter. Multiple parameter sets were then randomly and independently selected from these distributions (sampling). We measured the goodness of fit of simulated trajectories against the calibration targets (importance). The calibration targets were operationalized as the likelihood of observing the calibration data conditional on the simulated values. A subset of 1000 parameter sets was then resampled for final analysis with sampling probability proportional to goodness of fit (resampling). Figure S3 shows calibration targets and model trajectories resulting from the 1,000 resampled final parameter sets. Table S8 shows sources for calibration targets.

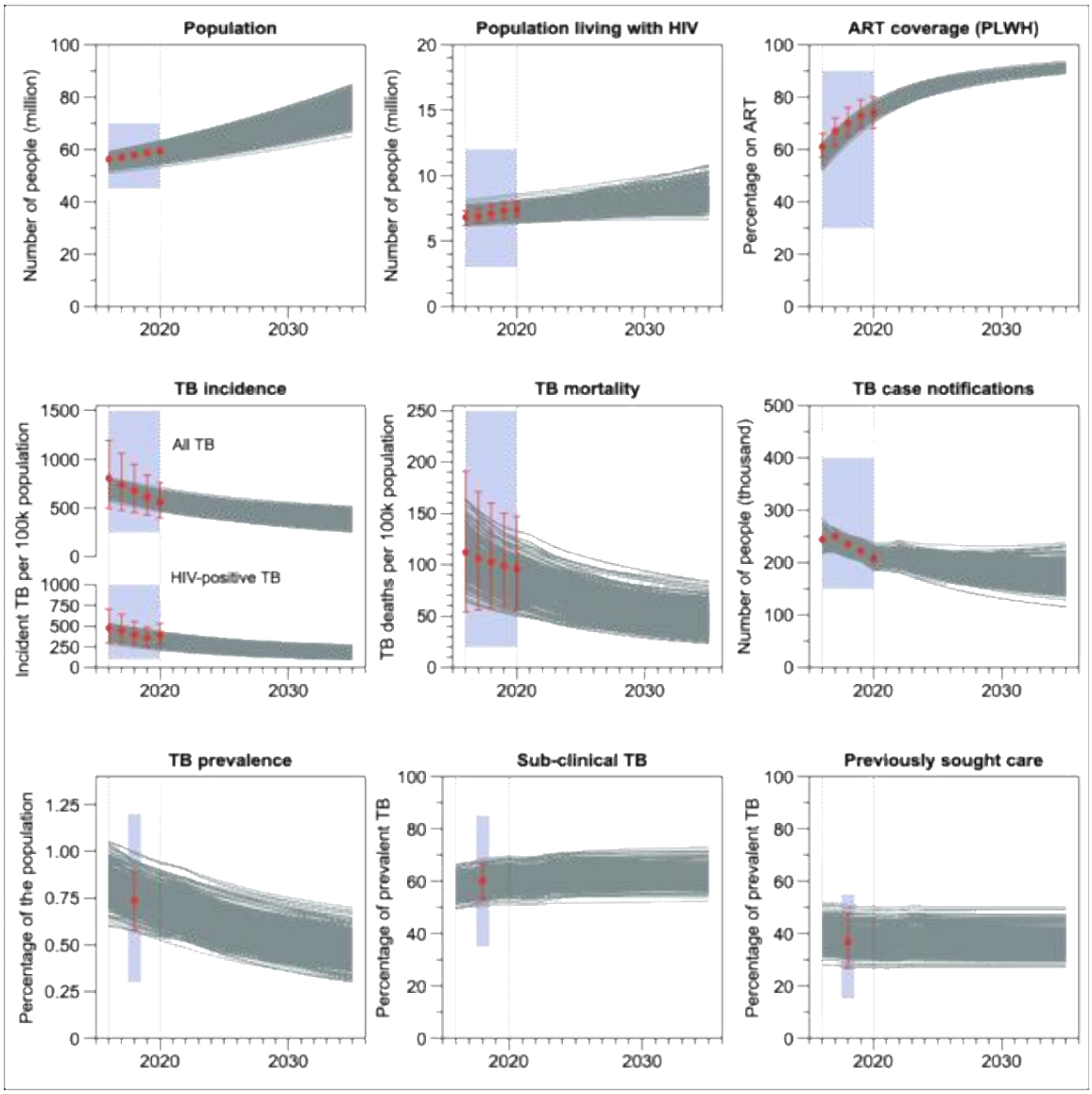

Figure S3. Model calibration (grey lines show 1,000 final model iterations; red circles with error bars show calibration targets with uncertainty intervals; blue intervals show feasible ranges, dashed lines show calibration period)

Table S8.

Calibration target	Source	Reference
Population size	United Nations	[1]
TB incidence	WHO Global TB Database	[39]
TB mortality	WHO Global TB Database	[39]
TB case notifications	WHO Global TB Database	[39]
HIV prevalence	UNAIDS	[33]
ART coverage	UNAIDS	[33]
TB prevalence	Moyo et. al, The First National TB Prevalence Survey - South Africa 2018	[40, 41]
Sub-clinical TB	Moyo et. al, The First National TB Prevalence Survey - South Africa 2018	[40, 41
Previously sought care	Moyo et. al, The First National TB Prevalence Survey - South Africa 2018	[40, 41

S5. Supplementary information references

1. United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition.
2. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008; 5(3): e74.
3. Johnstone-Robertson S, Lawn SD, Welte A, Bekker LG, Wood R. Tuberculosis in a South African prison - a transmission modelling analysis. S Afr Med J 2012; 101: 809-13.
4. Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet 1999; 353(9151): 444-9.
5. JC. OA02-600-19 Estimating the contribution of sub-clinical TB disease to transmission (Abstract) 52nd Union World Conference on lung health, 2021.
6. Huang CC, Tchetgen ET, Becerra MC, et al. The effect of HIV-related immunosuppression on the risk of tuberculosis transmission to household contacts. Clin Infect Dis 2014; 58(6): 765-74.
7. Espinal MA, Perez EN, Baez J, et al. Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: a prospective study. Lancet 2000; 355(9200): 275-80.
8. Andrews JR, Gandhi NR, Moodley P, et al. Exogenous reinfection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. J Infect Dis 2008; 198(11): 1582-9.
9. Marx FM, Yaesoubi R, Menzies NA, et al. Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. The Lancet Global Health 2018; 6(4): e426-e35.
10. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. PLoS Med 2012; 9: e1001347.
11. Marais BJ, Graham SM, Cotton MF, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis 2007; 196 Suppl 1: S76-85.
12. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibliotheca tuberculosea 1970; 26: 28-106.
13. Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Advances in Tuberculosis Research 1976; 19: 1-63.
14. Trauer JM, Moyo N, Tay EL, et al. Risk of Active Tuberculosis in the Five Years Following Infection . . . 15%? Chest 2016; 149(2): 516-25.
15. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect 1997; 119: 183-201.
16. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. Am J Respir Crit Care Med 2014; 190(9): 1044-52.
17. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet 1998; 352: 1886-91.
18. Ku CC, MacPherson P, Khundi M, et al. Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. BMC medicine 2021; 19(1): 298.
19. Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G. Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: a cross-sectional study. BMC Infect Dis 2008; 8: 72.
20. Van Wyk SS, Enarson DA, Beyers N, Lombard C, Hesseling AC. Consulting private health care

providers aggravates treatment delay in urban South African tuberculosis patients. Int J Tuberc Lung Dis 2011; 15(8): 1069-76.
21. Kweza PF, Van Schalkwyk C, Abraham N, Uys M, Claassens MM, Medina-Marino A. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. Int J Tuberc Lung Dis 2018; 22(3): 264-72.
22. Padingani M, Kumar A, Tripathy JP, Masuka N, Khumalo S. Does pre-diagnostic loss to follow-up among presumptive TB patients differ by type of health facility? An operational research from Hwange, Zimbabwe in 2017. Pan Afr Med J 2018; 31: 196.
23. Chihota VN, Ginindza S, McCarthy K, Grant AD, Churchyard G, Fielding K. Missed Opportunities for TB Investigation in Primary Care Clinics in South Africa: Experience from the XTEND Trial. PloS one 2015; 10(9): e0138149.
24. Christian CS, Gerdtham U-G, Hompashe D, Smith A, Burger R. Measuring Quality Gaps in TB Screening in South Africa Using Standardised Patient Analysis. International Journal of Environmental Research and Public Health 2018; 15(4): 729.
25. Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. Lancet 2018; 392(10144): 292-301.
26. Peter JG, Theron G, van Zyl-Smit R, et al. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 2012; 40(5): 1211-20.
27. Berhanu RH, David A, da Silva P, et al. Performance of Xpert MTB/RIF, Xpert Ultra, and Abbott RealTime MTB for Diagnosis of Pulmonary Tuberculosis in a High-HIV-Burden Setting. J Clin Microbiol 2018; 56(12).
28. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. The Lancet infectious diseases 2018; 18(1): 76-84.
29. McCarthy K, Fielding K, Churchyard GJ, Grant AD. Empiric tuberculosis treatment in South African primary health care facilities - for whom, where, when and why: Implications for the development of tuberculosis diagnostic tests. PloS one 2018; 13(1): e0191608.
30. Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet 2014; 383(9915): 424-35.
31. Osman M, Meehan S-A, von Delft A, et al. Reducing initial loss to follow-up among people with TB in Cape Town, south Africa. 52nd World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) Vol. 25. Virtual Event: The International Journal of Tuberculosis and Lung Disease, 2021:S350.
32. Johnson LF, May MT, Dorrington RE, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med 2017; 14(12): e1002468.
33. AIDSinfo: Global data on HIV epidemiology and response. UNAIDS, Geneva, 2022. Available from: https://aidsinfo.unaids.org.
34. Johnson LF. Access to antiretroviral treatment in South Africa, 2004 - 2011. SAMJ 2012; 13(1): 6.
35. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Natl Acad Sci U S A 2010; 107: 19485-9.
36. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005; 191(2): 150-8.
37. Ellis PK, Martin WJ, Dodd PJ. CD4 count and tuberculosis risk in HIV-positive adults not on ART: a systematic review and meta-analysis. PeerJ 2017; 5: e4165.
38. Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med 2012; 9(7): e1001270.
39. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Geneva, Switzerland, 2022.
40. Moyo S, Ismail F, Van der Walt M, et al. Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: a multistage, cluster-based, cross-sectional survey. The Lancet infectious diseases.
41. The First National TB Prevalence Survey - South Africa 2018. National Department of Health. Short report (online). Available from: https://www.knowledgehub.org.za/elibrary/first-national-tb-prevalence-survey-south-africa-2018
42. Menzies NA, Soeteman DI, Pandya A, Kim JJ. Bayesian Methods for Calibrating Health Policy Models: A Tutorial. Pharmacoeconomics 2017; 35(6): 613-24.

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